Anti-Xa Activity Relates to Survival and Efficacy in Unselected Acute Coronary Syndrome Patients Treated With Enoxaparin

G. Montalescot, MD, PhD; J.P. Collet, MD, PhD; M.L. Tanguy, MD; A. Ankri, MD; L. Payot, MD; R. Dumaine, MD; R. Choussat, MD; F. Beygui, MD; V. Gallois, BS; D. Thomas, MD

Background—Low-molecular-weight heparin (LMWH) is recommended in the treatment of unstable angina (UA)/non–ST-segment–elevation myocardial infarction (NSTEMI), but no relationship has ever been shown between anticoagulation levels obtained with LMWH treatment and clinical outcomes.

Methods and Results—In all, 803 consecutive patients with UA/NSTEMI were treated with subcutaneous enoxaparin and were followed up for 30 days. The recommended dose of enoxaparin of 1 mg/kg BID was used throughout the population except when physicians decided on dose reduction because of a history of a recent bleeding event or because of a high bleeding risk. Anti–factor Xa activity was >0.5 IU/mL in 93% of patients; subtherapeutic anti-Xa levels (<0.5 IU/mL) were associated with lower doses of enoxaparin. The 30-day mortality rate was significantly associated with low anti-Xa levels (<0.5 IU/mL), with a 3-fold increase in mortality compared with the patients with anti-Xa levels in the target range of 0.5 to 1.2 IU/mL (P=0.004). Multivariate analysis revealed low anti-Xa activity as an independent predictor of 30-day mortality at least as strong as age, left ventricular function, and renal function. In contrast, anti-Xa activity did not predict major bleeding complications within the range of anti-Xa levels observed in this study.

Conclusions—In this large unselected cohort of patients with UA/NSTEMI patients, low anti-Xa activity on enoxaparin treatment is independently associated with 30-day mortality, which highlights the need for achieving at least the minimum prescribed anti-Xa level of 0.5 IU/mL with enoxaparin whenever possible. (Circulation. 2004;110:392-398.)

Key Words: enoxaparin □ myocardial infarction □ acute coronary syndrome

Unfractionated heparin (UFH), even with a weight-adjusted dose regimen, has an unpredictable anticoagulant effect that is altered by numerous factors, such as age, diabetes, smoking status, and inflammation.1 There is a moderate correlation between activated partial thromboplastin time (aPTT) and UFH concentration.2–6 Official guidelines recommend aPTT monitoring and dose adjustment of UFH in the management of acute coronary syndromes (ACS), although the therapeutic range for UFH is uncertain, has not been validated in ACS patients, and is primarily extrapolated from venous thromboembolism studies.1,7,8 Suboptimal dosing and/or low aPTT have recently been suggested to be related to recurrent ischemic events in ACS patients.9,10

Low-molecular-weight heparin (LMWH) anticoagulation is also recommended in the treatment of ACS. Anticoagulation monitoring is not required with subcutaneous administration of a weight-adjusted LMWH dose regimen because of the better pharmacodynamic and pharmacokinetic profiles of LMWHs. Therapeutic ranges of LMWHs have been determined for the treatment of deep-vein thrombosis, using anti-Xa activity as a measurement of their biological activity.11 Like UFH, these therapeutic ranges have been extended to arterial thrombosis, and several studies have confirmed that patients receiving subcutaneously administered enoxaparin (1 mg/kg BID) have predictable anti-Xa levels within the target therapeutic range.12–14 However, no relationship has ever been shown between the anti-Xa levels and clinical outcomes of ACS patients treated with a LMWH.

The aim of the present study was to determine in “real life” whether there was a correlation between anti-Xa activity and the end points of death, death or myocardial infarction (MI), and major bleeding at 30 days in a large cohort of consecutive ACS patients treated with subcutaneous doses of the LMWH enoxaparin.

Methods

Study Population

After admission for unstable angina (UA) or non–ST-segment elevation MI (NSTEMI), 803 consecutive patients were treated with subcutaneous enoxaparin and were followed up for 1 month in the...
Anti-Xa Activity

The anti-Xa activity was measured after patients had received at least 2 subcutaneous injections of enoxaparin, and blood sampling was performed 4 to 6 hours after the morning subcutaneous injection. Blood was collected by use of Vacutainer tubes (Becton Dickinson) containing trisodium citrate 0.129 mol/L. Platelet-poor plasma for anti-Xa activity measurements was obtained by centrifugation at 3500g for 20 minutes at 10°C.

