A Unique, Low Dose of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention

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OBJECTIVES	This study was designed to examine a unique and low dose of intravenous enoxaparin in elective percutaneous coronary intervention (PCI) that would be applicable to an unselected population regardless of age, weight, renal function, or use of glycoprotein IIb/IIIa inhibitors.
BACKGROUND	There is limited experience of anticoagulation using intravenous (IV) low-molecular-weight heparin in PCI, which has been obtained with high doses causing elevated anticoagulation levels and delayed sheath withdrawal.
METHODS	A total of 242 consecutive patients undergoing elective PCI were treated with a single IV bolus of enoxaparin (0.5 mg/kg), and 26% of patients (n = 64) also received eptifibatide. Sheaths were removed immediately after the procedure in patients treated with enoxaparin only, and 4 h after the procedure in those also treated with eptifibatide.
RESULTS	A peak anti-Xa >0.5 IU/ml was obtained in 97.5% of the population, and 94.6% of patients had their peak anti-Xa level in the predefined target range of 0.5 to 1.5 IU/ml. Advanced age, renal failure, being overweight, and eptifibatide use did not alter the anticoagulation profile. At one-month follow-up, six patients (2.5%) had died, had a myocardial infarction, or undergone an urgent revascularization; all the patients had an anti-Xa level >0.5 IU/ml during PCI. Patients without an ischemic event and without a creatine kinase rise, but with a detectable troponin release in the next 24 h of PCI (>2 μg/ml, n = 21), had similar anti-Xa levels as those without troponin elevation. There were one major and three minor bleeding events that were not associated with anti-Xa overshoot.
CONCLUSIONS	Low-dose (0.5 mg/kg) IV enoxaparin allows a prespecified target level of anticoagulation (anti-Xa >0.5 IU/ml) in the vast majority of patients undergoing PCI, appears to be safe and effective, allows immediate sheath removal when used alone, and does not require dose adjustment when used with eptifibatide. (J Am Coll Cardiol 2002;40:1943–50) © 2002 by the American College of Cardiology Foundation

Subcutaneous enoxaparin has shown its superiority over unfractionated heparin (UFH) in the medical treatment of unstable angina (UA) and non–ST-elevation myocardial infarction (NSTEMI) (1,2). Recent studies have also shown good results with subcutaneous enoxaparin anticoagulation of patients with UA/NSTEMI undergoing percutaneous coronary intervention (PCI) on such subcutaneous enoxaparin treatment (3–5). Although PCI has improved dramatically because of innovations in techniques, stents, and antiplatelet agents, the optimal anticoagulant treatment remains uncertain. Low doses of UFH are currently recommended, especially if glycoprotein (GP) IIb/IIIa inhibitors are also being used (6–8). Intravenous (IV) low-molecular-weight heparins (LMWH) in elective PCI have been evaluated in various registries recruiting patients not pretreated by LMWH before the catheterization laboratory (9–11).

Kereiakes et al. (10) tested two different doses of the LMWH dalteparin used concomitantly with the GP IIb/IIIa inhibitor abciximab, and the National Investigators

Collaborating on Enoxaparin (NICE)-4 and -1 studies tested two different doses of enoxaparin with and without concomitant use of abciximab (11). In the NICE-1 and NICE-4 studies, mean anti-Xa activities peaked abruptly at 2.1 IU/ml with 1 mg/kg enoxaparin and at 1.5 IU/ml with 0.75 mg/kg enoxaparin. Although abciximab was used concomitantly in the NICE-4 study, the rate of major bleeding using 0.75 mg/kg enoxaparin was lower than that using 1 mg/kg enoxaparin in NICE-1. Sheath withdrawals were delayed in both studies.

