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Enoxaparin in Unstable Angina Patients Who Would Have Been Excluded From Randomized Pivotal Trials

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OBJECTIVES In the present study, we describe the characteristics and examine the anticoagulation levels and safety of subcutaneous enoxaparin in unstable angina (UA)/non–ST-segment elevation myocardial infarction (NSTEMI) patients who would not have been eligible in the Efficacy Safety Subcutaneous Enoxaparin in Non–Q-wave Coronary Events (ESSENCE) and Thrombolysis In Myocardial Infarction (TIMI)-11B trials.

BACKGROUND It is not known whether the benefit shown with enoxaparin in the selected population of pivotal trials can be extended to the real world.

METHODS In our center, all patients with UA/NSTEMI are anticoagulated with subcutaneous enoxaparin adjusted to creatinine clearance. Among 515 consecutive patients, we identified 174 who would not have been eligible for ESSENCE or TIMI-11B ("EP" group for excluded patients). We evaluated cardiovascular death or non-fatal myocardial infarction (MI), as well as major and minor bleeding events, at 30 days in the EP group and in patients without any of the exclusion criteria ("NEP" group for non-excluded patients).

RESULTS This EP group was older, had a higher female/male ratio, and more frequently had a history of MI or a diagnosis of non-Q_MI on admission than the NEP group. The distribution of the anti-Xa activity was similar in both groups. The bleeding rates (major and minor) at 30 days were similar in the EP and NEP groups (2.3% vs. 2.9%, respectively, p = NS). On multivariate analysis, the use of glycoprotein IIb/IIIa inhibitors and the presence of hypertension were the only independent predictors of bleeding found in the whole population. Compared with the NEP group, the EP group had a fourfold increased rate of death or MI at 30 days (15.5% vs. 4.1%, $p < 0.01$). On multivariate analysis, the independent predictors of death or MI at 30 days were NSTEMI on admission, creatinine clearance, and heart failure.

CONCLUSIONS Patients who do not fit the enrollment criteria of ESSENCE/TIMI-11B have higher risk baseline characteristics for both bleeding and ischemic events. In these patients, enoxaparin with dose adjustment to creatinine clearance provides adequate anti-Xa levels and no excess of bleeding. (J Am Coll Cardiol 2003;41:8–14) © 2003 by the American College of Cardiology Foundation

There is now strong evidence for the superiority of the low-molecular-weight heparin (LMWH) enoxaparin over unfractionated heparin (UH) in the medical management of patients with unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI) (1–3). However, the populations of these randomized studies are highly selected, and it is not known how the conclusions of these studies can be applied to all patients in routine practice.

A considerable proportion of the "real world" population with UA/NSTEMI does not meet the inclusion criteria of the randomized pivotal trials performed with enoxaparin (1–3), and little information is available on the incidence and risk profile of these patients. Moreover, the safety of enoxaparin use in this population is unknown. In our center, all patients with UA/NSTEMI are treated with enoxaparin, regardless of the baseline characteristics. However, particular attention is paid to the dosing regimen and monitoring of the elderly and those with renal failure (4). We therefore evaluated the baseline characteristics and risk profile of these patients who would have been excluded from the Thrombolysis In Myocardial Infarction (TIMI)-11B and Efficacy Safety Subcutaneous Enoxaparin in Non–Q-wave Coronary Events (ESSENCE) trials (excluded patients, or "EP" group) and compared them with the rest of the population, resembling more of the patients enrolled in the two enoxaparin pivotal trials (non-excluded patients, or "NEP" group). The main objective was to examine, in both groups, anticoagulation levels and the safety of enoxaparin treatment used in addition to aspirin.