Plasma anti-Xa activity was determined by an amidolytic assay using the specific chromogenic substrate CBS 52.44 and bovine factor Xa as a reagent and simultaneous thermal analyzers (STA, Diagnostica Stago).

The conventional therapeutic range of anti-Xa levels was considered to be between 0.5 IU/mL and 1.2 IU/mL. The latter corresponded both to the steady-state levels in healthy volunteers treated with 1 mg/kg BID subcutaneously and to the 75th percentile of anti-Xa levels measured in the 1 mg/kg enoxaparin arm of the phase II Thrombolysis in Myocardial Infarction (TIMI 11A) study conducted in ACS. Three groups of patients were specified according to their anti-Xa levels. The first group consisted of patients with an anti-Xa activity <0.5 IU/mL, which we considered as underanticoagulated according to the predefined therapeutic range. The second group of patients had anti-Xa levels within the prespecified therapeutic range, i.e., ≥0.5 IU/mL and <1.2 IU/mL. The third group consisted of patients with anti-Xa levels ≥1.2 IU/mL. Special attention was paid to the patients with anti-Xa levels ≥1.8 IU/mL, a threshold that may be associated with an increased risk of bleeding.

Clinical Follow-Up

Troponin I levels were determined on admission and every 6 hours during the first 24 hours, then once daily until discharge. In patients with recurrent ischemia, troponin I was measured every 6 hours during the 24 hours after the recurrent ischemia. After PCI, creatine kinase and troponin I levels were measured at the time of sheath removal and the next morning. All patients in this study were followed up at 1 month through written questionnaires and telephone interviews, but no systematic ECG was performed to rule out silent infarctions.

The end points studied were death, death or MI, and major bleeding at 30 days. Death was defined as all deaths occurring within 30 days of admission. Recurrent MI was defined as recurrent ischemic symptoms and/or ECG changes with at least 1 of the following criteria: (1) creatine kinase >2-fold the upper limit of normal with a rise >50% of the previous value that was associated with a positive troponin I test or (2) the appearance of a new left bundle-branch block or new Q waves. The definitions of major bleeding included (1) bleeding resulting in death, (2) bleeding in an intracranial or intraocular location, (3) a drop in the serum concentration of hemoglobin ≥3 g/dL, (4) bleeding requiring urgent surgery, (5) bleeding resulting in hemodynamic instability, and (6) bleeding requiring blood transfusion of at least 2 U of blood.

Statistical Analysis

Categorical variables were expressed as percentages, and continuous variables as the mean ± SEM. Simple linear regression was used to test the association between continuous variables. Potential associations between clinical and biological parameters were tested by univariate procedures using the Student t test or ANOVA for continuous variables and the χ² or Fisher exact test for categorical variables. Comparisons between the 3 prespecified groups were performed by use of the Bonferroni or Scheffé methods to address the multiple testing problems.

Independent predictors of mortality, death or MI, or major bleeding up to 30 days were identified by use of a stepwise multivariate logistic analysis. All baseline characteristics as well as important variables such as catheterization, revascularization, troponin levels, and TIMI scores were entered into the model. To prevent the elimination of potentially interesting risk factors, variables with a value of P < 0.15 after univariate analysis were included in the multivariate analysis. The α level was set at 0.05. All analyses were performed with the SAS software version 8.2 (SAS Institute).

Results

Baseline Characteristics

The baseline characteristics of the study population, an unselected group of 803 consecutive patients admitted for UA/NSTEMI at a single center, are shown in Table 1. Anti-Xa levels were obtained in 94% of patients (n = 754), and clinical follow-up was achieved in 97% (n = 778) at 30 days: The cumulative distribution curve of anti-Xa levels is shown in Figure 1, with 93% of patients above the lower limit of the target range.