Studies have shown that target anti-Xa levels >0.5 IU/ml are effective for performing PCI while using enoxaparin, or for treating UA (3,12,13). Data on the co-administration of LMWH and GP IIb/IIIa inhibitors in PCI are rare and are limited to the GP IIb/IIIa inhibitor abciximab (10,11). A new dosing regimen of eptifibatide has recently been shown to be effective in elective PCI (14), but data are needed on eptifibatide's concomitant use with LMWH. Considering the available pharmacokinetic data obtained with IV enoxaparin in healthy volunteers and the anti-Xa levels obtained in previous PCI studies, we aimed at a dose giving a median anti-Xa activity close to 1 IU, expecting then a Gaussian distribution of anti-Xa levels with 95% of patients above 0.5 IU, just as in our previous study (3). On the basis of the available data with enoxaparin (3,11–13), we hypothesized

Abbreviations and Acronyms	
ACT	= activated clotting time
aPTT	= activated partial thromboplastin time
CI	= confidence interval
CK	= creatine kinase
ECG	= electrocardiogram
GP	= glycoprotein
IV	= intravenous
LMWH	= low-molecular-weight heparin
MI	= myocardial infarction
NICE	= National Investigators Collaborating on Enoxaparin
NSTEMI	= non–ST-elevation myocardial infarction
PCI	= percutaneous coronary intervention
PEPCI	= Pharmacokinetic study of Enoxaparin in Patients undergoing Coronary Intervention
TIMI	= Thrombolysis In Myocardial Infarction
UA	= unstable angina
UFH	= unfractionated heparin

that an IV dose of enoxaparin of only 0.5 mg/kg could provide adequate anticoagulation irrespective of patient characteristics such as age, weight, renal function, or the use of the GP IIb/IIIa inhibitor eptifibatide. Indeed, some concerns have been raised about the safety of LMWH in patients with renal failure because of their preferential kidney elimination, and in obese patients because of possible variations in subcutaneous resorption and volume distribution of these drugs. This unique and low dose of enoxaparin would also offer the advantage of preventing excessive anticoagulation following bailout prescription of GP IIb/IIIa inhibitors, which is common in many centers. We also expected that such a low dose of enoxaparin would improve safety in all indications and allow immediate sheath removal.

The aim of our study was to show that a single IV bolus of 0.5 mg/kg enoxaparin in elective PCI would provide adequate anticoagulation, defined as a peak anti-Xa level >0.5 IU/ml in >95% of patients (3), and would not cause over-anticoagulation, defined as a peak anti-Xa level >1.5 IU/ml, in patients at increased risk of overdosage or bleeding. These patients were defined as groups with renal dysfunction, overweight, advanced age, or GP IIb/IIIa inhibition (15–17). Ischemic end points were considered a secondary objective of the study.

METHODS

Patient population. A total of 242 consecutive patients admitted for elective PCI were enrolled in the study. All patients were >18 years old and were referred for elective PCI of a native or vein graft stenosis of >70%. Exclusion criteria were primary PCI for ST-elevation MI, admission to the cardiac care unit for initial medical therapy, LMWH or UFH within the last 48 h before PCI, or a GP IIb/IIIa antagonist within the previous two weeks. Renal dysfunction was defined as a calculated creatinine clearance of <40

ml/min (3), elderly was defined as age >75 years, and overweight was defined as >100 kg. The study was approved by the Pitié-Salpêtrière Ethical Committee for Clinical Studies, and informed oral consent was obtained from all patients.

Procedures for PCI. Percutaneous coronary intervention was performed immediately after a coronary angiogram using standard techniques, the femoral approach, and 6F guiding catheters in all patients. Sheaths were removed with manual or pneumatic compression (FemoStop II plus, Radi Medical Systems, Uppsala, Sweden) immediately after PCI when eptifibatide was not used (n = 178), or 4 h later when PCI was performed with eptifibatide (n = 64). Vascular closure devices were not used. Patients were allowed to walk on the next morning (bed-rest time >12 h) and left the hospital on the same day.

Study medications. Intravenous enoxaparin, 0.5 mg/kg single IV bolus, was used in all patients due to undergo PCI irrespective of the age or renal function of the patient or the use of GP IIb/IIIa inhibitors. There was no weight-related upper limit for the dose of enoxaparin. Percutaneous coronary intervention was performed without the administration of UFH or an additional bolus of enoxaparin, and no antithrombin treatment was administered after the procedure. There was no on-site monitoring of coagulation either during or after the procedure. Sheaths and catheters were flushed with a saline solution containing 23 mg/l of enoxaparin. All patients received a loading dose of aspirin (500 mg IV) before the start of the procedure, followed by a daily dose of 75 to 300 mg. Clopidogrel (300 mg) was administered immediately after stenting, except to patients who had previously received clopidogrel (n = 22), and then 75 mg/day was administered for one month. Eptifibatide was the only GP IIb/IIIa inhibitor used in this study. A first bolus of 180 μg/kg eptifibatide was given simultaneously with the enoxaparin bolus, and a 2.0 μg/kg/min continuous infusion was started immediately and continued for 18 h. A second 180 μg/kg eptifibatide bolus was given 10 min after the first bolus and just before the start of the procedure.