METHODS

Patient population. A total of 515 consecutive patients with UA/NSTEMI were treated with subcutaneous enoxaparin in the Pitié-SAlpétrière Registry on Ischemic coronary Syndromes (PARIS) registry. Admission NSTEMI was defined by an initial troponin I level ≥ 0.2 μg/ml. The only patients excluded from the study were those with

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Abbreviations and Acronyms

EP	= excluded patients
ESSENCE	= Efficacy Safety Subcutaneous Enoxaparin in Non–Q-wave Coronary Events study
GP	= glycoprotein
HF	= heart failure
LMWH	= low-molecular-weight heparin
MI	= myocardial infarction
NEP	= non-excluded patients
NSTEMI	= non–ST-segment elevation myocardial infarction
PCI	= percutaneous coronary intervention
UA	= unstable angina
UH	= unfractionated heparin

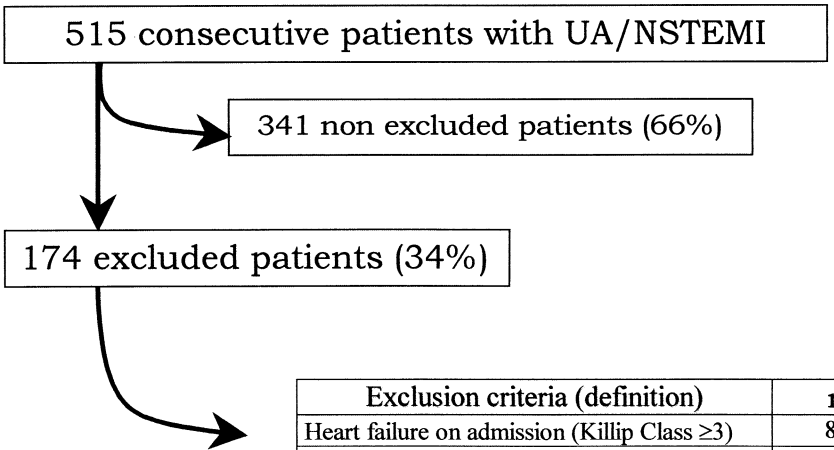
contraindications to anticoagulant treatment. All the patients were recruited before the publication of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, and none of them was treated with combined aspirin and clopidogrel before catheterization (5). The global risk profile of the patients was assessed with the TIMI risk score (6).

All patients received a loading dose of aspirin (500 mg intravenously) followed by 75 to 250 mg/day of oral aspirin, beta-blockers, and intravenous nitrates, unless these treatments were contraindicated. Patients with a recurrent ischemic episode and an elevated troponin I level received intravenous glycoprotein (GP) IIb/IIIa inhibitors (n = 45). Enoxaparin was used in all patients. Subcutaneous injections of 1 mg (100 IU)/kg at 12-h intervals were prescribed, but elderly patients and patients with renal failure received reduced doses of enoxaparin, as previously described (4,7). Briefly, when the creatinine clearance was ≤30 ml/min, 65% of the recommended dose was given (4). In these patients, the anti-Xa activity was measured 4 h after the third subcutaneous injection, and, when needed, the enoxaparin dosage was adjusted, aiming for an anti-Xa activity between 0.5 and 1.0 IU/ml.

Catheterization was performed at the treating physician's discretion, with immediate percutaneous coronary intervention (PCI), if needed. Enoxaparin was never interrupted before going to the catheterization laboratory, and patients were scheduled for catheterization within 8 h of the morning injection (7). The PCI was performed without UH or additional enoxaparin. Enoxaparin was not restarted after PCI. In stent-implanted patients, ticlopidine (250 mg twice a day) or clopidogrel (loading dose of 300 mg, then 75 mg/day) was given for one month to prevent stent thrombosis.

Definition of EP. Seven exclusion criteria from the randomized ESSENCE or TIMI-11B trials were applied to the PARIS registry and were used to define the EP group. The study design including the flow of patients, and the definitions of the exclusion criteria are given in Figure 1.

Clinical follow-up. In-hospital follow-up was based on a physical examination, electrocardiogram (ECG), creatine kinase (CK) levels, and troponin I levels. Troponin I levels were determined on admission and every 6 h during the first 24 h, then once daily until hospital discharge (6). In case of recurrent ischemia, troponin I was measured again every 6 h during the following 24 h. After PCI, CK and troponin I were measured at the time of sheath removal (>10 h after the morning injection of enoxaparin) and the next morning



Exclusion criteria (definition)	n	%
Heart failure on admission (Killip Class ≥3)	82	47.1
Creat. Clear. ≤30 mL/min	62	36.8
LBB or Pacemaker	35	20.1
Stroke (<2 months)	21	12.0
Recent surgery (with general anaesthesia)	19	10.9
Evolving Cancer, n=19	19	10.9
Acute anemia (drop in serum Hb>4g/dl)	5	2.8

Figure 1. Flow chart of patients in the PARIS registry, including definitions of exclusion criteria and the number of patients in each category. Creat. Clear. = creatinine clearance; Hb = hemoglobin; LBB = left bundle branch block; NSTEMI = non–ST-segment elevation myocardial infarction; UA = unstable angina.

