Efficacy and safety of enoxaparin in unselected patients with ST-segment elevation myocardial infarction

Uwe Zeymer[1,2], Anselm Gitt[1,2], Claus Jünger[2], Timm Bauer[1], Tobias Heer[1], Oliver Koeth[1], Harm Wienbergen[1], Ralf Zahn[1], Jochen Senges[1,2]

[1]Herzzentrum Ludwigshafen, Medizinische Klinik B, Germany; [2]Institut für Herzinfarktforschung Ludwigshafen an der Universität Heidelberg, Ludwigshafen, Germany

Summary

In randomized clinical trials the low-molecular-weight heparin enoxaparin has been shown to reduce ischemic complications in patients with acute ST elevation myocardial infarction (STEMI) treated with fibrinolysis. Little is known about the use and efficacy of enoxaparin in unselected patients with STEMI in clinical practice. In a retrospective analysis of the prospective ACOS registry we compared the outcomes of patients with STEMI treated with enoxaparin or unfractionated heparin. A total of 6,299 patients with STEMI < 12 hours were included in this analysis, 609 (10%) were treated with enoxaparin and 5,690 (90%) with unfractionated heparin. In the multivariable propensity score analysis enoxaparin was associated with a reduction in the combined endpoint of death and non-fatal reinfarction in the entire group (odds ratio 0.59; 95% CI 0.43–0.80) and the subgroups of patients treated without early reperfusion (odds ratio 0.65, 95% CI 0.43–0.97), fibrinolysis (odds ratio 0.64; 95% CI 0.33–1.26) and primary percutaneous coronary intervention (odds ratio 0.33; 95% CI 0.15–0.72). There was no significant increase in severe bleeding complications with enoxaparin (6.5% versus 5.5%, p=0.4). In clinical practice in unselected patients with STEMI treated with or without early reperfusion therapy early treatment with enoxaparin compared to unfractionated heparin is associated with a significant reduction of the combined endpoint of inhospital death and reinfarction without a significant increase in severe bleeding complications.

Keywords

Acute myocardial infarction, thrombolysis / thrombolytic agents, clinical trials, heparins / LMWH

Thromb Haemost 2008; 99: 150–154

Introduction

In patients with ST-elevation myocardial infarction (STEMI) early mechanical or pharmacological reperfusion, antithrombotic therapy with aspirin, thienopyridines and unfractionated heparin (UFH) is standard of care and has been shown to reduce the rate of death or non-fatal myocardial infarction in randomized clinical trials. Therefore these agents are recommended in current STEMI guidelines (1, 2). UFH has some shortcomings including its indirect mechanism of thrombin inhibition, direct platelet activation, the inability to inactivate clot-bound thrombin, the tendency to promote thrombin binding to fibrin, and avid and non-specific protein binding (3). The low-molecular-weight heparin (LMWH) enoxaparin is a potential replacement for UFH. It provides a more stable and level of anticoagulation without the need for therapeutic monitoring. Furthermore, it demonstrates less protein binding and platelet activation and relatively greater inhibition of the coagulation cascade compared to UFH because it has a a ratio of 4.3:1 in its anti-factor Xa to antifactor IIa activity (4). In randomised clinical trials the LMWH enoxaparin has decreased ischemic complication rates in patients with STEMI who are treated with fibrinolysis (5–11). It is well known that the results of randomized clinical trials do not necessarily apply to the results observed in everydays clinical practice. Therefore, the aim of our analysis was to determine the effectiveness and safety of enoxaparin in unselected patients with STEMI in clinical practice in the German Acute COronary Syndromes (ACOS)-registry.

Correspondence to:
PD Dr. Uwe Zeymer
Herzzentrum Ludwigshafen
Bremserstrasse 79, 67063 Ludwigshafen
Tel.: +49 621 503 4045, Fax: +49 621 503 4002
E-mail: Uwe.Zeymer@t-online.de

Financial support:
Supported by an unrestricted grant of Sanofi-Aventis AG, Berlin, Germany.

Received July 13, 2007
Accepted after minor revision October 3, 2007

Prepublished online December 5, 2007
doi:10.1160/TH07–07–0449

Table 1: Baseline characteristics of the 6,299 patients with STEMI.

