Percutaneous Coronary Intervention After Subcutaneous Enoxaparin Pretreatment in Patients With Unstable Angina Pectoris

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Background—Subcutaneous low-molecular-weight (LMW) heparins can effectively replace unfractionated heparin in patients with unstable angina or non–Q-wave myocardial infarction. However, the optimal anticoagulation strategy for these patients when they require cardiac catheterization is still unclear. Therefore, we evaluated a new and simple strategy of anticoagulation in these patients.

Methods and Results—A total of 451 consecutive patients with unstable angina/non–Q-wave myocardial infarction were treated for at least 48 hours with subcutaneous injections of enoxaparin (1 mg [100 IU]/kg every 12 hours, cycled at 6 AM and 6 PM). Of this unselected population, 293 patients (65%) underwent a coronary angiography within 8 hours of the morning LMW heparin injection, followed by immediate percutaneous coronary intervention (PCI) in 132 patients (28%). PCI was performed without any additional bolus of unfractionated/LMW heparin and without coagulation monitoring. Anti-Xa activity at the time of catheterization was 0.98±0.03 IU/mL, was >0.5 IU/mL in 97.6% of patients, and did not relate to the LMW heparin injection-to-catheterization time. There were no in-hospital abrupt closures or urgent revascularizations after PCI. The death/myocardial infarction rate at 30 days was 3.0% in the PCI group (n=132) but 6.2% in the whole population (n=451) and 10.8% in the patients not undergoing catheterization (n=158). The 30-day major bleeding rate was 0.8% in the PCI group, which was comparable to that of patients without catheterization (1.3%).

Conclusions—PCI within 8 hours of the last enoxaparin subcutaneous injection seems to be safe and effective. The safety of subcutaneous LMW heparin in combination with platelet glycoprotein IIb/IIIa blockade awaits further study.

Key Words: coronary disease ▪ angioplasty ▪ anticoagulants ▪ coagulation ▪ pharmacology

Enoxaparin has been shown to be superior to unfractionated heparin (UH) in patients with unstable angina (UA) or non–Q-wave myocardial infarction (NQMI). However, when catheterization is required, the management of anticoagulation in patients treated with subcutaneous low-molecular-weight heparin (LMWH) remains unclear. Although illogical and inconvenient, recommendations based on the experience of percutaneous coronary intervention (PCI) in the Efficacy Safety Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) and Thrombolysis in Myocardial Infarction (TIMI)-11B trials indicate switching from enoxaparin to UH before and during catheterization. Other LMWH trials in which an invasive approach to unstable coronary artery disease was tested did not clarify this specific issue.

Scant clinical data are available on the efficacy and safety profile of LMWHs during cardiac catheterization, but some studies suggest that LMWHs are superior to UH because of the lack of intrinsic platelet activation/aggregation and the improvement in clinical outcomes in patients with unstable angina and after PCI. Moreover, anticoagulation is more rapidly effective and stable with LMWHs than with UH, mainly because of better bioavailability, a reduction in nonspecific protein binding, a reduced susceptibility to neutralization by platelet factor 4, and better control of von Willebrand factor release.

Therefore, we prospectively evaluated the safety and efficacy of subcutaneous enoxaparin given twice a day for a 48-hour period of medical stabilization before catheterization; this treatment duration has been associated with a significant 20% reduction in death and/or myocardial infarction (MI). Coronary angiograms were always scheduled within the 8 hours after the morning injection of enoxaparin, when the highest levels of anti-Xa activity are present.
Methods

Patient Population
We studied 451 consecutive patients who were admitted with unstable coronary artery disease, which was defined as typical chest pain lasting >10 minutes in the 24 hours before admission, ECG changes, and/or raised serum levels of cardiac enzymes including creatinine kinase and troponin. A NQMI was considered to be present on admission if troponin-I levels were >0.5 μg/mL within the first 12 hours of hospitalization. The only patients excluded from the study were those with persistent ST-segment elevation or and/or ECG changes with ≥1 of the following criteria: (1) creatinine kinase >2 times the upper limit of normal with a rise >50% of the prior value, associated with a positive troponin I test, or (2) 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. Bleeding definitions were derived from TIMI criteria. Major hemorrhage corresponded to (1) bleeding resulting in death, (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 (epistaxis, ecchymosis, hematoma, or macroscopic hematuria) or that was not clinically identified but was associated with a drop in the serum hemoglobin concentration >4 g/dL (or >12% of the hematocrit level). At 30 days, we evaluated the composite end point of all-cause mortality or recurrent MI. The main safety end point included all major bleeding events.

