

# Enoxaparin injection for the treatment of high-risk patients with non-ST elevation acute coronary syndrome

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**Abstract:** Non-ST elevation acute coronary syndrome (NSTEMI) refers to a cardiovascular disorder characterized by intracoronary thrombus formation on a disrupted atherosclerotic plaque with partial or transient occlusion. Generation of thrombin resulting from exposure of collagen leads to activation of platelets and conversion of fibrinogen to fibrin, thus forming a platelet-rich thrombus. The main therapeutic objective is to protect the patient from thrombotic complications, independent of the choice of antithrombotic agents. The management of NSTEMI myocardial infarction (MI) is constantly evolving. For primarily conservative strategy, enoxaparin has been proven superior to unfractionated heparin (UFH). With early invasive strategy providing better clinical outcome compared with conservative strategy, the effectiveness of enoxaparin in reducing death and MI rates is now being reconsidered in the era of poly-pharmacotherapy, early percutaneous coronary interventions and drug eluting stents. Bleeding complications can be minimized by avoiding cross-over from UFH to enoxaparin or vice versa, or by reducing the dosage of enoxaparin. We review the studies of enoxaparin and discuss its current role in the contemporary treatment of NSTEMI.

**Keywords:** low-molecular weight heparin, NSTEMI, treatment

## Introduction

With the ongoing development of mechanical revascularization approaches and new generation pharmacological agents, the use of well established therapeutic cornerstones such as unfractionated heparins (UFH) and low-molecular-weight heparins (LMWH) is being reconsidered. In this review, we focus on the role of enoxaparin in view of the most recent clinical trials (see Table 1) for anticoagulant therapies in non-ST elevation acute coronary syndrome (NSTEMI).

## Pathophysiology of the culprit lesion

Acute coronary syndrome refers to cardiovascular disorders characterized by plaque rupture or erosion with consequent intracoronary thrombus formation. Exposure of collagen and tissue factor to the circulating blood leads to activation of the intrinsic and extrinsic coagulation system, thereby generating thrombin (factor IIa). Thrombin transforms circulating fibrinogen into fibrin, which in turn polymerizes, consolidating the developing thrombus. The fibrin strands are further reinforced by cross-linking with factor XIIIa, derived both from plasma and platelet granules. In addition to activating a positive feedback loop that initiates further factor X activation, thrombin itself is among the most potent direct stimulators of platelet activation and recruitment. The pivotal role of this protein led to sustained efforts to develop therapies that block thrombin generation or activity.

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**Table 1** Studies of enoxaparin in the contemporary treatment of non-ST elevation acute coronary syndrome