	Enoxaparin (n= 609)	Unfractionated heparin (n = 5,690)	P-value
Age (median, years)	67.9 (59.2–77.6)	65.7 (55.8–74.3)	<0.0001
Women	205 (33.7%)	1682 (29.6 %)	<0.05
Hypertension (%)	390 (64.0 %)	3314 (58.2 %)	<0.01
Smoker	190 (31.2 %)	2072 (36.4 %)	<0.05
Hyperlipidaemia	364 (59.8 %)	3535 (62.1 %)	0.28
Diabetes mellitus	180 (29.6 %)	1468 (25.8 %)	<0.05
Prior stroke	49 (8.0 %)	330 (5.8 %)	<0.05
Peripheral artery disease	46 (7.6 %)	365 (6.4 %)	0.28
Prior myocardial infarction	109 (17.9 %)	908 (16.0 %)	0.22
Prior coronary revascularization (PCI or CABG)	60 (9.9 %)	552 (9.7 %)	0.90
Renal impairment (creatinine > 2 mg/dl)	17 (2.8 %)	179 (3.1 %)	0.63
Median time from symptom onset to admisson (min)	236 (100–724)	190 (90–598)	0.05
Anterior infarct location	288 (47.3 %)	2810 (49.4 %)	0.2
Cardiogenic shock	44 (7.2 %)	649 (11.0 %)	<0.01
TIMI risk score (median).			

Methods

ACOS was a prospective registry aimed to evaluate baseline data, acute therapies and the in-hospital clinical course of consecutive patients admitted with an acute coronary syndrome (12). Inclusion criteria were STEMIs within 24 hours (h) after symptom onset or non-ST elevation myocardial infarction and unstable angina within 48 h after symptom onset. Baseline data and therapies during the first 48 h after admission were collected on two pages of the case record form. In addition the clinical course, diagnostic and therapeutic measures during the hospital stay were documented on two additional pages.

STEMI was diagnosed in the presence of the two following criteria: persistent angina pectoris for ≥20 minutes (min) and ST-segment elevation of ≥1 mm in ≥2 standard leads or ≥2 mm in ≥2 contiguous precordial leads, or the presence of a left bundle branch block. It was later confirmed by the elevation of cardiac enzymes to more than twice the upper limit of normal.

The Thrombolysis in Myocardial Infarction (TIMI) risk score for STEMI-patients was calculated using the score parameters as they have been published by Morrow et al. in the year 2000 (13).

Major bleeding was defined as any intracranial bleeding, bleeding associated with the need for blood transfusion, or any other clinically relevant bleeding as judged by the investigator.

Data sampling, control of the data quality, generation of queries, and statistical handling of the data were performed centrally in the Institut für Herzinfarktforschung in Ludwigshafen, Germany.

Patients

For this retrospective analysis we created a subgroup patients with STEMI of < 24 h duration treated with aspirin and UFH or enoxaparin within 48 h after admission. Patients treated with both UFH and enoxaparin and patients receiving LMWHs other than enoxaparin were excluded from the analysis.

Statistics

The absolute numbers, percentages, medians as well as 25% und 75% quartiles were used for the description of the patient population. For categorical variables we used the Chi^2- or Fisher`s exact test and calculated the odds ratios (OR) with 95% confidence intervals (CI). A p-value of < 0.05 was considered significant. A multivariable propensity score analysis was performed adjusting for age, gender, prior myocardial infarction, diabetes mellitus, prior stroke, peripheral arterial disease, smoking habit, hyperlipidemia, renal insufficiency, prehospital delay and cardiogenic shock. The analyses were performed with the SAS statistic package (SAS Institute version 8.2, Inc, Cary, NC, USA).