Biological Measurements
Troponin-I level was determined by a florogenic enzyme-linked immunosassay (ELISA) using the Opus Plus assay (Dade-Behring SA). Blood samples were taken from an antecubital vein and collected in Vacutainer tubes (Becton Dickinson) containing 0.129 mol/L trisodium citrate (1 volume). Troponin-I levels were measured on admission, every 6 hours during the first 24 hours, and then once daily. In cases of recurrent ischemia, troponin-I was measured again every 6 hours during the next 24 hours. After PCI, troponin-I levels were measured at the time of sheath removal (>10 hours after the morning injection of enoxaparin) and the next morning (ie, roughly 18 hours after PCI). These two samples may have picked up most of the procedure-related myonecrosis. The test sensitivity was 0.1 μg/L, and the cut-off value that we used to define a NQMI was 0.5 μg/L.

Immediately before catheterization, blood samples were taken for further measurement of anti-Xa activity. Venous blood was collected in Vacutainer tubes (Becton Dickinson) containing 0.129 mol/L trisodium citrate (1 volume). Platelet-poor-plasma was obtained by centrifugation at 3500g at 10°C for 20 minutes. Plasma anti-Xa activity was determined by an amidolytic assay using the specific chromogenic substrate CBS 52.44 and bovine Factor Xa as reagents (Diagnostica Stago) and Stago analyzers. The therapeutic range with duration of enoxaparin treatment in patients scheduled for CABG indicates coronary artery bypass grafting.

Clinical Follow-Up
In-hospital follow-up was based on physical examination, ECG, and creatine kinase and troponin I levels, as measured at the time of sheath removal (ie, >4 PM) and on the following morning (roughly 18 hours after PCI) before hospital discharge. All patients in this study were followed-up for 1 month through written questionnaires and telephone interviews. Deaths were classified as cardiovascular or noncardiovascular. Recurrent MI was defined as recurrent chest pain and/or ECG changes with ≥1 of the following criteria: (1) creatinine kinase >2 times the upper limit of normal with a rise >50% of the prior value, associated with a positive troponin I test, or (2) 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. Bleeding definitions were derived from TIMI criteria. Major hemorrhage corresponded to (1) bleeding resulting in death, (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 (epistaxis, ecchymosis, hematoma, or macroscopic hematuria) or that was not clinically identified but was associated with a drop in the serum hemoglobin concentration >4 g/dL (or >12% of the hematocrit level). At 30 days, we evaluated the composite end point of all-cause mortality or recurrent MI. The main safety end point included all major bleeding events.

Statistics
Results are expressed as 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 Student’s t or χ² tests, as appropriate. The α level was set at 0.05.

Results
Clinical Characteristics
The population of patients with unstable coronary artery disease in this study had a high-risk profile: 19% were >80 years old, 25% were diabetic, 24% had a prior history of MI, and 44% had NQMI on admission (Table 1). The mean duration of enoxaparin treatment in patients scheduled for
TABLE 1. Baseline Characteristics of the Whole Population, Patients Without Catheterization, and Patients With PCI on Enoxaparin Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole Population (n=451)</th>
<th>Without Catheterization (n=158)</th>
<th>PCI (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>67</td>
<td>64</td>
<td>74</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>67±14</td>
<td>72±14</td>
<td>65±13</td>
</tr>
<tr>
<td>&gt;80, %</td>
<td>19</td>
<td>28</td>
<td>15*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±5</td>
<td>26±6</td>
<td>26±6</td>
</tr>
<tr>
<td>Killip class 3 to 4, %</td>
<td>15</td>
<td>26</td>
<td>8*</td>
</tr>
<tr>
<td>Creatinine clearance &lt;40 mL/min, %</td>
<td>22</td>
<td>28</td>
<td>17*</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>36</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>42</td>
<td>38</td>
<td>49</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>24</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>48</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>Family history of CAD, %</td>
<td>11</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>24</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>10</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>ECG changes, %</td>
<td>69</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>ST depression</td>
<td>34</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>30</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>NQMI on admission, %</td>
<td>44</td>
<td>44</td>
<td>50</td>
</tr>
</tbody>
</table>

Values are mean ± SEM or percent of patients. CAD indicates coronary artery disease; CABG, coronary artery bypass grafting; and BMI, body mass index.