Study	Study date	Number of patients	Design	% of PCI	Primary endpoint	Result (enoxaparin vs UFH)
ESSENCE (Cohen et al 1997)	1994–1996	3171	Enoxaparin (1 mg/kg body weight sc bd) vs UFH	< 20%	Death, MI, or recurrent angina	19.8% vs 23.3% (30 days; $p = 0.02$ )
TIMI 11b (Antman et al 1999)	1996–1998	3910	Enoxaparin (30 mg bolus, followed by 1 mg/kg body weight sc bd) vs UFH	< 20%	Death, MI, revascularization	17.3% vs 19.6% (43 days; $p = 0.049$ )
ACUTE II (Cohen et al 2002)	Up to 2001	525	Enoxaparin (1 mg/kg body weight sc bd) vs UFH on top of ASA and tirofiban	< 15%	Frequency bleeding complication	(9.0% vs 9.2%; $p = 0.77$ )
INTERACT (Goodman et al 2003)	2000–2001	746	Enoxaparin (1 mg/kg body weight sc bd) vs UFH on top of ASA and eptifibatid	~ 30%	Non-CABG related major bleeding at 96 hours	2% vs 5%; $p = 0.03$
NICE-3 (Ferguson et al 2003)		628	Observational study, enoxaparin (1 mg/kg body weight sc bd) + ASA	45%	30-day incidence of non-CABG major bleeding	1.9% vs 2.0% in historical control
A phase of A to Z (Blazing et al 2004)	1999–2002	3967	Enoxaparin (1 mg/kg body weight s. c. bd) vs UFH on top of ASA and tirofiban	Early invasive subgroup 55%	Death, recurrent MI, or refractory angina after 7 days	OR 0.88; 95% CI, 0.71–1.08
GRUISE (Bhatt et al 2003)	Up to 2002	261	Enoxaparin (0.75 mg/kg body weight iv bd) vs UFH on top of ASA and eptifibatid	46%	Bleeding index (change of hemoglobin corrected for transfusion)	0.8 vs 1.1; $p = 0.15$
SYNERGY (SYNERGY Trial Investigators 2004)	2001–2003	9974	Enoxaparin (1 mg/kg body weight sc bd) vs UFH on top of ASA and GP IIb/IIIa (optional); if enoxaparin was given >8 hours prior to PCI, additional 0.3 mg/kg were given iv	46%	Death or acute MI at 30 days	14.0% vs 14.5% (OR, 0.96; 95% CI, 0.86–1.06)
STEEPLE (Montalescot et al 2006)	Up to 2005	3528	Enoxaparin (0.5 or 0.75 mg/kg body weight once iv) vs UFH	Non-urgent PCI	Non-CABG major or minor bleeding	(6.0% for 0.5 mg/kg enoxaparin ( $p = 0.014$ vs UFH); 6.6% for 0.75 mg/kg enoxaparin ( $p = 0.052$ vs UFH), and 8.7% for UFH
Chen et al 2006	2003–2005	966		47%	Hematoma on the puncture site	3.1 vs 7.3; $p = 0.03$

**Abbreviations:** ASA, aspirin; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; UFH, unfractionated heparins.

## Indirect thrombin inhibitors

UFH is a glycosaminoglycan composed of polysaccharides of mixed-length and molecular weights varying from 3000 to 50 000 Da. UFH is an indirect thrombin inhibitor, requiring binding to the cofactor antithrombin III (AT III) before being fully activated. The UFH/AT III complex binds to thrombin leading to its deactivation. In aspirin-treated patients with ACS, UFH is associated with a 30% additional reduction in the risk of recurrent myocardial infarction (MI) at 1 week (Eikelboom et al 2000). Shortcomings of UFH include individual saturation dosages, the inability to inactivate clot-bound thrombin, direct platelet activation, immunologically mediated thrombocytopenia, inactivation by plasma proteins and platelet factor 4, rebound increase after cessation of infusion, and, ultimately, a narrow therapeutic window with the need for close laboratory monitoring of its anticoagulant effect. These limitations may be especially problematic in the context of ACS, in which patients are already at high risk of ischemic events because of heightened baseline platelet reactivity, pre-existing thrombus, and an inflammatory state characterized by the release of cellular proteins into the bloodstream (Fuster et al 1992).

To overcome these limitations, better heparin preparations led to the development of LMWH. LMWH are fractions of standard heparins with average molecular weights between 4000 and 6000 Da, glycosaminoglycans with chains of alternating residues of D-glucosamine and uronic acid. Because of their biophysical difference they inactivate thrombin less and are more selective inhibitors of factor Xa. The anti-Xa/anti IIa ratio of LMWH (ardeparin, dalteparin, nandroparin, reviparin, tinzaparin, and enoxaparin) varies according to the preparation between 1.5 and is highest for enoxaparin with 3.8 (Weitz 1997). Enoxaparin has greater bioavailability with longer half-life and higher effectiveness, providing a more predictable anticoagulant response than UFH.

## LMWH in NSTEMI-ACS

Data comparing UFH with LMWH in randomized, controlled trials for the treatment of NSTEMI-ACS are best for the most commonly used compound enoxaparin (Petersen et al 2004). Studies using other LMWH (nadroparin in FRAX.I.S [The Frax.I.S. Study Group 1999]; dalteparin in FRIC [Klein et al 1997] and FRISC II [Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) 1999; FRagmin Fast Revascularisation during In Stability in Coronary artery disease (FRISC II) 1999]) have been disappointing.