Results

Between July 1st, 2000 und Novemer 30th, 2002, a total of 16,814 patients with acute coronary syndromes were enrolled in 146 hospitals in Germany. From the latter a total of 6,299 patients fulfilled our inclusion criteria for this analysis (STEMI of < 24 h duration treated with aspirin and UFH or enoxaparin within 48 h after admission), 609 (10%) were treated with enoxaparin and 5,690 (90%) with UFH. In 92 of the hospitals only UFH was used, while treatment with both UFH or enoxaparin was given in 53 hospitals and enoxaparin only in one hospital. There was no difference in mortality between the hospital groups (UFH only 9.6%, UFH or enoxoparin 9.9%). In the multivariate analysis the treating hospital was not an independent predictor of the combined endpoint of death and re-infarction. The baseline charater-

Table 2: Treatments within 48 hours after admission.

	Enoxaparin (n=609)	Unfractionated heparin (n=5,690)	P-value
Aspirin	574 (94.3 %)	5297 (93.1%)	0.28
Clopidogrel	347 (57.0 %)	2666 (46.9 %)	<0.001
GP IIb/IIIa inhibitors	180 (29.6 %)	2089 (36.7 %)	<0.001
Statins	394 (64.7 %)	3574 (62.8 %)	0.36
Beta-blockers	484 (79.5 %)	4568 (80.3 %)	0.63
ACE-inhibitors	398 (65.4 %)	3589 (63.1 %)	0.27
Percutaneous coronary intervention	225 (36.5 %)	2146 (37.7%)	0.70
Fibrinolysis	125 (20.5 %)	1896 (33.3 %)	<0.001

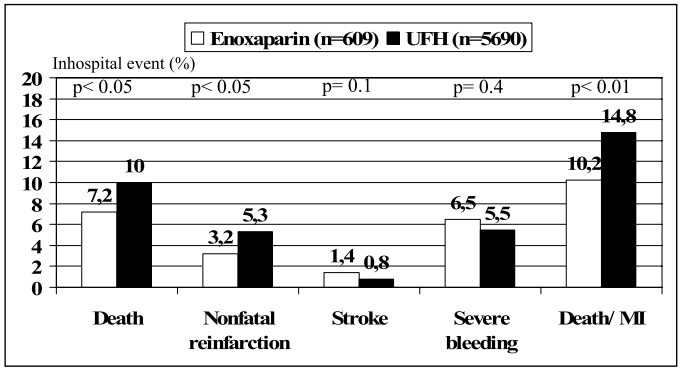

Figure 1: In-hospital clinical events in the patients with STEMI treated with enoxaparin or unfractionated heparin (UFH).

istics were comparable between the two groups (Table 1). However, patients treated with enoxaparin were significantly older, more often women and more often diabetics and had more often a history of stroke. On the other hand patients treated with UFH more often experienced cardiogenic shock. The significant higher TIMI risk score in the enoxaparin group indicates an overall higher risk profile of these patients.

The acute therapies applied within the first 48 h after admission are shown in Table 2. While clopidogrel was given more often in the enoxaparin group, GP IIb/IIIa inhibitors were used more often in the patients with UFH. The rate of patients treated with early percutaneous coronary intervention (PCI) was about 37% in both groups. Fibrinolyis was given more often in the UFH group.

All patients were prospectively followed until hospital discharge. In the total patient population enoxaparin was associated with a significant lower incidence of death and reinfarction, while there was no significant difference in stroke or major bleeding complications (Fig. 1). The advantage of enoxaparin in the reduction of mortality was seen predominantly in the higher risk patients as assessed by the TIMI risk score (Fig. 2). We divided patients into three groups: patients without early reperfusion therapy (n=1,906), patients treated with fibrinolysis (n=2,021) or with primary PCI within the first 48 h (n=2,371). In the patients treated conservatively during the first 48 h 16.8% and 17.5% (p=0.67) underwent late PCI during in index hospitalisation in the enoxaparin and UFH group, respectively. As shown in Table 3 the combined endpoint of death and non-fatal