The group with the poorest anticoagulation (anti-Xa levels of <0.5 IU/mL) had significantly worse baseline characteristics than the other 2 groups. Patients in this underanticoagulated group were older (25% being >80 years of age), had impaired renal function, and presented more frequently ST-segment depression and higher TIMI risk score (Table 1).

The group of patients with a high anti-Xa activity of ≥1.2 IU/mL had characteristics similar to those of the group of patients who had target anti-Xa levels (≥0.5 and <1.2 IU/mL). Overanticoagulation, defined as an anti-Xa level ≥1.8 IU/mL, occurred in only 3 patients (0.4%), and anti-Xa levels never exceeded 2.0 IU/mL.

Anticoagulation Data

All patients were treated with enoxaparin and aspirin, and 75% of the population also received an ADP receptor antagonist. The mean anti-Xa activity was 0.31 ± 0.02, 0.86 ± 0.01, and 1.38 ± 0.01 IU/mL in the <0.5, ≥0.5 and
A more conservative strategy was applied to the patients with anti-Xa levels <0.5 IU/mL, with significantly less catheterization and a trend toward reduced GP IIb/IIIA receptor antagonist use (Table 2). In this poorly anticoagulated and less aggressively managed group of patients, the average dose of enoxaparin was significantly lower than in the other 2 groups.

Bleeding risk factors were identified as reasons for the decrease in dosing in the group of patients with low anti-Xa levels: advanced age, previous history of bleeding, recent surgery or recent episode of bleeding, severe renal function impairment, and other associated diseases.22 The enoxaparin dose was adjusted down in 34.7% of all patients, and it occurred primarily in renal failure patients (84.6% in patients with creatinine clearance <30 mL/min), in the elderly (68.9% in patients >80 years old), and in patients considered to be at high risk of bleeding (65.7%). Interestingly, dose reduction in renal failure patients allowed anti-Xa levels to be reached that were similar to those obtained in patients with a creatinine clearance ≥30 mL/min receiving standard enoxaparin doses.23 Indeed, both patients with and without renal failure exhibited the same correlation between the dose of enoxapa-
The mean anti-Xa activity was 0.61 ± 0.05 IU/mL; patients with anti-Xa levels >0.5 and <1.2 IU/mL had a significantly lower final enoxaparin dosage (0.72 ± 0.05 versus 0.92 ± 0.01 IU/mL; P < 0.01). Patients who experienced in-hospital bleeding complications underwent more frequent enoxaparin dose adjustment than those free of bleeding events and had a significantly lower final enoxaparin dosage (0.72 ± 0.05 versus 0.83 ± 0.01 IU in patients without and with major bleedings, respectively; P = 0.004). The multivariate analysis also confirmed anti-Xa activity as a significant predictor of the double end point (death or MI) at 30 days, along with more classic risk factors, such as age, non–Q-wave MI, and left ventricular or renal function (Figure 4B).

Anti-Xa activity was not related to bleeding complications, and the average anti-Xa levels were 0.91 ± 0.01 IU versus 0.83 ± 0.01 IU in patients without and with major bleedings, respectively (P = NS). Patients who experienced in-hospital bleeding complications underwent more frequent enoxaparin dose adjustment than those free of bleeding events and had a significantly lower final enoxaparin dosage (0.72 ± 0.05 versus 0.83 ± 0.01, respectively; P = 0.02). The comparatively worse baseline risk for bleeding complications in the low-anticoagulation group is evident in Figure 3. Despite a more conservative approach and lower anti-Xa levels, these patients had 2.7-fold and 3.7-fold higher bleeding rates than patients in the ≥0.5 and <1.2 IU/mL, and ≥1.2 IU/mL, respectively (P = 0.0004). A multivariate analysis was performed, including all baseline clinical, biological, and therapeutic variables that were significant (P < 0.15) after univariate analysis identified lower anti-Xa activity as a strong independent predictor of death at 30 days (Figure 4A). The other independent predictors of mortality were age, non–Q-wave MI, and parameters of left ventricular function (ejection fraction and Killip class).

