ABSTRACT

Therapy for unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI) should combine antithrombotic as well as antianginal agents. Until recently, the standard antithrombotic regimen included unfractionated heparin (UFH) and aspirin. However, clinical trials suggest that low-molecular-weight heparins (LMWHs) can replace UFH in most patients, even those receiving glycoprotein (GP) IIb/IIIa receptor antagonists. Enoxaparin, an LMWH, has demonstrated a sustained clinical and economic benefit in comparison to UFH in the management of UA/NSTEMI. There is also substantial evidence that cardiac catheterization is safe in patients receiving LMWH for acute coronary syndromes. Clinical trials with enoxaparin indicate that LMWHs are effective and safe as adjunctive therapy in patients undergoing percutaneous coronary intervention, with or without the use of GP IIb/IIIa receptor antagonists. (Advanced Studies in Medicine. 2002;2(12):452-456)

All patients admitted with a diagnosis of acute coronary syndromes (ACS), either with or without ST-segment elevation, should receive medical therapy when they are admitted to the hospital. Although healthcare providers tend to dichotomize ACS, the mortality rates for these 2 different presentations are nearly identical: 10% for ST-segment elevation and 11% for non-ST-segment elevation. Generally high-risk patients proceed to early intervention such as percutaneous coronary intervention or coronary artery bypass graft (CABG), but the PURSUIT, PARAGON B, and TACTICS studies suggest that such patients are under medical care anywhere from 25 hours to 107 hours prior to coronary revascularization. Medical therapy prescribed by the physician at the initial diagnosis is critical for these patients as it precedes any definitive mechanical correction of the coronary problem.

The underlying logic of the American College of Cardiology/American Hospital Association 2000 practice guidelines for treatment of unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI) is that the intensity of the therapy should be relatively commensurate to the risk of the patient. Higher-risk patients should be given multiple drugs, including aspirin, heparin, glycoprotein (GP) IIb/IIIa receptor blockers, and possibly the oral platelet inhibitors clopidogrel and ticlopidine (Figure 1). However, in March 2002, those guidelines were revised to include the class 1A recommendation that patients receive the anticoagulants low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH). The level 2A recommendation is that enoxaparin is preferable to
UFH in UA/NSTEMI, unless CABG is planned within 24 hours.

**Enoxaparin in Unstable Angina and Non-ST-Elevation Myocardial Infarction**

Investigators in the ESSENCE study group conducted a double-blind placebo-controlled study that randomly assigned 3171 patients with angina at rest or non-Q-wave myocardial infarction to receive either 1 mg of enoxaparin per kilogram of body weight SC twice daily or continuous IV UFH for at least 48 hours. The investigators found that at the 14-day follow-up, patients in the enoxaparin study arm experienced fewer ischemic recurrent events (16.6%) than did those patients in the UFH study arm (19.8%; \( P = .019 \)). At the 30-day follow-up, patients in the enoxaparin group continued to fare better than did those in the UFH group for the primary endpoints of death, myocardial infarction (MI), and recurrent angina: 19.8% as compared to 23.3% (\( P = .016 \)). This benefit continued up to 1 year (Figure 2). The 30-day incidence of major bleeding complications was 6.5% in the enoxaparin group and 7.0% in the UFH group. The incidence of bleeding overall was significantly higher in the enoxaparin group (18.4% vs 14.2%, \( P = .001 \)), primarily because of ecchymoses at injection sites.

In the Thrombolysis in Myocardial Infarction (TIMI) 11B Trial, a randomized controlled trial with 3910 subjects, investigators reported that as early as 48 hours (the high-risk period preceding intervention or surgery), the group receiving enoxaparin experienced fewer recurrent ischemic events than did the group receiving UFH: 5.5% versus 7.3% (\( P = .026 \)). The primary endpoint (death, MI, or urgent revascularization) occurred by 8 days in 14.5% of patients in the UFH group and in 12.4% of patients in the enoxaparin group (\( P = .048 \)), and by 43 days in 19.7% of the UFH group and 17.3% of the enoxaparin group (\( P = .048 \)). During the first 72 hours and throughout the patients' entire initial hospitalization, there was no difference in the rate of major hemorrhage in the 2 treatment groups.

Both the ESSENCE and TIMI 11B trials demonstrate not only significant benefits in terms of overall efficacy with use of enoxaparin but also suggest an opportunity for significant cost benefits. The cost of enoxaparin therapy is approximately $64 per day, as compared to $500 to $1200 per day for GP IIb/IIIa
receptor blockers, and approximately $1500 per day for 1 stent. The results of the TIMI risk-score analysis provide a practical and useful tool for healthcare professionals seeing UA/NSTEMI patients in the emergency department for the first time (Figure 3). This simple prognostication scheme categorizes a patient’s risk for death and ischemic events and provides a basis for therapeutic decision making. The 7 TIMI risk-score predictor variables were 65 years or older, at least 3 risk factors for coronary artery disease, prior coronary stenosis of 50% or more, ST-segment deviation on electrocardiogram at presentation, at least 2 anginal events in prior 24 hours, use of aspirin in prior 7 days, and elevated serum cardiac markers. Event rates increased significantly as the TIMI risk score increased in the test cohort in TIMI 11B: 4.7% for a score of 0/1, 8.3% for 2, 13.2% for 3, 19.9% for 4, 26.2% for 5, and 40.9% for 6/7 (P <.001 by χ² for trend). The pattern of increasing event rates with increasing TIMI risk score was confirmed in all 3 validation groups (P <.001). The slope of the increase in event rates with increasing numbers of risk factors was significantly lower in the enoxaparin groups in both TIMI 11B (P =.01) and ESSENCE (P =.03), and there was a significant interaction between TIMI risk score and treatment (P =.02). This analysis demonstrates that in very-low-risk patients, efficacy of UFH and LMWH are comparable. However, in intermediate-risk patients, enoxaparin treatment appears to be more efficacious than does UFH treatment. What is even more compelling is that in the higher-risk groups, enoxaparin event rates are substantially lower than UFH event rates. The tool presented in Figure 3 allows clinicians to allocate the intensity of treatment relative to the acuity, offering a better sense as to when the use of newer therapies is most appropriate.