(i.e., roughly 18 h after PCI). All patients in this study were followed up at one month by means of written questionnaires and telephone interviews. Deaths were classified as cardiovascular or non-cardiovascular. Recurrent myocardial infarction (MI) was defined as recurrent chest pain and/or ECG changes, with at least one of the following criteria: 1) CK greater than two times the upper limit of normal, with a >50% rise over the previous value, associated with a positive troponin I test; and 2) the appearance of a new left bundle branch block or new Q-waves.

Bleeding definitions were adapted from the TIMI criteria. Major hemorrhage corresponded to: 1) bleeding resulting in death; 2) bleeding in an intracranial or intraocular location; 3) a drop in the serum concentration of hemoglobin ≥5 g/dl (or >15% of the hematocrit value); and 4) bleeding requiring urgent surgery. Minor bleeding corresponded to: 1) any clinically important bleeding that did not qualify as major (e.g., epistaxis, ecchymosis, hematoma, or macroscopic hematuria) but with a drop in the serum concentration of hemoglobin ≥3 g/dl (or >10% of the hematocrit value); 2) bleeding not clinically identified but associated with a drop in the serum hemoglobin concentration >4 g/dl (or >12% of the hematocrit level); and 3) bleeding that required a blood transfusion of at least 2 U.

The main safety end point was major and minor bleeding events at 30 days. Cardiovascular death and non-fatal MI were also evaluated at 30 days.

Statistical analysis. Categorical variables were expressed as frequencies and percentages, and continuous variables as the mean value ± SEM (except for age, body mass index, and creatinine clearance, which were given as the mean ± SD. 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* test and chi-square test for continuous and categorical variables, respectively. The alpha level was set at 0.05. Independent predictors of either bleeding (bleeding at 30 days) or ischemic events (death or non-fatal MI at 30 days) were identified using stepwise multivariate logistic analysis with the SAS software version 6.12 (SAS Institute, Cary, North Carolina). Variables included in the model were univariate predictors with $p < 0.05$.

RESULTS

Baseline characteristics. The characteristics of our study population were those of all comers presenting with UA/NSTEMI and who therefore had a higher risk profile than the populations enrolled in ESSENCE and TIMI-11B. Heart failure (HF) and chronic renal failure were the most frequent exclusion criteria, the former being present in 16% of the whole population (47% of the EP population) (Fig. 1). In addition, 19% of all patients were above 80 years of age; 23% were diabetics; 24% had a prior history of MI; 12% had severe renal failure; and 42% had NSTEMI on admission (Table 1). One-third (n = 174) of all patients met at least one of the seven exclusion criteria from the ESSENCE/TIMI-11B trials (Fig. 1), and 12.6% had two or more criteria. Compared with the NEP population, the EP population had a higher risk profile and a significantly higher TIMI risk score (2.38 ± 0.06 vs. 2.79 ± 0.08, $p < 0.01$).

Table 1. Baseline Characteristics and Risk Factors in Excluded and Non-Excluded Patients

	Non-Excluded (n = 341)	Excluded (n = 174)
Demographic data		
Age (yrs)	62.5 ± 12.7	74.8 ± 12.2*
>80 yrs (%)	8.5	39.1*
Female (%)	25.8	38.5*
Risk factors		
Smoker (%)	42.8	29.3*
Hypercholesterolemia (%)	42.6	27.6*
Hypertension (%)	43.3	48.8
Diabetes (%)	22.8	24.7
BMI (kg/m^2)	26.0 ± 4.6	25.0 ± 5.3
Cardiac history of		
MI (%)	19.9	32.2*
CABG (%)	12.3	6.8
PCI (%)	18.4	16.1
Aspirin medication (%)	31.3	36.7
NSTEMI (%)	33.1	59.2*
ST-segment depression (%)	29.5	32.3
Creatinine clearance (ml/min)	82.2 ± 33.6	46.0 ± 27.6*

*Significant difference between non-excluded patients and excluded patients ($p < 0.01$). Data are presented as the mean value ± SD for age, body mass index (BMI), and creatinine clearance.