Biologic measurements. Serial blood samples were taken to measure anti-Xa activity: before the IV bolus of enoxaparin, 10 min after the bolus (start of PCI), at the end of the PCI, 3 h after the PCI, and on the morning after PCI. Blood was collected into vacutainer tubes (Vacutainer, Becton Dickinson, Plymouth, United Kingdom) containing 0.129 M trisodium citrate. Platelet-poor plasma was obtained by centrifugation at 3,500 g at 10°C for 20 min.

Plasma anti-Xa activity was determined by an amidolytic assay using the specific chromogenic substrate CBS 52.44 and bovine factor Xa as reagents and STA analyzers (Diagnostica Stago, Asnières, France). Activated partial thromboplastin time (aPTT) was measured using Automated aPTT (Organon Teknika Corporation, Durham, North Carolina), and anti-IIa activity was measured using an indirect method based on the plasma thrombin clotting

time. The coefficients of variation for aPTT, anti-Xa, and anti-IIa assays were all <5%.

Troponin-I levels were determined by a fluorogenic enzyme-linked immunoassay using a monoclonal antibody and OPUS-PLUS analyzers (Dade-Behring SA, Paris La Défense, France). Levels of troponin-I and creatine kinase (CK) were measured before PCI, 3 h after PCI, and on the morning (approximately 18 h) after PCI. In case of recurrent ischemia, troponin-I and CK levels were measured again every 6 h and throughout the following 24 h. A troponin-I level >2 μg/ml within 24 h of PCI was considered as a periprocedural MI, even if the level of CK was normal.

In all patients, platelet counts were measured before and after PCI, and in patients receiving eptifibatide, platelet counts were repeated 1, 4, and 24 h after the bolus administration. Thrombocytopenia was defined as a platelet count of <50,000 or as a decrease of 50% from the previous platelet count.

Clinical follow-up. In-hospital follow-up was based on physical examination, electrocardiogram (ECG), and CK and troponin-I levels. All patients in this study were followed up at one month by written questionnaires or telephone interviews. Information obtained was relative to living status, rehospitalization, reinfarction, subsequent cardiac catheterization or revascularization, and any form of bleeding. In case of an event during follow-up, more information was sought from hospital records and interviews with physicians. The outcome end point was defined as a composite of death, myocardial infarction (MI), and urgent target vessel revascularization. Myocardial infarction was defined as recurrent chest pain and/or ECG changes with at least one of the following: troponin-I positive, with levels of CK >2 times the upper limit of normal and an increase of >50% of the previous value, or the appearance of a new left bundle branch block or new Q waves. Urgent revascularization was defined as urgent PCI or coronary artery bypass grafting necessitated by recurrent ischemia of the target vessel. Bleeding definitions were adapted from the Thrombolysis In Myocardial Infarction (TIMI) criteria. Major hemorrhage corresponded to: 1) bleeding resulting in death or requiring surgery; 2) a bleed in an intracranial or intraocular location; or 3) a drop in the serum concentration of hemoglobin ≥5 g/dl (or >15% of the hematocrit value). Minor bleeding was any clinically important bleeding that did not qualify as major or that was not clinically identified but associated with a drop in the serum hemoglobin concentration >4 g/dl (or >12% of the hematocrit level).

Statistics. The percentage of patients with a peak anti-Xa activity >0.5 IU/ml and <1.5 IU/ml was calculated for the overall patient population and for the predefined subgroups. Simple linear regression was used to test the association between continuous variables. Potential associations between clinical and biologic parameters were tested by univariate procedures using the Student *t* or chi-square test.