Similarly, a higher rate of the double end point (death or MI) was found in the group of patients with the lowest anti-Xa levels (P = 0.002, Figure 3). Recurrent episodes of ischemia occurred in 12.5%, 9.2%, and 2.8% of patients in the groups with anti-Xa activities <0.5, ≥0.5 and <1.2, and ≥1.2 IU/mL, respectively (P = 0.0004). The multivariate analysis also confirmed anti-Xa activity as a significant predictor of the double end point (death or MI) at 30 days, along with more classic risk factors, such as age, non–Q-wave MI, and left ventricular or renal function (Figure 4B).

### TABLE 2. Antithrombotic Regimen and Invasive Procedures in the Whole Population and the 3 Prespecified Groups, Defined by Anti-Xa Level (Available in 93.9% of Patients)

<table>
<thead>
<tr>
<th>Anti-Xa Levels</th>
<th>Whole Population (n = 803)</th>
<th>&lt;0.5 IU/mL (n = 54)</th>
<th>≥0.5 and &lt;1.2 IU/mL (n = 570)</th>
<th>≥1.2 IU/mL (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of enoxaparin, mg/kg</td>
<td>0.84 ± 0.02</td>
<td>0.66 ± 0.03†</td>
<td>0.82 ± 0.01</td>
<td>0.91 ± 0.02‡</td>
</tr>
<tr>
<td>No. of enoxaparin injections before catheterization</td>
<td>4.1 ± 0.1</td>
<td>3.7 ± 0.3</td>
<td>4.4 ± 0.2</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>GP IIb/IIIa-RA, %</td>
<td>32</td>
<td>26</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>ADP-RA, %</td>
<td>74</td>
<td>79</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>Coronary angiography, %</td>
<td>88</td>
<td>77†</td>
<td>89</td>
<td>93</td>
</tr>
<tr>
<td>Revascularization, %</td>
<td>56</td>
<td>56</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>PCI, %</td>
<td>9</td>
<td>4</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>CABG, %</td>
<td>†</td>
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</tbody>
</table>

ADP-RA indicates ADP receptor antagonist; CABG, coronary artery bypass graft; GP IIb/IIIa-RA, glycoprotein IIb/IIIa receptor antagonist; and PCI, percutaneous coronary intervention.

*Significant difference between the <0.5 IU/mL group and the ≥0.5 and <1.2 IU/mL group.
†Significant difference between the <0.5 IU/mL group and the >1.2 IU/mL group.
‡Significant difference between the ≥1.2 IU/mL group and the ≥0.5 and <1.2 IU/mL group.
analysis. Anti-Xa activity did not predict major bleeding complications within the range of anti-Xa levels measured in our population. Independent correlates of major bleeding at 30 days were hypertension (OR, 5.23; 95% CI, 1.16 to 23.6; P = 0.03) and ST-segment depression (OR, 3.03; 95% CI, 1.01 to 9.11; P = 0.05). Paradoxically, it was observed that patients with a bleeding complication were less likely to have undergone catheterization (OR, 0.25; 95% CI, 0.08 to 0.76; P = 0.01), which probably reflects the physician’s decision to use a more conservative approach in patients with a high bleeding risk or suffering from a spontaneous bleeding complication.

Discussion

In this large cohort of ACS patients, the vast majority of patients (93%) had an anti-Xa activity above the lower limit of the prespecified therapeutic range (0.5 IU/mL).12–14,19–21,23 In contrast, it must be noted that only 70% of patients were above the lower limit of the therapeutic range of aPTT (60 seconds) in one of the most recent and well-conducted randomized trials using UFH in ACS.10 This is also the first report showing an association between suboptimal anticoagulation with LMWH (anti-Xa activity < 0.5 IU/mL) and a risk of recurrent ischemic events at 30 days. In this study, patients who received suboptimal anticoagulation had worse baseline clinical and biological characteristics and underwent more conservative management of the index ischemic event than patients with higher anti-Xa levels. An important finding of this study is that low anti-Xa activity remained a strong predictor of death after adjustment for the other adverse characteristics. Interestingly, neither anti-Xa activity nor creatinine clearance were independently associated with bleeding, which is probably a result of the adjustment of the dose in patients with severe renal failure to “normalize” anti-Xa levels, which led to a distribution of levels around 1 IU/mL, with few patients (0.4%) exceeding 1.8 IU/mL.