CABG = coronary artery bypass graft surgery; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

The NEP population was more likely to undergo invasive diagnostic procedures or revascularizations (Table 2). Glycoprotein IIb/IIIa inhibitors were more frequently used in the NEP population than in the EP population.

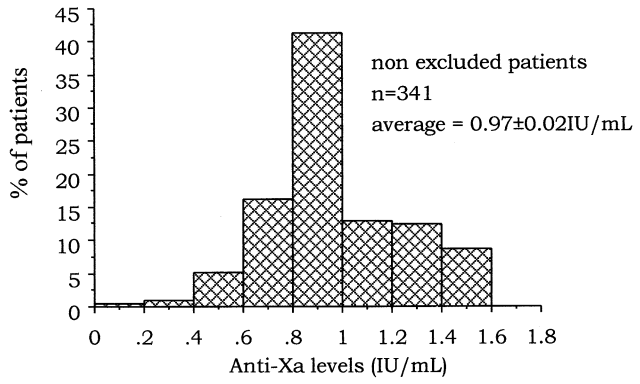
Anticoagulation profile. All patients were treated with combined enoxaparin and aspirin. The EP group was treated for a longer period than the NEP group (5.6 ± 0.5 vs. 4.4 ± 0.2 days, $p = 0.01$). Patients with severe renal failure (creatine clearance ≤30 ml/min) were treated with a

Table 2. Pharmacologic Interventions and Invasive Diagnostic or Therapeutic Procedures in Excluded and Non-Excluded Patients

	Non-Excluded (n = 341)	Excluded (n = 174)
ADP RA (%)	19.3	14.3
GP IIb/IIIa RA (%)	11.1	4.6*
Coronary angiography (%)	68.6	50.0*
Revascularization (%)	35.4	25.3*
PCI (%)	26.1	20.7
CABG (%)	9.3	4.6
Urgent revascularization (%)	2.0	2.3

*Significant difference between excluded patients and non-excluded patients ($p < 0.01$).

ADP = adenosine diphosphate (include ticlopidin and clopidogrel); GP = glycoprotein; RA = receptor antagonists; other abbreviations as in Table 1.



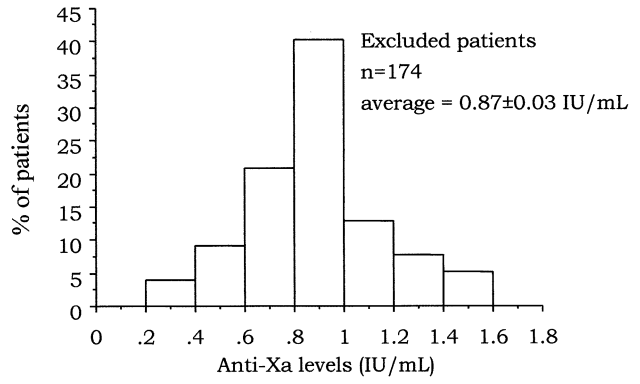


Figure 2. Anti-Xa activity in excluded and non-excluded patients measured after the third injection or just before the coronary angiogram. The distribution of anti-Xa activity matches perfectly in both groups. Nearly all patients (94.4%) had an anti-Xa level above the lower limit of the therapeutic range (0.5 IU/ml), most of them being close to the upper limit (1 IU/ml).