Table 1. Baseline Clinical Characteristics of Enrolled Patients

Age, yrs	64 ± 11*
Age >75 yrs, n (%)	33 (14)
Men, n (%)	190 (78)
Body mass index, kg/m^2	27 ± 5*
Overweight (>100 kg), n (%)	21 (9)
Creatinine clearance, ml/min	70 ± 28*
Creatinine clearance <40 ml/min, n (%)	30 (12)
Left ventricular ejection fraction, %	62 ± 13*
Risk factors, n (%)	
Smoking	50 (21)
History of hypercholesterolemia	159 (66)
Hypertension	146 (60)
Diabetes mellitus	84 (35)
Previous MI (>1 month)	76 (31)
Recent MI (<1 month)	4 (2)
Previous coronary angioplasty	95 (39)
Previous coronary bypass	29 (12)
Peripheral vascular disease	36 (15)
Previous stroke	19 (8)
Target vessel of PCI, n (%)	
Left anterior descending coronary artery	116 (39)
Left circumflex coronary artery	75 (25)
Right coronary artery	94 (32)
Saphenous vein graft	11 (4)
Left main	1 (0.4)

*Mean value ± SD.
MI = myocardial infarction; PCI = percutaneous coronary intervention.

Results are expressed as mean ± SD. The alpha level was set at 0.05.

RESULTS

Patient characteristics. A total of 242 consecutive patients, who underwent elective PCI to treat 303 coronary lesions, were enrolled in the study. Table 1 shows the patients' baseline and angiographic characteristics. Multiple-vessel angioplasty was performed in 56 patients (23%). Most of the coronary lesions that were treated were in class B (54%) or C (23%) of the American College of Cardiology/American Heart Association classification. A stent was implanted in 169 of the 233 de novo lesions (72%). The decision to implant a stent or prescribe eptifibatide was made at the discretion of the physician. Administration of eptifibatide was always begun before PCI (n = 64, 26%); no bailout prescription of GP IIb/IIIa inhibitors occurred in the patients not originally administered eptifibatide (n = 178).

Anticoagulation during and after PCI. A peak anti-Xa >0.5 IU/ml was obtained in 97.5% of patients, and 94.6% of patients had a peak anti-Xa level in the target range of 0.5 to 1.5 IU/ml. Effective levels of anticoagulation were obtained 10 min after the administration of the enoxaparin bolus corresponding to the start of procedure: the mean anti-Xa activity was 0.88 ± 0.31 IU/ml (Table 2, Fig. 1A). Anti-Xa activity was stable throughout the procedure, confirming a high and constant degree of anticoagulation (Table 2, Fig. 1B). Throughout the procedure (as detected by two coagulation measurements, at the start and the end of the procedure), the anti-Xa activity remained <0.5

Table 2. Measurements of Anticoagulation Before, During, and After PCI*

	Anti-Xa Activity, IU/ml	aPTT, s	Anti-IIa Activity, IU/ml
Before enoxaparin bolus	0.07 ± 0.08	35 ± 4	0.05 ± 0.09
Start of PCI	0.88 ± 0.31	86 ± 23	0.37 ± 0.12
End of PCI	0.83 ± 0.26	64 ± 17	0.26 ± 0.1
3 h after PCI	0.47 ± 0.19	42 ± 11	0.11 ± 0.09
18 to 24 h after PCI	0.07 ± 0.08	35 ± 9	0.02 ± 0.05

*Mean values ± SD.
aPTT = activated partial thromboplastin time; PCI = percutaneous coronary intervention.

IU/ml in only 6 patients (2.5%), was >1 IU/ml in 27 patients (11.1%), and did not exceed 1.5 IU/ml in any patient. This unique dose of enoxaparin provided similar, safe levels of anti-Xa activity in the patient subgroups considered to have an increased risk of bleeding (Table 3). The percentage of patients who were not over-anticoagulated (peak anti-Xa activity <1.5 IU/ml) was similar in the elderly versus the non-elderly subgroups (97% in both, $\Delta p = 0\%$, confidence interval [CI] −5 to +5%), in patients with versus without renal dysfunction (100% vs. 97%, $\Delta p = 3.5\%$, CI 1 to +5.5%), and in overweight versus nonoverweight patients (95% vs. 97%, $\Delta p = -2\%$, CI −10 to +6%). No significant relationships were found between anti-Xa activity and creatinine clearance or weight. No interaction was found between smoking status and anti-Xa activity at any of the five time points.