*P<0.01 between PCI and no catheterization.

cardiac catheterization was 3.8±0.2 days. Recurrent ischemia led to urgent catheterization within the first 24 hours in 5 patients, followed by immediate PCI in 4 of them. The average delay between the morning injection of enoxaparin and catheterization was 5.3±1.8 hours (n=293). The average delay between the morning injection of enoxaparin and catheterization with PCI was 5.6±1.9 hours (n=132). PCI was necessary to treat a single coronary artery in 79% of patients and to treat 2 or 3 coronary arteries in 21% of patients. The left main trunk was dilated in 2.8% of patients, and the left anterior descending artery and right and circumflex coronary arteries were treated in 44%, 30%, and 31% of patients, respectively. Coronary artery bypass grafts were treated in 6% of patients.

Anticoagulation at the Time of Catheterization

The anti-Xa activity was >0.5 IU/mL in 97.6% of the patients coming into the catheterization laboratory. The average anti-Xa activity was 0.99±0.02 IU/mL in patients undergoing coronary angiography only (n=293) and 0.98±0.03 IU/mL in patients undergoing a coronary angiogram immediately followed by PCI (n=132). The distributions of anti-Xa activity levels were similar in these 2 groups: the vast majority of patients were close to the upper limit of the therapeutic range (Figure 2). Importantly, the anti-Xa activity was stable over the 8-hour period after the injection of enoxaparin, confirming that our time window for catheterization corresponded to a high and constant degree of anticoagulation (Figure 3). Subsequently, the anti-Xa activity did not correlate with the injection-to-catheterization time in the 2 groups of patients.

The anti-Xa activity did not correlate with plasma creatinine clearance or with the age of the patients, reflecting the adequate reduction of enoxaparin doses in elderly patients and in patients with renal failure, conditions that are associated with a risk of overdosage. Patients with chronic renal failure (creatinine clearance <40 mL/min) had the same level of anti-Xa activity as patients with normal renal function (0.99±0.05 versus 0.97±0.02, respectively; P=0.79). Although patients >80 years old had significantly lower values of plasma creatinine clearance, their anti-Xa activity did not differ from that of patients ≤80 years old (0.98±0.02 versus 1.02±0.06, respectively, P=0.51). The average aPTT value was 41.7±0.7 s, and a weak but significant correlation was found with anti-Xa activity (r=0.256, P<0.001).

30-Day Clinical Outcome

The incidence of the composite end point of death or MI, along with each component of this end point, is given in Table 2 for the different subgroups of the population. In the PCI group, 2 patients aged 78 and 86 years died in the hospital (1.5%), one from cardiac death (day 5) and the other from refractory renal failure aggravated by the contrast media administration (day 6). The 1-month reinfarction rates were comparable in the whole population and in the PCI group when considering Q-wave MI and NQMI diagnosed by new rises in the serum levels of creatine kinase during the hospital stay (2.7% versus 3.0%). No abrupt closures and no urgent revascularizations occurred after PCI.

The high-risk profile of our unselected population was confirmed by the high rate of mortality in the whole group: 78% of the mortality was due to cardiovascular deaths. Mortality was statistically associated with advanced age.
(81±10 years old), the presence of NQMI on admission (86.4%), chronic renal failure (55.5% had a creatinine clearance <40 mL/min), a contraindication to cardiac catheterization (68.2% had no cardiac catheterization), and heart failure on admission (54.6% were in Killip class 3 or 4). The mortality rate for patients with a NQMI and a contraindication to catheterization was 20.6% at 30 days (Figure 4). In this subgroup of patients, other factors may have played an important role in the decision against catheterization, as well as in the adverse outcome; these factors could include the associated diseases (cancer, disabling stroke, dementia, recent surgery, severe renal failure, and other organ failure) or the known coronary status, which excluded the possibility of revascularization, as determined on a previous coronary angiogram.

The rates of major hemorrhages were very low: 0.7% and 0.8% in the whole population and PCI group, respectively. The single case of major hemorrhage in the PCI group was a groin hematoma after sheath removal in a patient treated with abciximab; in this patient, the anti-Xa activity was 0.91 IU/mL and the aPTT was 36/30 s. The incidence of major bleeding in patients without catheterization was 1.3%, and no major bleeding was observed in patients undergoing a coronary angiography without PCI.