lower dosage of enoxaparin than those without severe renal dysfunction (creatine clearance >30 ml/min) (0.70 ± 0.07 vs. 0.90 ± 0.08 mg/kg, $p < 0.001$). A dose adjustment was performed in 47% of the EP group that corresponded to patients with severe renal failure. Among the whole population, 94.4% of the patients had an anti-Xa level above 0.5 IU/ml when measured after the third injection or at the time of catheterization. Most of them were close to the upper limit (1 IU/ml). Although the EP population was at a higher risk of accumulation of enoxaparin (i.e., advanced age, renal dysfunction, longer treatment duration, the distribution of the anti-Xa activity did not differ from that of the NEP group (Fig. 2). The average anti-Xa activity was slightly lower in EP group than in the NEP group (0.87 ± 0.03 vs. 0.97 ± 0.02 IU/ml, respectively, $p = 0.01$), reflecting the adequate adjustment of enoxaparin doses in elderly patients and in patients with renal failure, conditions that are associated with a risk of overdosage. Indeed, patients with chronic renal failure (creatine clearance ≤30 ml/min) had anti-Xa levels similar to those of patients without severe renal dysfunction (0.85 ± 0.05 vs. 0.95 ± 0.02, p = NS). Finally, the anti-Xa activity of patients ≥80 years of age did not differ from that of patients <80 years of age (0.94 ± 0.02 vs. 0.92 ± 0.05, respectively, p = NS).

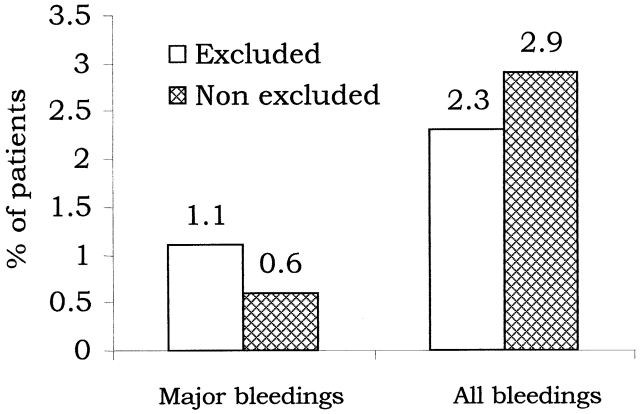


Figure 3. Rates of bleeding events at 30 days in excluded and non-excluded patients. There were no significant differences between the two groups.

Bleeding at 30 days. The use of enoxaparin was well tolerated in both groups of patients, with <2% rates of major bleeding at 30 days. No significant difference was observed between the EP and NEP populations regarding the incidence either of major bleeding events or of all bleeding events (Fig. 3). On univariate and multivariate analyses, hypertension and the use of GP IIb/IIIa inhibitors were the only predictors of bleeding (both major and minor) (Table 3). Although differences existed, age, female gender, severe chronic renal failure, invasive strategies, and the use of adenosine diphosphate receptor antagonists were not independent predictors of bleeding. Regarding the group with severe renal failure (creatine clearance ≤30 ml/min), the bleeding rate (both major and minor) did not differ significantly from that of patients with a creatine clearance >30 ml/min (4.7% vs. 2.5%, $p = 0.53$).

Ischemic events at 30 days. One-month follow-up was available in 88.5% of the patients. There was a fourfold increase in the end points of both death and death or MI in the EP group compared with the NEP group (Fig. 4). Among the pre-specified exclusion criteria used in the PARIS registry, HF and severe renal dysfunction were factors strongly associated with adverse clinical outcomes on univariate analysis (Table 4). In the multivariate model, HF, creatinine clearance, and NSTEMI on admission were the only independent predictors of death or MI at 30 days (Table 4).

On univariate analysis, the TIMI risk score was significantly increased in patients with an adverse outcome, in the whole population (Table 4) and in the NEP group (3.3 ± 0.3 vs. 2.3 ± 0.1 in patients with and without death or MI at 30 days, respectively; $p < 0.001$), but not in the EP group (3.0 ± 0.2 vs. 2.7 ± 0.1 in patients with and without death or MI at 30 days, respectively; $p = 0.14$). On multivariate analysis, the TIMI risk score did not predict outcome.