No difference in anti-Xa activity was observed between patients treated with enoxaparin alone and those who received enoxaparin and eptifibatide (Fig. 2). The proportion of patients with a peak anti-Xa activity <1.5 IU/ml was very similar whether eptifibatide was used or not used (98% vs. 96%, $\Delta p = 2\%$, CI −1.5 to +5%).

The aPTT and anti-IIa activity increased significantly after the administration of the enoxaparin bolus, as shown in Table 2. The prolongation of aPTT measured here is in concordance with previous studies using IV injections of enoxaparin (9,10). Finally, no patient developed thrombocytopenia.

Clinical outcomes at day 30. Follow-up was obtained in all patients. Table 4 shows the incidence of the composite end point of death, MI, or urgent target vessel revascularization and of each of its components, as well as the incidence of major and minor bleeding. None of the ischemic or bleeding events correlated with the levels of anti-Xa activity measured at any of the time points. Four days after the PCI, one patient developed an out-of-laboratory abrupt closure with ST-segment elevation because of a coronary dissection. After receiving abciximab, the patient underwent unsuccessful urgent revascularization and died suddenly eight days later. Two patients had nonfatal non–Q-wave MI: one case was related to a coronary dissection treated by stent implantation on day 4, and the other case was a result of a side-branch occlusion with

no angiographic complication of the target vessel. The five patients who underwent urgent revascularization had a coronary dissection on the angiogram. Importantly, all six patients with an ischemic complication had anti-Xa levels >0.5 IU/ml from the beginning to the end of the procedure.

We also examined the patients who had no clinical ischemic complications or significant increase in CK but had increased troponin-I levels, detected by serial measurements during the first 24 h after PCI (>2 µg/ml, n = 21). In these patients, the mean anti-Xa activity was 0.84 ± 0.09 IU/ml at the start of PCI and 0.81 ± 0.04 IU/ml at the end, and was similar to mean anti-Xa activity in patients with negative troponin-I levels. The global rate of both MI and periprocedural MI was 10% in this study.

The only case of major bleeding was a groin hematoma with a false aneurysm in an 82-year-old woman who was treated with eptifibatide, which necessitated a transfusion of two units of blood and urgent vascular surgery. This patient's anti-Xa activity was 0.90 IU/ml at the beginning of, 0.92 IU/ml at the end of, and 0.54 IU/ml 3 h after the procedure. Three other patients had minor bleeding complications (groin hematomas).

DISCUSSION

Our data strongly suggest that a single IV bolus of 0.5 mg/kg enoxaparin is feasible in elective PCI. This reduced dose allows reaching the prespecified level of anticoagulation without dose adjustment or coagulation monitoring, which simplifies anticoagulation management during the procedure; allows immediate sheath removal when PCI is performed with enoxaparin alone; and provides similar anticoagulation and safety in patients irrespective of advanced age, renal dysfunction, being overweight, or the use of a double bolus of eptifibatide. No thrombocytopenia was observed in this group of patients. The few periprocedural ischemic events observed were not related to low anti-Xa levels but mainly to coronary dissections.

Unfractionated heparin has been the primary anticoagulant therapy for PCI for more than 20 years, but the optimal dose and the ideal target activated clotting time (ACT) remain uncertain and controversial (6,18). The low bioavailability, unpredictable anticoagulant response, activation of platelets, unsatisfactory correlations between measurements of ACT and aPTT, device-to-device variations in ACT measurements, and the lack of net prospective evaluations to correlate ACT measurements to clinical outcomes associated with UFH have led to empirical recommendations for both UFH doses and ACT target values. However, the most recent recommendations recognize the possible need for lower doses of UFH than before, even in the absence of GP IIb/IIIa inhibitors (6).