## Enoxaparin without glycoprotein IIb/IIIa inhibitors

ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events) (Cohen et al 1997) and TIMI 11B (Thrombolysis in Myocardial Infarction 11B) (Antman et al 1999) were the first large clinical trials comparing enoxaparin with UFH. They were conducted in the era of predominantly conservative management of NSTEMI-ACS as less than 20% underwent percutaneous coronary intervention (PCI). The primary endpoint at 14 days was lower with enoxaparin (composite triple endpoint of death, MI or reinfarction, or recurrent angina;  $n = 3171$ ; 19.8% vs 16.6%;  $p = 0.019$ ) and remained lower at 30 days in ESSENCE and similarly, in TIMI-11B (death, MI, or urgent revascularization by 8 days;  $n = 3910$ ; 12.4% vs 14.5%;  $p = 0.048$ ). In a meta-analysis (Antman et al 1999) of the two trials, the relative risk reduction was around 20% in rates of death and MI in patients treated with enoxaparin from day 2 to 43. The benefit of enoxaparin was achieved with an increase in minor bleeding (18.4% vs 14.8%;  $p = 0.001$ ) in ESSENCE (Cohen et al 1997) and in major bleeding (1.4% vs 2.1%;  $p < 0.001$ ) in TIMI 11B (Antman et al 1999).

In view of these trials enoxaparin and UFH were both recommended as class I indications in patients undergoing medical therapy for ACS without GPIIb/IIIa inhibitors (Braunwald et al 2002) by the Association Task Force on Practice Guidelines American College of Cardiology/American Heart 2002, and enoxaparin was made preferable to UFH (class IIa, level of evidence A).

## Enoxaparin with glycoprotein IIb/IIIa Inhibitors

Enoxaparin evolved in parallel, but separately, with the platelet glycoprotein (GP) IIb/IIIa inhibitor era. Thus, subsequent studies have used a more aggressive approach using early revascularization and more frequent use of clopidogrel and GP IIb/IIIa antagonists. There is a substantial and growing body of evidence supporting the use of enoxaparin in the cardiac catheterization laboratory both with and without GP IIb/IIIa inhibitors.

The ACUTE II (Anti-Thrombotic Combination Using Tirofiban and Enoxaparin) trial (Cohen et al 2002) included 525 patients with NSTEMI-ACS who were randomized to receive enoxaparin or UFH on top of tirofiban and aspirin. The study was powered to assess bleeding incidences. The primary endpoint of death or MI after 30 days occurred with similar frequency in both groups (9.0% with enoxaparin vs

9.2% with UFH;  $p = 0.77$ ). TIMI major bleeding rates were 0.3% with enoxaparin vs 1.0% with UFH (OR 3.0; 95% CI, 0.30–33.8). Fewer than 30% of patients underwent coronary angiography while on study medication.

In 748 patients with high-risk NSTEMI-ACS enrolled in the INTERACT (Integrillin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment) trial (Goodman et al 2003), enoxaparin improved outcomes compared with UFH on the background of aspirin and eptifibatide. The primary safety endpoint of non-CABG related major bleeding at 96 hours was 2% in enoxaparin vs 5% with UFH ( $p = 0.03$ ). Although not powered to prove efficacy, the endpoint of death and/or MI at 30 days was 5% with enoxaparin vs 9% with UFH (OR 0.52; 95% CI, 0.30–0.96;  $p = 0.031$ ). Less than 15% of patients enrolled underwent coronary angiography within 48 hours of randomization.