UFH concentrations correlate poorly with aPTT,2 and the therapeutic range of aPTT has never been validated in arterial thrombosis but rather has been extrapolated from studies of patients with venous thromboembolism.24–26 In the Global Use of Strategies To open Occluded coronary arteries (GUSTO) IIb study, a complex and nonsignificant association was found between the weight-indexed UFH rate and 30-day mortality, whereas there was a surprising, positive association between increasing aPTT levels and an adverse ischemic outcome.10 In contrast, in the Organization to Assess the Strategies for Ischemic Syndromes pilot study (OASIS)-2 study, recurrent ischemic events occurred more frequently in patients with a low aPTT (<60 seconds), but when examined as a continuous variable, aPTT was not associated with recurrent cardiovascular death, MI, or refractory ischemia.9 Usually, bleeding is associated with elevated aPTT results, although the pattern is also complex and is tightly linked to the individual risk of the patients.9 LMWHs have been developed for the treatment of ACS because of their predictable anticoagulant effect. However, different dosages of dalteparin,27,28 nadroparin,29,30 and enoxaparin18,31,32 have

Figure 3. Event rates at 30-day follow-up according to levels of anticoagulation obtained with enoxaparin. *Significant difference between <0.5 IU/mL group and ≥0.5 and <1.2 IU/mL group; †significant difference between <0.5 IU/mL group and ≥1.2 IU/mL group.

Figure 4. A, Independent predictors of mortality at 30 days after multivariate analysis for whole study population. B, Independent predictors of death or MI at 30 days.
been used in these large trials,18,27–32 which may lead to different plasma levels of the drugs and different antithrombotic effects.21 Similar to the way in which aPTT is used for UFH, anti-Xa activity targets for LMWH therapy were derived from studies performed in patients with venous thromboembolism, but in contrast to UFH, we lack information on the relationship between anti-Xa levels and the clinical outcome of ACS patients.

In the present study, low anti-Xa activity was linked to suboptimal dosing, which occurred primarily because of the risk profile of the patients. The absence of bleeding exclusion criteria (unlike in randomized studies) meant that ACS patients with a recent history of bleeding or high bleeding risk characteristics were enrolled in the present cohort. They were subsequently treated with reduced catheterization and anticoagulation. Whether this strategy decreased their bleeding risk is unknown, but they still exhibited nonsignificantly higher rates of major bleeding and significantly more ischemic events than patients with adequate anti-Xa levels. The finding that low anti-Xa levels predicted mortality independently of all the other risk factors and strategies of treatment supports the recommendation for the use of an adequate anticoagulation level as often as possible in the real-world management of ACS.

Interestingly, the group of patients with anti-Xa levels ≥1.2 IU/mL tended to show nonsignificantly lower rates of death, death or MI, and major bleeding. This raises the issue of the optimal level of anti-Xa activity associated with LMWH use needed to protect ACS patients, a question that cannot be answered by the present data. Enoxaparin also exhibits other important biological properties that may play significant roles in the prevention of recurrent ischemic events.33–36

Although the present study provides important data on a diverse patient population, complementing the randomized trials that have more restrictive inclusion criteria, it must be noted that decisions regarding invasive management, treatment strategy, enoxaparin dosing, and timing of anti-Xa measurement were also less controlled than is usually the case in randomized trials. Our pharmacokinetic data must be interpreted with caution, especially in patients with severe renal dysfunction, and are applicable only to short-term treatments. Finally, 30-day follow-up by questionnaire and telephone is a potential limitation of our study.

In conclusion, in this large unselected cohort of enoxaparin-treated patients with UA and NSTEMI, low anti-Xa activity is strongly and independently associated with early mortality, and this relationship seems to be more potent than that observed in other studies measuring aPTT in UFH-treated patients. This finding highlights the need for achieving at least the minimum prescribed anti-Xa level of 0.5 IU/mL with enoxaparin whenever possible in ACS patients. Physicians must be aware that a dose reduction leading to lower anti-Xa levels may increase the risk of mortality and recurrent ischemic events. In this scenario, mortality risk must be weighed against the bleeding risk of patients who present with a recent history of bleeding or a particularly high risk of bleeding.

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