Although LMWH does not have the same disadvantages as UFH, the ideal regimen for its use in PCI is yet to be determined. However, the predictable anticoagulant response following a single IV dose of LMWH suggests that
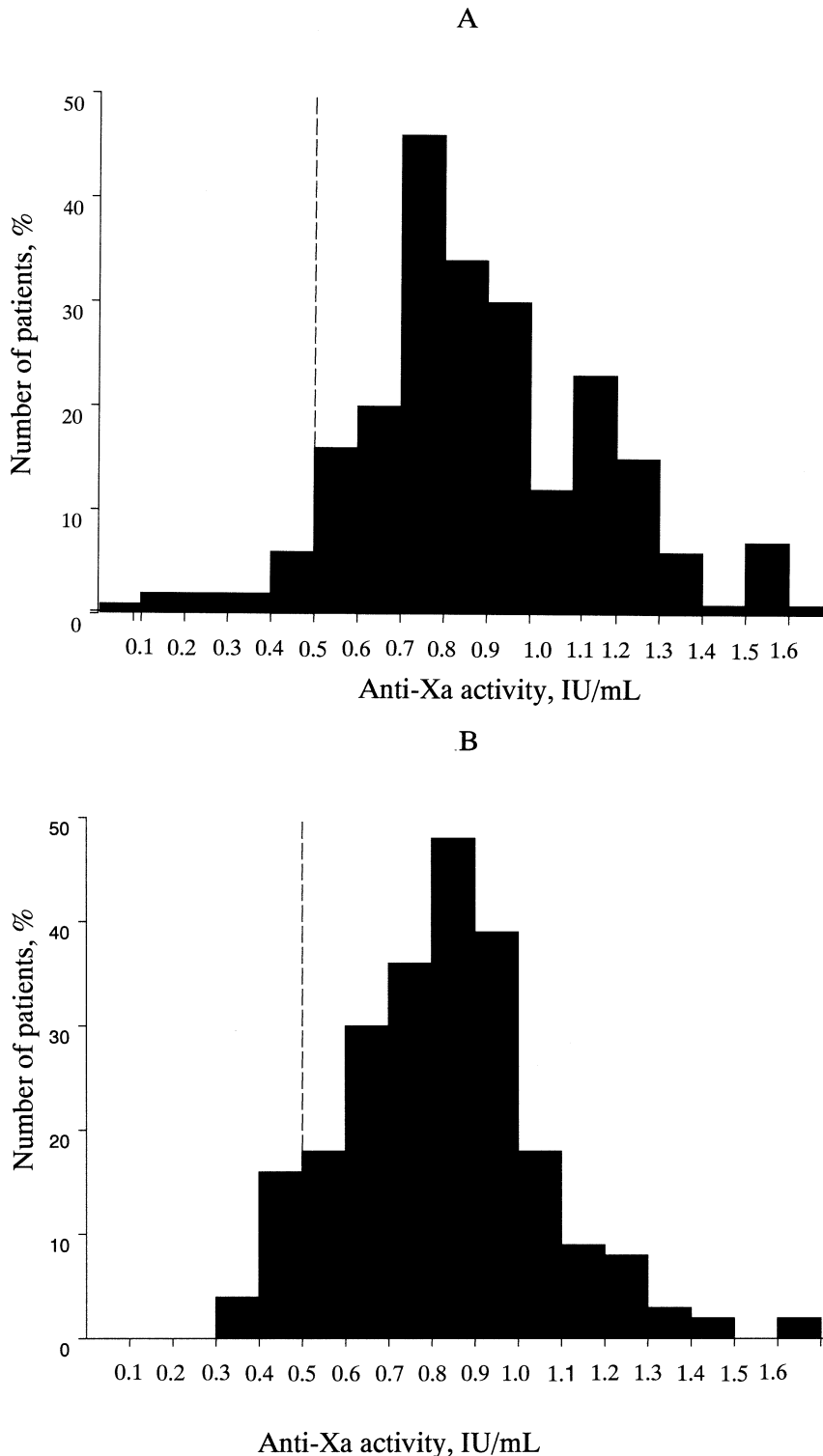
A

B

Figure 1. Distribution of anti-Xa activity levels at the beginning **(A)** and end **(B)** of percutaneous coronary intervention.

neither dose adjustments nor on-site coagulation monitoring are necessary (19). The safety profile of a single IV bolus of LMWH should be even better than that of the repeated subcutaneous injections evaluated in UA trials (1,2,20). The risk of overdose with a single IV dose is not related to the degree of subcutaneous resorption, and should be much less

dependent on renal function (15,21). In addition to the pharmacologic benefits and enhanced ratio of anti-Xa:anti-IIa activity of LMWH over UFH, other positive effects include more effective release of tissue factor pathway inhibitor and blunting of von Willebrand factor release, a rise of which is associated with poor outcomes in UA

Table 3. Levels of Anti-Xa Activity in Patients Undergoing PCI, According to Age, Renal Failure, and Weight