The NICE-3 (National Investigators Collaborating on Enoxaparin-3) (Ferguson et al 2003) study was a open-label observational study analyzing the combination of enoxaparin with abciximab, tirofiban, or eptifibatide in 628 patients. The primary end point was the incidence of major bleeding not related to coronary artery bypass graft (CABG) surgery. Forty-five per cent of patients enrolled underwent PCI. The 30-day incidence of non-CABG major bleeding was 1.9%, and was not significantly higher than a prespecified historical control rate of 2.0%. The study was not randomized but used a historical cohort as controls, and as such these results must be interpreted with caution.

The Phase A of the A to Z trial (Blazing et al 2004) (Agrastat to Zocor) assessed the efficacy and safety of enoxaparin with the GP IIb/IIIa inhibitor tirofiban compared with UFH with tirofiban in 3987 patients with ACS. In this trial, cardiac catheterization was performed in only 61% of patients at a mean of 4.5 days. The study was powered to test the safety and superiority of enoxaparin over UFH. In this setting, enoxaparin was a suitable alternative to UFH with a 12% relative and a 1% absolute reduction (8.4% vs 9.4%,  $p = 0.23$ ) in the primary endpoint consisting of death, recurrent MI, or refractory angina after 7 days (Blazing et al 2004) (OR 0.88; 95% CI, 0.71–1.08). The occurrence of the safety endpoint (consisting of TIMI major, minor, or unknown site) was similar in both treatment groups (3% with enoxaparin vs 2.2% with UFH,  $p = 0.13$ ). In this study, 45% of the patients were prespecified to be treated conservatively (de Lemos et al 2004). In this cohort, enoxaparin reduced the absolute risk of the primary endpoint significantly (7.7% vs 10.6%, OR 0.72; 95% CI, 0.53–0.99,  $p = 0.04$ ), whereas at 30 days, there was only a trend favoring enoxaparin (11%

vs 13%,  $p = 0.10$ ). The overall occurrence of bleeding was not different between the treatment groups in the conservative subgroup of this study, although there was a small, but statistically significant increase in TIMI major bleeding in the enoxaparin group (0.8% with enoxaparin vs 0% with UFH,  $p = 0.02$ ). In the 55% of patients prespecified for an early invasive treatment strategy, the absolute risk of the primary endpoint was similar in both groups (8.8% vs 8.5%).

It appears from these studies that for patients with NSTEMI-ACS undergoing early conservative strategy combined with a GPIIb/IIIa inhibitor, enoxaparin is at least as effective as, or may even be better than, UFH in reducing death, MI, and refractory angina, at cost of an increased risk of major bleeding. The updated American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with NSTEMI ACS (released in March 2002) give class IA recommendations for early invasive management combined with GP IIb/IIIa inhibitor therapy but do not differentiate between LMWH and UFH in the class IA recommendation for concomitant antithrombotic therapy. The results of the SYNERGY and A to Z studies have not yet found their way into AHA/ACC guidelines (Braunwald et al 2002).

## Enoxaparin in acute interventions

With an early invasive strategy providing better clinical outcome than a conservative strategy, the paradigm of ACS management has shifted in favor of early (within 48 hours of admission) cardiac catheterization, and studies have now been designed to meet these recommendations.

Several recent studies such as Evaluation of Prolonged Anti-thrombotic Pretreatment (cooling-off strategy) Before Intervention in Patients with Unstable Coronary Syndrome (ISAR-COOL) Trial (Neumann et al 2003), Comparison of Early Invasive and Conservative Strategies in Patients with Unstable Coronary Syndromes Treated with GP IIb/IIIa Inhibitor Tirofiban (TACTICS TIMI-18) trial (Cannon et al 2001), the Fragmin and fast Revascularization during instability in Coronary artery disease multicenter study (FRISC II) (Fragmin and Fast Revascularisation during Instability in Coronary artery disease (FRISC II) 1999), The British Heart Foundation RITA-3 trial (Fox et al 2005) have provided evidence for the benefit of early revascularization in NSTEMI-ACS. However, there is still dispute whether, given optimized medical therapy, an early invasive strategy is superior to a selectively invasive strategy in patients with acute coronary syndromes without ST-segment elevation and with an elevated cardiac troponin T level (de Winter

et al 2005). Current guidelines (Braunwald et al 2002) recommend an early invasive strategy for patients without serious comorbidities who have acute coronary syndromes without ST-segment elevation, with an elevated cardiac troponin T level, impaired cardiac function, sustained ventricular tachycardia, or PCI within the 6 months.