Table 3. Predictors of Major or Minor Bleeding in the Whole Population

	Incidence of Bleeding With/Without Criterion (%)	p Value (Univariate Analysis)	p Value (Multivariate Analysis)	Odds Ratio (95% CI)
Age >80 years	4.1/2.4	0.15	—	
Female gender	4.5/1.9	0.17	—	
BMI <23 kg/m^2	3.3/2.3	0.73	—	
Hypertension	4.3/1.4	0.05	0.049	3.3 (1.0–10.8)
Creatinine clearance <30 ml/min	4.7/2.4	0.53	—	
Killip class ≥3	2.8/2.4	0.99	—	
Cardiac catheterization	2.8/2.6	0.9	—	
ADP RA	4.4/2.3	0.4	—	
GP IIb/IIIa RA	10.9/1.9	0.002	0.0014	6.6 (2.1–20.8)
ADP RA + GP IIb/IIIa RA	15.0/2.2	0.006	—	

BMI = body mass index; CI = confidence interval; other abbreviations as in Table 2.

DISCUSSION

This study demonstrates that UA/NSTEMI patients who would have been excluded from the randomized enoxaparin trials can be safely treated with a weight-adjusted regimen of subcutaneous enoxaparin, as long as particular attention is paid to age and renal function to further adjust the dosing regimen. The EP population represents a high-risk group of patients who had a fourfold increase in death or MI at 30 days. Hypertension and the use of GP IIb/IIIa inhibitors were the only predictors of bleeding found in our study population.

There is strong evidence that antithrombin therapy is beneficial in UA/NSTEMI patients and that subcutaneous enoxaparin is superior to UH in this setting (1–3). However, this demonstration has been obtained in selected populations, and it is not known whether these results can be applied to all comers who present with UA/NSTEMI, including those who would have been excluded from these randomized trials. Furthermore, the safety of enoxaparin in a population at a high risk of bleeding and with a high percentage of elderly, renal dysfunction, and HF remains to be determined. In the present study of 515 unselected consecutive cases, one-third had at least one exclusion criterion of the ESSENCE/TIMI-11B trials. This proportion is certainly underestimated because only the most relevant exclusion criteria of the randomized trials were quoted in our PARIS registry and this may have decreased the differences between the two populations.

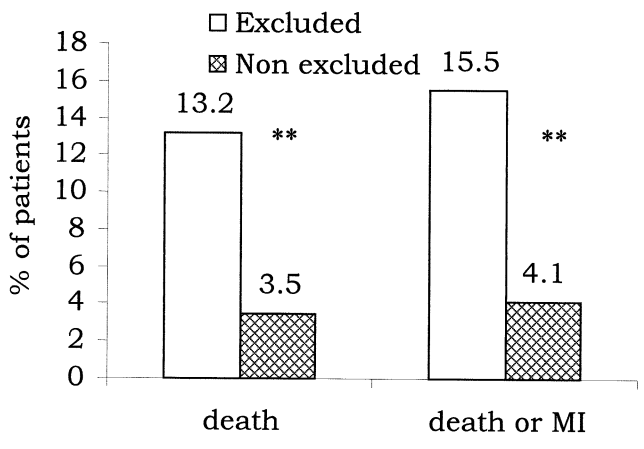


Figure 4. Rates of major coronary events at 30 days in excluded and non-excluded patients. **p < 0.001 between the two groups.

Renal failure was present in one-third of the EP population and is certainly one of the most frequent exclusion criterion found in all comers who have a serious risk of bleeding. Scant clinical data are available on the safety and efficacy of LMWH in UA patients with renal insufficiency (4,8,9). Renal insufficiency has been shown to be a risk factor for bleeding (10), and the safety of LMWH has been questioned in patients with low creatinine clearance, because of the risk of accumulation over time. Our strategy of reducing the dose and monitoring the anti-Xa activity in these patients appears to be effective because the anti-Xa levels in renal failure patients were comparable to those of patients without renal failure, although the treatment duration was found to be significantly longer in those with renal failure. The average enoxaparin dosage was significantly lower in renal failure patients than in patients with no severe renal dysfunction, reflecting the dose adjustment. These results highlight the importance of anti-Xa monitoring to avoid accumulation of anticoagulant activity and to limit the risk of bleeding in this specific subset. It further supports previous findings showing that two-thirds of the recommended dose produces an adequate anticoagulation level in most patients with severe chronic renal failure (4).