	Age, yrs		Creatinine Clearance, ml/min		Weight, kg	
	<75	>75	>40	<40	<100	>100
	(n = 209)	(n = 33)	(n = 212)	(n = 30)	(n = 221)	(n = 21)
Before enoxaparin bolus	0.07 ± 0.08	0.08 ± 0.08	0.06 ± 0.07	0.07 ± 0.07	0.07 ± 0.08	0.05 ± 0.04
Start of PCI	0.90 ± 0.32	0.75 ± 0.19	0.88 ± 0.32	0.88 ± 0.23	0.88 ± 0.31	0.88 ± 0.26
End of PCI	0.87 ± 0.26	0.71 ± 0.21	0.83 ± 0.27	0.79 ± 0.18	0.82 ± 0.26	0.91 ± 0.24
3 h after PCI	0.48 ± 0.19	0.43 ± 0.12	0.46 ± 0.19	0.51 ± 0.12	0.46 ± 0.15	0.57 ± 0.41
18 to 24 h after PCI	0.07 ± 0.08	0.06 ± 0.06	0.06 ± 0.07	0.13 ± 0.12	0.07 ± 0.07	0.11 ± 0.13

*Mean value ± SD.
PCI = percutaneous coronary intervention.

(22,23). More recently, both the release of von Willebrand factor and changes in platelet GP Ib/IX complexes (receptors for von Willebrand factor) have been shown to predict adverse outcomes in UA, and both were affected favorably by enoxaparin (24).

Our initial hypothesis that there would be no differences in the anti-Xa levels during elective PCI in patients at increased risk of overdosage or bleeding has been verified in all the high-risk subgroups. Although reassuring, the data obtained in obese and renal failure patients would deserve further confirmation; however, the similar degrees of anticoagulation that we have shown among these subgroups strongly suggest that this dose has a good safety and efficacy profile across all clinical indications. One unique dose that can be used in all patients whatever their age, weight, renal function, and use or not of GP IIb/IIIa inhibitors offers obvious practical advantages to medical staff. The concept of a unique dose may also yield safety advantages, owing to the simplification of the dosing regimen and subsequent reduction in the risk of dosing errors.

The optimal anti-Xa target has not yet been precisely evaluated and may differ with various LMWHs. Most experience (although limited) has been obtained with enoxaparin (9,11,12). In UA, 1 mg/kg subcutaneous enoxaparin every 12 h (tested in TIMI 11A (13), then used in TIMI 11B (2) was associated with mean anti-Xa levels of 1.0 IU/ml (peak) and 0.5 IU/ml (trough). In patients with UA receiving 1 mg/kg subcutaneous enoxaparin, peak anti-Xa activities were close to 1.2 IU/ml in the Pharmacokinetic study of Enoxaparin in Patients undergoing Coronary Intervention (PEPCI) (12) and close to 1 IU/ml in our previous study (3).

In the present study, we selected an IV dose that would reproduce levels of anticoagulation similar to those obtained using subcutaneous injection: a peak anti-Xa level >0.5 IU/ml in >95% of patients, a median close to 1 IU/ml, and an upper limit of 1.5 IU/ml for safety considerations. A peak anti-Xa >0.5 IU/ml was obtained in 97.5% of patients (97.6% in the previous study) (3). The majority of patients were close to 1 IU/ml, as shown in Figures 1 and 2.
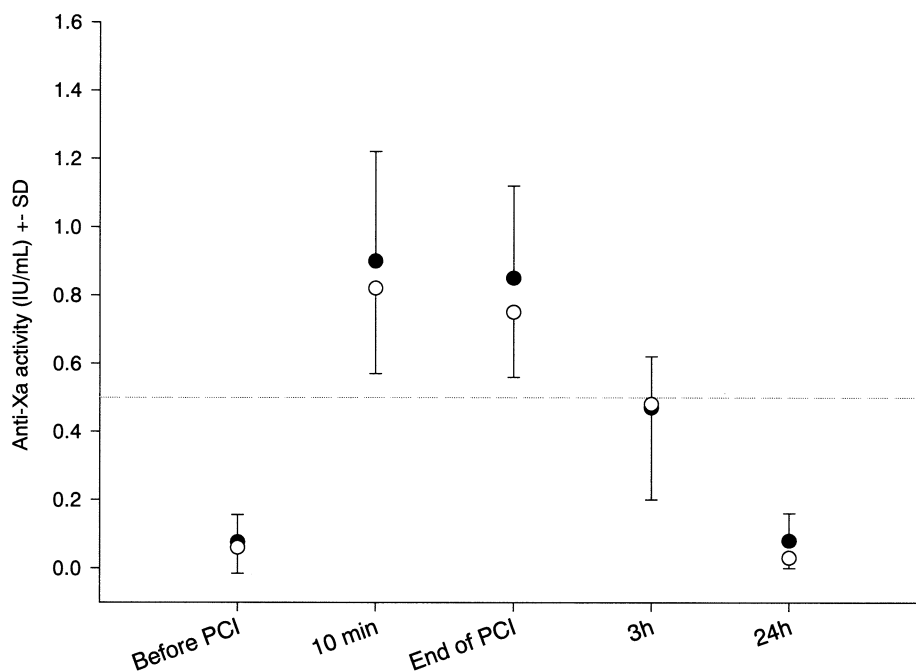