The CRUISE (Bhatt et al 2003) (Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin) study was designed to assess whether the use of enoxaparin during elective or urgent PCI increased bleeding compared with unfractionated heparin, in addition to background therapy with eptifibatide. Of the 261 patients enrolled, 98% and 99% randomized to 0.75 mg/kg enoxaparin intravenously or UFH, respectively, had PCI performed. Around 46% underwent urgent PCI for NSTEMI-ACS in either group. Stents were placed in 86.5% and 85.4% of the enoxaparin and UFH arms, with thienopyridine pretreatment in 94.6% and 93.8%, respectively. The primary endpoint of the study, the bleeding index, was 0.8 with enoxaparin and 1.1 with UFH ( $p = 0.15$ ). The study demonstrated similar rates of vascular access complications, angiographic complications, and ischemic complications.

The SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularisation and GP IIb/IIIa Inhibitors) trial (SYNERGY Trial Investigators 2004), designed to define the role of enoxaparin in high risk patients with NSTEMI-ACS managed with an early invasive approach, enrolled 9978 patients. The primary efficacy outcome (death or MI) during the first 30 days occurred in 14.0% with enoxaparin and 14.5% with UFH (OR, 0.96; 95% CI, 0.86–1.06). More bleeding was observed with enoxaparin, with a statistically significant increase in TIMI major bleeding (9.1% vs 7.6%,  $p = 0.008$ ). Forty-six per cent of patients underwent PCI within a median time of 22 hours. A total of 58.8% of patients received GPIIb/IIIa.

An important message from SYNERGY is that changing antithrombotic agents from LWMH to UFH or vice versa leads to an increased bleeding and less clinical benefit (SYNERGY Trial Investigators 2004). In the subgroup with no cross-over, there was a benefit with enoxaparin reducing the primary endpoint (OR 0.82; 95% CI, 0.72–0.94).

In the recently presented STEEPLE (Safety and Efficacy of intravenous Enoxaparin in Elective Percutaneous Coronary Intervention) trial (Montalescot et al 2006), efficacy of a *reduced* intravenous enoxaparin dose (0.5 mg/kg) and 0.75 mg/kg enoxaparin given once vs UFH were compared in *non-urgent* PCI in 3528 patients. GPIIb/IIIa were used in 41% of patients. The primary endpoint of non-CABG major or

minor bleeding was lower in those groups treated with enoxaparin (6.0% for the reduced dose [ $p = 0.014$  vs UFH], 6.6% for regular dose [ $p = 0.052$  vs UFH], and 8.7% for UFH); major bleeding occurred in 1.2% of each of the enoxaparin groups ( $p = 0.005$  and  $p = 0.007$ , respectively, vs UFH) and 2.8% in the UFH group. The composite endpoint of non-CABG major bleed through 48 hours, all-cause mortality, MI, or urgent target vessel revascularization at 30 days was numerically lower among the two enoxaparin groups (7.2% and 7.9%) compared with the UFH group (8.4%). Patient enrollment in the enoxaparin 0.5 mg/kg treatment group was discontinued near the end of the trial, due to a difference in mortality between the three groups ( $p = 0.02$ ). The authors conclude that enoxaparin at a lower dose in the catheterization laboratory may result in lower bleeding events.

Whether the results of this study may be transferred to the setting of unstable angina remains to be evaluated.