**Low-Molecular-Weight Heparin and Acute Coronary Syndromes**

Although many physicians are familiar with the GP IIb/IIIa receptor blockers as part of the drug arsenal for ACS, the original studies (PURSUIT and PRISM-PLUS) evaluated those drugs in combination with UFH. However, new data from the ACUTE study (presented at the American College of Physicians annual meeting in Philadelphia in April 2002) shows that use of the LMWH enoxaparin as the adjunct therapy to GP IIb/IIIa receptor blockers was very safe, with no liability in terms of major or minor bleeding. Moreover, total ischemic-event rates were significantly lower in the enoxaparin group (11.4%, N =315), as compared to the UFH group (20.5%, N =210; P =.02).

The INTERACT study also compared the safety and efficacy of LMWH to UFH as an adjunct to IIb/IIIa receptor blockers. That data was presented at the American College of Cardiology meeting in Atlanta in March 2002. Again, use of LMWH was associated with a lower bleeding-complication rate, as compared to UFH (5.3%, N =365 vs 8.5%, N =379 [P =.083]). Furthermore, LMWH was associated with a statistically significant reduction in death and recurrent ischemic events than was the traditional UFH/GP IIb/IIIa receptor blockade therapy: 5.0%, N =379 versus 9.0%, N =9.0 (P =.031). Findings from the ACUTE and INTERACT studies provide new medical evidence regarding the potential role of LMWH as an adjunct to GP IIb/IIIa receptor blockers.

It is always important for clinicians who are treating patients with ACS to determine whether drug choices are compatible with catheter laboratory situations, since many patients with cardiac problems eventually are referred there for additional intervention. The LMWHs have a rapid onset of action and sustain

![Figure 3. ESSENCE: Validation and Treatment Interaction](image-url)
a relatively therapeutic level of anti-Xa activity for 12 hours following administration of the drug. More importantly, the first 1 hour to 8 hours of drug action represent peak anti-Xa activity, with a uniform antithrombotic pattern. Such uniformity of action suggests that when a patient who receives LMWH is referred to the catheter laboratory, it is not necessary to switch to UFH therapy—a switch that would delay the intervention. Moreover, if it is necessary to neutralize the effects of LMWH, protamine does so by approximately 50% to 60%.

Dalteparin is another LMWH that is FDA approved for use in UA. In clinical trials, dalteparin is comparable in efficacy to UFH, whereas enoxaparin trials have demonstrated superior efficacy over UFH, as illustrated in Figure 4.

The final element in the clinical strategy for patients with UA is recognition of a duality of approach, beginning with intensive medical therapy (with either aspirin and the LMWHs, either of the GP IIb/IIIa receptor blockers, clopidogrel as clinically indicated) and coupled with early invasive therapy. As demonstrated in the TIMI 18 trial, this approach is now considered the standard of care (Figure 5). The SYNERGY trial, which is currently underway, is randomly assigning 8000 patients to either LMWH therapy or UFH in the setting of early invasive treatment.

**Conclusion**

There is substantial evidence that cardiac catheterization is safe in patients receiving LMWH for ACS. Concerns regarding the transition of these patients from the medical service to the cardiac catheterization laboratory should not impede the upstream use of LMWH. Clinical trials with enoxaparin indicate that LMWHs are effective and safe as adjunctive therapy in patients undergoing percutaneous coronary intervention, with or without the use of GP IIb/IIIa receptor antagonists. Initial results of investigations of the role of enoxaparin in the management of ST-elevation MI indicate that by substituting LMWH or abciximab as the adjunctive therapy, the composite recurrent ischemic-event rate can be reduced by an absolute rate of 4% or more. This is a major step forward, and in the future, enoxaparin may replace UFH as adjunctive therapy in thrombolytic regimens that incorporate both fibrin-specific agents (alteplase and tenecteplase) and

**Figure 4. Treatment of UA/NSTEMI with LMWH: Composite Endpoints at 14 Days**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Risk Ratio (RRR)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRAXIS II (nadroparin)</td>
<td>3.9%</td>
<td>NS</td>
</tr>
<tr>
<td>FRIC IV (dalteparin)</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI IIb (enoxaparin)</td>
<td>-14.9%</td>
<td>P = .03</td>
</tr>
<tr>
<td>ESSENCE (enoxaparin)</td>
<td>-16.2%</td>
<td>P = .02</td>
</tr>
</tbody>
</table>

UA = unstable angina; NSTEMI = non-ST-elevation myocardial infarction; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin. Reprinted with permission from reference 13.

**Figure 5. TACTICS-TIMI 18**

UA or NSTEMI → ASA, UFH, tirofiban → Baseline troponin → Early conservative → Medical Rx → ETT + Ischemia → Cath PCI/CABG → PCI/CABG;

UA = unstable angina; NSTEMI = non-ST-elevation myocardial infarction; ASA = aspirin; UFH = unfractionated heparin; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; ETT = exercise treadmill testing. Reprinted with permission from reference 3.
streptokinase-based regimens. This further supports the clinical evidence presented here, suggesting that internists should be comfortable using LMWH in a broad spectrum of ACS patients.

REFERENCES