**Table 2. Clinical Outcome at 30 Days in the Whole Population, in Patients Without Catheterization, and in Patients Undergoing PCI on Enoxaparin Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Whole Population (n=451)</th>
<th>No Catheterization (n=158)</th>
<th>PCI (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI, % (n)</td>
<td>6.2 (28)</td>
<td>10.8 (17)</td>
<td>3.0 (4)</td>
</tr>
<tr>
<td>Death, % (n)</td>
<td>4.9 (22)</td>
<td>10.1 (16)</td>
<td>1.5 (2)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4.0 (18)</td>
<td>8.9 (14)</td>
<td>0.7 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>0.9 (4)</td>
<td>1.2 (2)</td>
<td>0.7 (1)</td>
</tr>
<tr>
<td>MI, % (n)</td>
<td>2.7 (12)</td>
<td>4.4 (7)</td>
<td>3.0 (4)</td>
</tr>
<tr>
<td>NQMI</td>
<td>2.2 (10)</td>
<td>1.3 (2)</td>
<td>2.3 (3)</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0.4 (2)</td>
<td>3.1 (5)</td>
<td>0.7 (1)</td>
</tr>
<tr>
<td>Bleeding, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>0.7 (3)</td>
<td>1.3 (2)</td>
<td>0.8 (1)</td>
</tr>
<tr>
<td>Minor</td>
<td>2.0 (9)</td>
<td>1.9 (3)</td>
<td>2.4 (3)</td>
</tr>
</tbody>
</table>

**Figure 3.** Anti-Xa activity according to time interval from morning enoxaparin injection to catheterization in patients undergoing coronary angiography alone (A) and in patients with immediate PCI after coronary angiography (B). No differences were present, thus indicating a stable anticoagulation profile of enoxaparin over the 8-hour time period after last injection of enoxaparin.

**Figure 4.** Mortality rates at 30 days in different subgroups of patients according to clinical presentation and use of catheterization. A positive troponin test was considered to be any value >0.5 μg/L within first 12 hours.

**Discussion**

The most important finding of the study reported here is that PCI can be performed without additional anticoagulation and without coagulation monitoring in a high-risk population of consecutive UA/NQMI patients pretreated with subcutaneous enoxaparin for at least 48 hours. This new strategy seems to be safe and effective when cardiac catheterization is performed within 8 hours of an enoxaparin injection and sheaths are pulled out ≥10 hours after the enoxaparin injection. There was no increase in the major bleeding rate of PCI patients compared with patients not undergoing catheterization. No instances of abrupt closure or urgent revascularization after PCI were reported. The low incidence of the double end point (death or MI) at 30 days also compares favorably with the results of recent PCI trials in unstable angina.6,16

Enoxaparin was recently shown to be superior to UH in the management of UA/NQMI, with a significant reduction of 18% in death or MI at 43 days.1-3 However, the management of anticoagulation remains a problem when these patients need cardiac catheterization. The current recommendations are derived from the protocol guidelines and the limited PCI
experience obtained in 2 large, phase III enoxaparin trials,\textsuperscript{1,2} which suggest interrupting subcutaneous enoxaparin and switching to intravenous UH before catheterization. This strategy is inconvenient, has not really been evaluated, and is questionable because it may expose the patient to over-anticoagulation and bleeding. The prolonged half-life of enoxaparin can be associated with significant residual anti-Xa activity, which cannot be measured by activated clotting time, and can cause over-anticoagulation when intravenous UH is also administered before and during procedures. The risk of variations in anticoagulation is much less important when subcutaneous enoxaparin is used alone, providing stable and effective anticoagulation, as reflected by the anti-Xa levels of our patients at the time of catheterization.

To our knowledge, this is the first study of PCI performed with subcutaneous injections of a LMWH as the only anticoagulant treatment. A few studies yielding negative results have tested prolonged anticoagulation with LMWH (versus placebo) to prevent restenosis after PCI, but the procedures were always performed with standard doses of UH.\textsuperscript{17–19} The limited information available on LMWH anticoagulation given intravenously during PCI shows the feasibility and possible interest in LMWH in interventional cardiology. In a randomized double-blind trial, the LMWH reviparin was given as an intravenous bolus immediately before PCI. Reviparin did not prevent restenosis as expected, but it did lead to fewer short-term complications and a reduced need for bail-out stents compared with the control UH group.\textsuperscript{9} In a feasibility study, 30 patients undergoing PCI received a single intravenous bolus of enoxaparin (1 mg/kg) and 30 other PCI patients were given UH (10 000 IU); both treatments seemed to be safe and prevented thrombin generation to the same extent.\textsuperscript{10} The NICE-1 and NICE-4 trials (National Investigators Collaborating on Enoxaparin) evaluated intravenous enoxaparin (0.75 mg/kg) plus abciximab, respectively, during PCI in selected populations without control arms. Preliminary results show low rates of ischemic events and bleeding, suggesting that this type of intravenous anticoagulation is possible in the cardiac catheterization laboratory without coagulation monitoring.\textsuperscript{20} However, unlike our study, the NICE-1 and NICE-4 trials were designed for expediting care without prior medical stabilization with the subcutaneous administration of enoxaparin.