In a randomized, controlled study 966 patients with coronary heart disease (Chen et al 2006), including 29.2% with NSTEMI-ACS, were randomized to enoxaparin (1 mg/kg bd) and UFH prior to catheterization. Four hundred and fifty-five patients underwent PCI. The incidence of hematoma on the puncture site was significantly higher in the UFH group than that in the enoxaparin group (7.3 vs 3.1, respectively  $p = 0.03$ ). The incidence of death, MI, revascularization at 30 days was 0 in enoxaparin group and 0.43% in UFH group, the study clearly being underpowered for these endpoints. The authors found that enoxaparin was safe and efficient during PCI.

A meta-analysis evaluated 6 large-scale randomized controlled trials (ESSENCE, TIMI-11B, ACUTE II, INTERACT, A to Z, and SYNERGY) comparing enoxaparin and UFH in NSTEMI-ACS with the endpoints of all-cause death and non-fatal MI, transfusion, and major bleeding (Petersen et al 2004). In 21946 patients, a statistically significant reduction of the combined endpoint death or MI at 30 days was observed (10.1% vs 11%; OR 0.91; 95% CI, 0.83–0.99; number needed to treat: 107) with enoxaparin. No difference was found in blood transfusion (OR 1.01; 95% CI, 0.89–1.14) or major bleeding (OR 1.04; 95% CI, 0.83–1.30) at 7 days after randomization (Petersen et al 2004).

ACUITY (Acute Catheterisation and Urgent Intervention Triage strategy) (Stone et al 2004) trial is an ongoing large-scale, prospective, multicenter, randomized study designed to determine the optimal anticoagulation regimen in patients with moderate- to high-risk ACS undergoing an early invasive strategy. Patients (13800) will be assigned to either unfractionated heparin or enoxaparin + GPIIb/IIIa



inhibition, vs bivalirudin + GPIIb/IIIa inhibition, vs bivalirudin + provisional IIB/IIIa inhibition. Cardiac catheterization is to be performed within 72 hours.

The trial is powered to examine whether: (1) bivalirudin with routine GPIIb/IIIa inhibition, compared with heparin (either UFH or enoxaparin) with routine GPIIb/IIIa inhibition, provides either non-inferior or superior overall 30-day clinical outcomes (composite incidence of death, MI, unplanned revascularization for ischemia, plus major bleeding); and (2) bivalirudin alone reduces major bleeding compared with heparin (either UFH or enoxaparin) with routine GPIIb/IIIa inhibition.

Efficacy endpoints in the above-mentioned studies were death and the combined endpoint of death or non-fatal MI. In ESSENCE recurrent angina and successful resuscitation of sudden death counted as death. Briefly, the definitions of spontaneous MI incorporated creatinin kinase-MB level of greater the upper limit of normal (ULN) in ESSENCE, TIMI 11B, and INTERACT, and 2 or more times the upper limit of normal in ACUTE and SYNERGY. Diagnosis of MI occurring around the time of PCI incorporated a criterion of  $\geq 3$  times the ULN of CK-MB and  $\geq 5$  times the ULN in the diagnosis of post-CABG MI. All studies included electrocardiographic definitions of MI. Different numbers in the efficacy endpoints of the single studies reflect the constant evolvement in the management of ACS in the past decade. Advances include an early invasive management strategy, improved stenting technology, adjunctive pharmacotherapy, and routine use of GPIIb/IIIa antagonists and thienopyridines. Furthermore, patients receiving prerandomization antithrombin therapy (from 30% in TIMI 11B to 75% in SYNERGY), or inclusion of the CABG surgery complications modify the number of the prespecified efficacy endpoints.