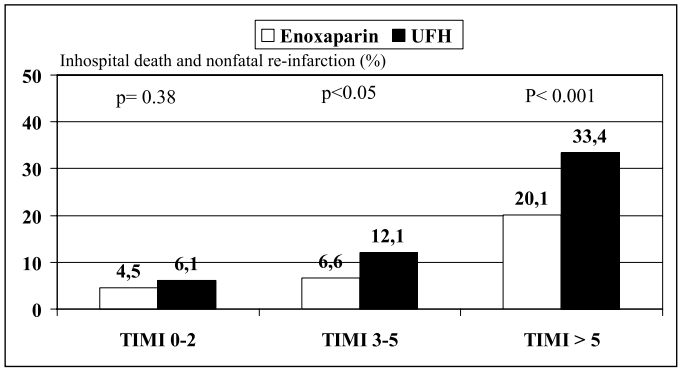

Figure 2: Impact of baseline risk of the patients as assessed by the TIMI risk score on combined endpoint death and reinfaction.

myocardial re-infarction was reduced by enoxaparin in all three subgroups. The reduction was statistically significant in the conservatively and interventionally treated patients. In a multivariable propensity score analysis for the occurrence of death and non-fatal myocardial re-infarction until discharge the use of enoxaparin was an independent predictor of a better clinical outcome (Fig. 3).

In the subgroup of patients with cardiogenic shock we observed no difference for in-hospital death (19/44 = 43.2% vs. 309/649 = 47.6% , p=0.57) and non-fatal re-infarction (1/44 = 2.2% vs. 15/649 = 2.2%, p=0.92). In contrast in patients without

	Enoxaparin	Unfractionated heparin	P-value	Odds ratio (95% CI)
Entire cohort (n=6299)	62/609 10.2 %	842/5690 14.8 %	<0.01	0.65 (0.50–0.86)
No early reper-fusion (n=2,683)	43/259 16.6 %	370/2424 22.5 %	<0.05	0.69 (0.49–0.97)
Fibrinolysis (n=2,021)	10/125 8.0%	261/1896 13.8 %	0.07	0.54 (0.28–1.05)
Primary PCI (n=2,371)	9/225 4.0 %	211/2146 9.8 %	<0.01	0.38 (0.19–0.76)

Table 3: Incidence of death and non-fatal myocardial re-infarction until discharge in the univariate analysis.

cardiogenic shock enoxaparin (n=565) compared to UFH (n=5,041) was associated with a trend towards a reduction in death (4.4% vs. 5.2%, p=0.4) and significant reductions in non-fatal re-infarction (3.1% vs. 5.4%, p<0.05) and in the combined endpoint of death and non-fatal re-infarction (7.4% vs. 10.3%, p<0.05).

There were no significant differences between enoxaparin and UFH in severe bleeding complications in the entire cohort (6.5% vs. 5.5%, p=0.3) and in the subgroups with fibrinolysis (8.1% vs 5.3%, p=0.3) and primary PCI (4.8% vs. 7.2%, 0.3%), while there were less bleeding with UFH in the conservatively treated patients (6.9% vs. 2.7%, p<0.05).

Discussion

Our analysis aimed to study the safety and effectiveness of enoxaparin in unselected patients with STEMI in clinical practice. It is well known that patients included in randomised trials do not necessarily represent every days clinical practice. Therefore we sought to investigate if the results of enoxaparin in randomised clinical trials can be reproduced in unselected patients in clinical routine.

In our analysis unselected consecutive patients admitted to different hospitals with and without interventional facilities were included. There were some differences in baseline characteristics with older and sicker (diabetics, prior stroke, higher TIMI risk score) patients in the enoxaparin group. The use of primary PCI was similar in the two groups, while more patients with UFH received fibrinolytic therapy.

In the entire group we observed a significant reduction in the incidence of both in-hospital death and non-fatal re-infarction in patients treated with enoxaparin. In all subgroups enoxaparin was associated with a reduction in the combined endpoint death and non-fatal re-infarction. In the multivariate propensity score analysis after adjustment for predictors of in-hospital death and myocardial re-infarction enoxaparin significantly reduced the odds for this combined endpoint.

Enoxparin has been studied in several trials in conjunction with fibrinolysis and compared to placebo or UFH. In the trials with UFH as the competitor a reduction in the combined rate of death and re-infarction was observed with enoxaparin (5–8). In a meta-analysis of these trials enoxaparin (9) compared with UFH during hospitalization at seven days reduced re-infarction by 45% (3.0% vs. 5.2%; OR, 0.57; 95% CI, 0.45 to 0.73; NNT=45), did not reduce death (4.8% vs. 5.3%; OR, 0.92; 95% CI, 0.74 to 1.13) or increase major bleeding (3.3% vs. 2.5%; OR, 1.30; 95% CI, 0.98 to 1.72), but increased minor bleeding (22.8% vs. 19.4%; OR, 1.26; 95% CI, 1.12 to 1.43). The reduction in re-infarction remained evident at 30 days.