Our data further suggest that subcutaneous pretreatment for 48 hours with enoxaparin in UA/NQMI patients allows safe PCI without additive anticoagulation in the cardiac catheterization laboratory. These results were obtained in a study population representative of the “real world” situation, because our only exclusion criterion was the presence of a contraindication to anticoagulation. Importantly, the strategy we propose here simplifies and improves the management of UA/NQMI patients pretreated with LMWH who require catheterization. However, it does not apply to expediting care centers, where patients undergo coronary angiography and/or PCI within the first few hours of admission.\textsuperscript{21,22}

Our new strategy was associated with an effective anti-Xa activity (>0.5 IU/mL) in 97.6% of the patients at the time of catheterization (most of the patients were close to 1 IU/mL), with no evidence of a relationship between anti-Xa activity and the enoxaparin injection-to-catheterization time. These findings indicate an adequate anticoagulant effect in the vast majority of patients, which was stable over the 8-hour period after the morning subcutaneous injection of enoxaparin. Our data also confirm the absence of accumulation of anti-Xa activity after multiple injections of a weight-adjusted regimen of enoxaparin over a mean period of 3.8 days, and none of the 293 catheterized patients exceeded 1.3 U of anti-Xa activity.\textsuperscript{12} This was also true in patients at a high risk of accumulation (ie, those with chronic renal failure and/or advanced age). In these high-risk patients, accumulation was avoided by systematically reducing the enoxaparin doses according to renal function and by measuring the anti-Xa activity after the third subcutaneous injection to adjust the dose of enoxaparin, if necessary.

Our data suggest that anticoagulation using subcutaneous enoxaparin during a period of medical stabilization of 48 hours is effective in preventing the early complications of PCI (ie, abrupt closure and urgent revascularization) and ensuring a low event rate at 1-month follow-up. The 1-month incidence of the double end point (death or MI) in our PCI group compares favorably with recent data from PCI trials in UA/NQMI patients.\textsuperscript{6,16} In our study population, the PCI group had much better outcomes than patients not selected for cardiac catheterization, reflecting the increased risk of the latter, particularly when such patients have a positive troponin test within the first 12 hours. The NQMI patients considered unsuitable for catheterization often bear several other major risk factors, such as advanced age, diabetes, severe congestive heart failure, renal failure, concomitant diseases, and known diffuse coronary disease with no possibility of revascularization. The decision against catheterization by the physician reflects the global clinical risk of each patient.

This study is limited by the lack of a control group receiving UH for PCI and the limited number of patients undergoing PCI, but our data can be used to help design a randomized study comparing our strategy with the current recommendations. The validated, weight-adjusted dose of enoxaparin to treat unstable coronary artery disease also seems to be suitable for PCI within 8 hours of the last injection. Whether the time window for PCI can be widened is another important issue. PCI 8 to 12 hours after subcutaneous enoxaparin administration might require an additive intravenous bolus of enoxaparin, and this regimen is currently being evaluated in the Pharmacokinetic study of Enoxaparin Percutaneous Coronary Interventions (PEPCI) trial. The role of coagulation monitoring with the use of LMWH in the catheterization laboratory must still be fully evaluated. In the present study, anti-Xa activity measurements were studied retrospectively and were not used for the clinical decisions regarding PCI. It is likely that anti-Xa measurements may not be necessary in routine practice for both PCI and sheath removal. However, the measurement of anti-Xa activity may be particularly useful in patients who require dose adjustments of enoxaparin, such as the elderly and those with renal failure. Finally, future studies should again evaluate both strategies of LMWH anticoagulation in the catheterization laboratory.
laboratory: either a single dose given intravenously before the procedure (like in the NICE trials) or a steady state obtained with subcutaneous injections (like in the present study)."^{20,21}

In conclusion, the global strategy of subcutaneous anticoagulation with enoxaparin that we evaluated in this report seems safe, effective, and easy to use in an unselected patient population with UA/NQMI, with or without cardiac catheterization and/or PCI. Although the superiority of enoxaparin over UH in PCI still remains to be proven, our data suggest that subcutaneous enoxaparin pretreatment for 48 hours provides adequate anticoagulation for PCI in UA/NQMI, with encouraging clinical results.

References
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