The safety endpoints in these studies were major bleeding and transfusion. The definitions of major hemorrhage incorporated bleeding that resulted in death, retroperitoneal bleeding, a decrease of hemoglobin of  $\geq 3$  g/dL in INTERACT and CRUISE, and additionally, requirement of  $\geq 2$  units of blood or intraocular and intracranial bleeding in ESSENCE and TIMI 11b. ACUTE II, A to Z, and SYNERGY defined major bleeding as a decrease of hemoglobin of  $\geq 5$  g/dL. STEEPLE assessed bleeding rates up to 48 hours, whereas in the study of Chen et al major bleeding was not prespecified, and only hematoma at the puncture site were reported. Differences regarding the incidence of bleeding may refer either to the duration of follow-up and data collection, to the definition of major hemorrhage, the concomitant use of GPIIb/IIIa inhibitors, patients receiving prerandomization therapy, or that

CABG surgery-related bleeding was not assessed (ACUTE II and A to Z). In A to Z and SYNERGY, switching antithrombin therapy evoked excess bleeding complications. In STEEPLE reduction of the dosage of enoxaparin resulted in lower incidence of bleeding complications.

## Registries

Systematic studies that compared the patterns of use of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) in patients with acute coronary syndromes (ACS) have been carried out in the "real-world" setting.

In the GRACE (Global Registry of Acute Coronary Events) (Klein et al 2003), the use of LMWH and UFH was analyzed in 13 231 ACS patients according to patient history, concomitant treatment, and invasive procedures. Results show that younger patients (<60 years), patients admitted to hospitals with PCI facilities, and patients undergoing invasive procedures were more likely to receive UFH, or both UFH and LMWH than LMWH alone (80.1% enoxaparin, 19.9% other LMWH). Patients receiving LMWH had significantly lower rates of hospital mortality ( $p = 0.009$ ) and major bleeding ( $p < 0.0001$ ). The authors conclude that UFH tends to be used more frequently than LMWH, but hospital outcomes appeared to be better with LMWH.

In a subanalysis from the CRUSADE Initiative (Bhatt et al 2004), LMWH and UFH were evaluated in high-risk NSTEMI ACS who had received early (<24 hours) GP IIB/IIIa inhibitor therapy and underwent early invasive management (Singh et al 2006). From a total of 11 358 patients treated at 407 hospitals in the US from January 2002 to June 2003, 60.6% received UFH and 39.4% received LMWH. According to information of the Institute of Medical Statistics (IMS) Health, enoxaparin accounts for about 80% of the LMWH prescribed in the USA. Therefore it is likely that most of the LMWH usage documented in CRUSADE represents enoxaparin. Patients treated with UFH were more often admitted to a cardiology inpatient service (73.6% vs 65.5%,  $p < 0.0001$ ) and more frequently underwent diagnostic catheterization (91.8% vs 85.9%,  $p < 0.0001$ ) and PCI (69.7% vs 56.9%,  $p < 0.0001$ ) than patients treated with LMWH. The point estimate of the adjusted risk of in-hospital death or reinfarction was slightly lower among patients treated with LMWH (OR 0.81, 95% CI 0.67–0.99) and the risk of red blood cell transfusion was similar (OR 1.01, 95% CI 0.89–1.15). Among patients who underwent PCI within 48 hours, adjusted rates of death (OR 1.14, 95% CI 0.71–1.85), death or reinfarction (OR 0.93, 0.67–1.31), and transfusion (OR 1.16, 0.89–1.50) were similar.

In a retrospective analysis of the prospective ACOS registry (Zeymer et al 2006), the outcome of high-risk patients with NSTEMI-ACS (according to those in SYNERGY) who were treated with enoxaparin or unfractionated heparin between July 2000 and November 2002 in 153 hospitals in Germany were compared. Twenty-five per cent of 4806 patients were treated with enoxaparin and 75% with unfractionated heparin. There were no differences between groups in baseline characteristics. There was a significant decrease in the combined endpoint of death or non-fatal reinfarction with enoxaparin in the entire study group (OR 0.51, 95% CI 0.37–0.70) and in subgroups treated with early PCI (n = 1333, OR 0.36, 95% CI 0.17–0.80), CABG (n = 270, OR 0.31, 95% CI 0.04–2.42), or conservatively (n = 3,203, OR 0.57, 95% CI 0.40–0.81). There was no significant increase in severe bleeding complications with enoxaparin (5.2% vs 4.5%).