Figure 2. Anti-Xa activity levels before, during, and after percutaneous coronary intervention (PCI), with the use **(open circles)** and nonuse **(closed circles)** of eptifibatide.

Table 4. Clinical Events and Bleeding Complications at
30 Days Follow-Up

	Patients, n (%)
Death	1 (0.4)
MI	3 (1.2)
Death or MI	3 (1.2)
Urgent target vessel revascularization	5 (2.1)
Death, MI, or urgent target vessel revascularization	6 (2.5)
Bleeding complications	
Major bleeding	1 (0.4)
Minor bleeding	3 (1.2)

MI = myocardial infarction.

Interestingly, the peak anti-Xa levels were 2.1 ± 0.7 IU/ml, 1.5 ± 0.6 IU/ml, and 0.9 ± 0.3 IU/ml in the NICE-1, NICE-4, and present study, respectively, and the incidences of major and minor bleeds were 6.1%, 7.0%, and 1.6%, respectively. These data suggest that bleeding may well increase with anti-Xa levels above 1.5 IU/ml. The study of Kereiakes et al. (10) using a low dose of dalteparin (60 IU/kg, n = 76) produced a similar anti-Xa profile (peak at 0.8 IU/ml) and similarly few bleedings as the present study. The lack of a relationship between the occurrence of ischemic events or periprocedural MI and periprocedural anti-Xa levels, as well as the low incidence of ischemic events in the present study when compared with other PCI trials, indicate the need for further evaluation of this low dose of enoxaparin (11,14,17,25–27).

In contrast with the NICE-1 study, the reduced dose of enoxaparin used here allowed safe immediate sheath withdrawal with manual compression, favoring expeditive care for these elective cases. In the present study, the average anti-Xa level was 0.83 ± 0.26 IU/ml when we removed the sheath immediately after the procedure, a level similar to that measured 4 h after PCI in NICE-1 at the time of sheath removal (0.8 ± 0.3 IU/ml). The combination of this low dose of enoxaparin with the successfully tested high dose of eptifibatide proved to be safe on the basis of anticoagulation levels and clinical outcomes (14). Following usual recommendations (14,17) for the use of GP IIb/IIIa inhibitors, sheath withdrawal was delayed for 4 h in patients receiving eptifibatide, allowing a new check of platelet count. It remains to be shown whether immediate sheath withdrawal is also possible in these patients. Finally, the use of both enoxaparin and eptifibatide should considerably decrease the risk of thrombocytopenia compared to UFH and abciximab, and indeed, no case of thrombocytopenia was observed in this study (28,29).

Clearly, our study is not sized or designed to draw any definite conclusion on the use of this low dose of enoxaparin. However, in the actual preliminary phase that evaluates the optimal anticoagulation target with enoxaparin in PCI, our study provides the first evaluation of a low dose of IV enoxaparin in nonselected patients. These data may aid the design of future randomized trials comparing LMWH with UFH in PCI. All the criteria for safety measured (target levels of anticoagulation, use in high-risk patient subgroups, administration of GP IIb/IIIa inhibitors, early sheath withdrawal, occurrence of thrombocytopenia) were favorable for this low, unique dose of enoxaparin.

Acknowledgment

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