Recently the results of the large clinical multi-center, double-blind, randomized EXTRACT-TIMI 25 trial with over 20,000 patients with STEMI treated with fibrinolysis were published (10, 11). It compared enoxaparin initiated with an intravenous bolus of 30 mg followed by 1 mg/kg twice daily subcutaneously for up to eight days and UFH initiated with a bolus of 60 IU/kg followed by an infusion of 12 IU/kg/h for 48 h. The primary endpoint, a composite of death and re-infarction, at 30 days was significantly reduced with enoxaparin (10% vs. 12%, p<0.001) (Fig. 4).

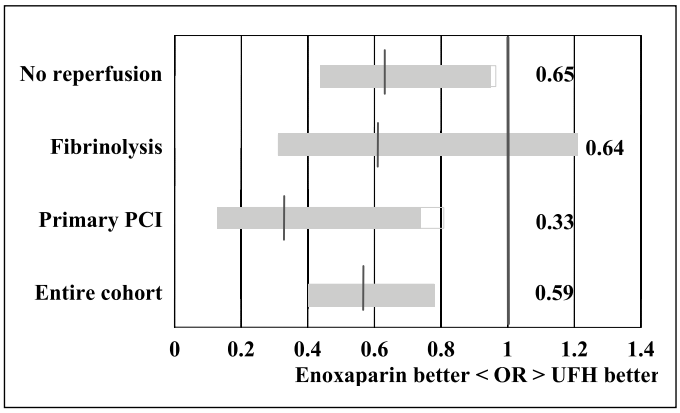

Figure 3: Odds ratios for the combined endpoint of death and reinfarction in the multivariate analysis.

While there was no increase in intracerebral bleeding there were significat more major bleeding complications with enoxaparin. In our analysis the number of patients treated with fibrinolysis was relatively small, therefore the 95% CIs crossed the line of identity, despite an OR of 0.61 for death and re-infarction, which is nearly identical to the OR in the entire cohort.

So far there are only a few data available about the use of enoxaparin in patients with primary PCI. In a small substudy of the WEST trial anti Xa activity was measured 55 min after a subcutaneous administration of 1 mg/kg enoxaparin in patients with primary PCI for STEMI. Of these patients 87% had anti Xa levels below 0.5. An additional intravenous bolus of 0.3–0.5 mg/kg at the time of PCI achieved in all patients a therapeutic anti-Xa level of 0.8–1.08 (14). In the ADVANCE-MI trial patients scheduled for primary PCI were randomized to receive half-dose tenecteplase and eptifibatide or placebo and eptifibatide and in a second randomization UFH or enoxaparin (open label bolus of 0.4 mg/kg not to exceed 40 mg). This study was stopped prematurely for low enrollment after 148 patients. In this small study there was no difference between UFH and enoxaparin with respect to ischemic events or bleeding complications (15). Therefore our analysis is one of the first to determine the effectiveness of enoxaparin in primary PCI. Enoxaparin reduced both death and myocardial infarction without any increase, but even a trend towards fewer, bleeding complications.

A difference occurred in concomitant antiplatelet medication with a higher use of clopidogrel in the enoxaparin and a higher use of GP IIb/IIIa inhibitors in the UFH group. This might be due to the fact that in Germany the combined use of enoxaparin and GP IIb/IIIa inhibitors is not a standard regimen, despite the positive results in randomised trials (16). However, it is unlikely that the differences in concomitant medication account for the differences in clinical event rates in the two groups, since the more potent platelet GP IIb/IIIa inhibitors were used more often in the UFH.

The advantages and disadvantages of UFH and LMWHs have been discussed extensively. The ease of administration and the lack of the need for monitoring make enoxaparin a convenient alternative to UFH in patients with acute coronary syndrome, especially in clinical routine.