In conclusion, in clinical practice, in unselected patients with NSTEMI-ACS who are treated conservatively or with early PCI, early treatment with enoxaparin is associated with a significant decrease in the combined endpoint of in-hospital death and reinfarction, without a significant increase in severe bleeding complications. Less than 30% of patients received LMWH in “real life”. Despite significant better outcome with enoxaparin, patients undergoing invasive procedures or PCI more often received UFH.

## Direct thrombin inhibitors (DTI) and pentasaccharides

The optimal combination of antiplatelet and antithrombin regimens that maximizes efficacy and minimizes bleeding among patients with NSTEMI-ACS undergoing PCI are under investigation in several trials involving other substances. In the recently published OASIS-5 trial, fondaparinux, a synthetic pentasaccharide, challenged the role of heparins and enoxaparin. Large-scale trials comparing enoxaparin with DTI are being performed currently.

In contrast to UFH and LMWH, direct thrombin inhibitors are able to inhibit both circulating and clot-bound thrombin. Bivalirudin, a synthetic, thrombin-specific anticoagulant approved for patients with unstable angina undergoing PCI (Bittl et al 2001; Lincoff et al 2003), is a bivalent DTI with linear kinetics that binds specifically to thrombin at its active catalytic site and at the exosite-1 docking locus.

In a meta-analysis (Kong et al 1999) of 4 randomized, controlled trials (n = 4973) comparing bivalirudin with UFH in patients with ACS treated either conservatively or with angioplasty (though before the GPIIb/IIIa era), bivalirudin sig-

nificantly reduced the composite incidence of death or MI by 23% (p = 0.02) and major hemorrhage by 59% (p = 0.01).

The PROTECT-TIMI-30 (Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-thrombotic Agents–Thrombolysis In Myocardial Infarction-30) is a randomized, open label, parallel-group, international, multicenter study to evaluate the angiographic and ischemic efficacy of eptifibatid in combination with a heparin (UFH or enoxaparin 0.5 mg/kg iv) compared with bivalirudin monotherapy in 857 high-risk patients with unstable angina or non-ST segment elevation MI (NSTEMI) undergoing PCI (Gibson et al 2006). Eptifibatid improved myocardial perfusion and reduced the duration of post-PCI ischemia but was associated with higher minor bleeding (2.5% vs 0.4%, p = 0.027) and transfusion rates (4.4%–0.4%, p = 0.001).

The OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial (MICHELANGELO OASIS 5 Steering 2005; The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators 2006) compared the efficacy and safety of fondaparinux and enoxaparin in 20 078 high-risk patients with unstable angina or MI without ST-segment elevation. Fondaparinux selectively binds antithrombin and causes rapid and predictable inhibition of factor Xa. The rate of major bleeding at 9 days was markedly lower with fondaparinux than with enoxaparin (2.2% vs 4.1%; OR, 0.52; p < 0.001). The primary endpoint (death, MI, or refractory ischemia at 9 days) occurred in 5.8% vs 5.7% with enoxaparin (OR in the fondaparinux group, 1.01; 95% CI, 0.90–1.13), satisfying the non-inferiority criteria.

## Conclusion

Optimal therapy of patients with NSTEMI-ACS comprises the combined use of coronary angiography and PCI within 24–48 hours, and combined administration of antithrombotic agents, like antithrombins and platelet inhibitors. It reduces ischemic coronary events but also increases bleeding in patients with acute coronary syndromes.

Enoxaparin has been shown to decrease ischemic complications in patients with acute coronary syndromes without ST elevations who are treated conservatively. Enoxaparin has been shown to be equally effective as unfractionated heparin in high-risk ACS patients with an early invasive approach. It seems of utmost importance to avoid cross-over from enoxaparin to UFH and vice versa.

The above-described randomized clinical trials highlight the relevance of enoxaparin in the setting of acute coronary interventions in high risk patients with NSTEMI-ACS.

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