The similar low rate of bleeding events reported in the NEP and EP groups further confirms the efficacy of our strategy and the excellent anticoagulation profile of enoxaparin in the EP group, with reduced dosing and adjustment according to anti-Xa activity if necessary. Indeed, the rate of bleeding in our study compares favorably with that of the ESSENCE and TIMI-11B trials (2,3). Age and severe renal failure are frequently found to be risk factors for bleeding (10), and one would have expected the EP group to have a much higher rate of bleeding considered in absolute terms as well as in comparison with the NEP group. Neither renal function nor age was a predictor of bleeding in our

Table 4. Predictors of Death or Myocardial Infarction at 30 Days in the Whole Population

	Rate of Death or MI With/Without Criterion (%)	p Value (Univariate Analysis)	p Value (Multivariate Analysis)	Odds Ratio (95% CI)
NSTEMI	15.7/2.3	<0.0001	0.001	4.2 (1.74–10.18)
Heart failure (Killip class ≥3)	21.7/5.3	<0.0001	0.035	2.18 (1.05–4.50)
Creatinine clearance ≤30 ml/min	25.0/5.6	<0.0001	—	—
Hypertension (ml/min)	10.7/5.7	0.048	—	—
Hypercholesterolemia	4.8/10.1	0.032	—	—
Previous MI	12.9/6.4	0.03	—	—
Previous stroke	19.0/7.5	0.043	—	—
Valvular disease	22.2/7.5	0.023	—	—
	Value* in Patients With/Without Death or MI at 30 Days			
Creatinine clearance (ml/min)	39.2 ± 3.7/72.7 ± 1.6	<0.0001	0.0002	0.97 (0.96–0.99)
Age (yrs)	77.9 ± 1.7/65.7 ± 0.7	<0.0001	—	—

*Mean value ± SD.
Abbreviations as in Tables 1 and 3.

study. These findings suggest that the superiority of enoxaparin over UH in providing more effective and stable anticoagulation (7,11,12) may also apply to the EP population, which showed a good safety profile. In contrast, the use of GP IIb/IIIa inhibitors was an independent predictor of bleeding in our study.

The extremely high rate of acute coronary events at 30 days is striking and confirms that the EP population has a much higher risk than the NEP population. Interestingly, the most frequent criteria used to define the EP group were renal failure and HF, both of which predicted major ischemic events at 30 days. The present study also highlights that kidney function is a major indicator of vascular risk, as previously reported in the Minnesota Heart Survey study (13). However, renal failure is a common exclusion criterion in randomized trials evaluating antithrombotic drugs. Obviously, clinical trials focusing on patients with renal failure would be necessary to better assess enoxaparin and other antithrombotic drugs in this high-risk subgroup (8). This high rate of coronary events in the EP group may also reflect less aggressive strategies in these patients, driven mainly by the risk profile. Indeed, the EP population was less frequently referred to the catheterization laboratory, less frequently underwent coronary revascularization, and had less aggressive pharmacologic interventions. These patients are also often excluded from studies evaluating aggressive strategies. Patients >75 years of age were excluded in the FRagmin during InStability in Coronary artery disease (FRISC) II trial, and those with severe renal insufficiency or HF were excluded from the TACTICS-TIMI 18 trial (14,15) and the TIME study (16). In addition, although age was not an exclusion criterion, patients >65 years of age represented <15% of the whole population in the TIMI-11B and ESSENCE trials (17).

Whether more aggressive antithrombotic and invasive approaches would be beneficial in the EP group remains to be established, granted the fact that this group had a higher risk of bleeding and ischemic events (10,18). There is also evidence that GP IIb/IIIa inhibitors are effective in patients with severe renal failure (19), but they had an increased risk of bleeding in our EP group (10). Whether a dose adjustment of GP IIb/IIIa inhibitors is also necessary in the elderly and in those with renal failure remains to be explored. Finally, it remains to be shown whether the association of enoxaparin and clopidogrel would have a better risk/benefit ratio in the EP group. Renal failure and severe congestive HF were also exclusion criteria in the CURE study (5).

Conclusions. This study first confirms that a significant proportion of all comers presenting with UA/NSTEMI would have been excluded from randomized pivotal trials performed with enoxaparin. It also suggests that these patients can be treated safely with enoxaparin, with a specific dose adjustment in patients with low creatinine clearance. Whether the benefit of enoxaparin in terms of reducing ischemic events is similar in the EP and NEP populations cannot be shown from the present data.

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