One explanation for our observations might be that UFH is closely and well monitored in clinical trials, which is associated with a more stable level of anticoagulation as might be achieved in clinical practice. On the other hand the efficacy and safety of enoxaparin is not linked to close monitoring, except for an adjustment of the dose in patients with impaired renal function. Therefore this advantage seems to be even more important in clinical practice.

Here the assumed more stable level of anticoagulation achieved by enoxaparin was associated with a reduction of ischemic complications. We did not observe a significant difference im major bleeding complications between the two groups. In the group of patients with primary PCI a trend towards less bleeding was observed with enoxaparin. This is in line with the findings of the STEEPLE trial performed in patients with elective PCI (17). Again the high inter- and intra-individual variability of heparin without close monitoring might contribute to these results.

Limitations

Our analysis derived from a registry and not a randomised clinical trial. However, there were no major differences between the groups in the baseline characteristics and revascularisation procedures. Still a selection bias can not be fully excluded even after adjusting for multiple predictors of outcome. We do not have information about the duration of treatment with either enoxaparin or UFH, and the activated partial thromboplastin times (aPTTs) achieved with UFH, all factors which might have influenced the clinical event rate. However, potential differences in the duration of treatment reflect the actual clinical practice, possibly favouring a longer treatment with the more convenient subcutaneous regimen with enoxaparin without the need for laboratory controls.

Conclusions

In clinical practice in unselected patients with STEMI enoxaparin in comparison with UFH is associated with a significant reduction of the combined endpoint of in-hospital death and re-infarction without a significant increase in major bleeding complications.

References

1. Van de Werf F, Ardissino D, Betriu A, et al.; Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2003; 24: 28–66.

2. Antman EM, Anbe DT, Armstrong PW, et al.; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004; 110: e82–292.

3. Hirsh J. Heparin. N Engl J Med 1991; 324: 1565–1574.

4. Hirsh J, Warketin TE, Slaughnessy Sg, et al. Heparin and low molecular weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy and safety. Chest 2001; 119: 64S-94S.

5. Baird SH, Menown IB, McBride SJ, et al. Randomized comparison of enoxaparin with unfractionated heparin following fibrinolytic therapy for acute myocardial infarction. Eur Heart J 2002; 23: 627–632.

6. Ross AM, Molhoek P, Lundergan C, et al. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II). Circulation 2001; 104: 648–652.

7. The ASSENT-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001; 358: 605–613.

8. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin in the prehospital setting. The ASSENT-3 PLUS randomized trial in acute myocardial infarction. Circulation 2003; 108: 135–142.

9. Eikelboom JW, Quinlan DJ, Metha SR, et al. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. Circulation 2005 ; 112: 3855–3867.

10. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). Am Heart J 2005; 149: 217–226.

11. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with thrombolysis for ST-elevation myocardial infarction. N Engl J Med 2006; 354: 1477–1488.

12. Zeymer U, Senges J. Qualitätsregister in der Kardiologie. Bundesgesundheitsbl-Gesundheitsforsch-Gesundheitsschutz 2004; 47: 533–539.

13. Morrow DA, Antman EM, Charlesworth A, et al. TIMI Risk Score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation. Circulation 2000; 102: 2031.

14. Welsh RC, Gordon P, Westerhout CM, et al. A novel enoxaparin regimen for ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: intravenous but not subcutaneous enoxaparin achieves adequate anti-Xa levels. J Am Coll Cardiol 2006; 47 (Suppl. A): 228A (Abstract).

15. The ADVANCE MI Investigators. Facilitated percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: results from the prematurely terminated Adressing the Value of facilitated Angioplasty after combination therapy or Eptifibatide monotherapy in acute Myocardial infarction trial (ADVANCE MI) trial. Am Heart J 2005; 150: 116–122.

16. Goodman SG, Fitchett D, Armstrong PW, et al. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. Circulation 2003; 107: 238–244.

17. Montelascot G, White HD, Gallo R, et al. Enoxaparin versus unfractionated heparin in elecetive percutaneous coronary intervention. N Engl J Med 2006; 355; 1006–1017.