Future Prospects in the Management of Acute Coronary Syndrome and Thrombosis

2006 Update Newsletter

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This activity has been designed to meet the educational needs of registered nurses involved in the management of patients with acute coronary syndrome.

Coryonary heart disease is the leading cause of death in the United States, accounting for more than 500,000 deaths annually. Acute coronary syndrome (ACS) is a constellation of clinical symptoms related to acute myocardial infarction. ACS represents a spectrum of life-threatening disorders that are a major cause of emergency medical care and hospitalizations in the US. Annually, an estimated 2 million Americans are admitted to the hospital with acute myocardial infarction, and more than 250,000 others die before reaching a hospital, within 1 hour of the onset of symptoms.

Despite the use of aspirin, heparin, and anti-ischemic therapy, current research has shown that the prognosis of patients presenting with ACS remains poor. Within 4 to 6 weeks of presentation, the risk of death or myocardial infarction is 8% to 14%. The rate of death, MI, or refractory ischemia is even more excessive (approximately 15% to 25%). Advances in the understanding of the pathophysiology of ACS and thrombosis have led to the development of novel therapeutic agents and treatment strategies that hold promise for better clinical outcomes. Trials investigating the use of antithrombotics in patients with ACS are currently comparing the efficacy of new and established agents in preventing death, myocardial infarction, and refractory ischemia.

The educational goal of this program is to increase awareness of the results of recent research on how antithrombotic medications in the management of patients with, or at risk for, ACS.

PURPOSE
To increase awareness of the results of recent research on use of antithrombotic medications in the management of patients with, or at risk for, acute coronary syndrome.

LEARNING OBJECTIVES
After completing this activity, the participant should be better able to:

- List the cornerstone of current treatment and the recommended use of antithrombotic therapies for UA/NSTEMI
- Implement the treatment recommendations from the ACC/AHA guidelines on UA/NSTEMI
- Discuss recent clinical trials, ongoing studies, and their impact on clinical practice in patients with UA/NSTEMI
- Identify strategies for preventing bleeding events to maximize the substantial health and cost benefits of antithrombin therapy

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4. Review the evaluation form with answer key to Postgraduate Institute for Medicine.
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INTRODUCTION
Patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) continue to experience an unacceptably high incidence of both short- and long-term adverse outcomes. Emerging alternatives to standard periprocedural anticoagulation with unfractionated heparin (UFH) include low-molecular-weight heparins (LMWHs), factor Xa inhibitors, and direct thrombin inhibitors. This issue examines new clinical trial evidence supporting the use of different agents in acute cardiovascular care, such as enoxaparin, the most commonly used LMWH; fondaparinux, a factor Xa inhibitor; and bivalirudin, a direct thrombin inhibitor.

CONSERVATIVE VS EARLY INVASIVE STRATEGIES
Treatment decisions for patients hospitalized with non–ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA) typically involve 2 therapeutic approaches: conservative or early invasive therapy. A recent meta-analysis of 7 UA/NSTEMI clinical trials—TIMI IIIB, VANQWISH, MATE, FRISC II, TACTICS, VINO, and RITA 3—showed that early invasive therapy yielded an 18% lower risk of death or MI compared with conservative therapy \( P=0.001 \). Improving the overall risk-benefit profile of UA/NSTEMI interventions is an important goal for new treatment strategies.

OPTIONS FOR UPSTREAM ANTITHROMBOTIC THERAPY DURING EARLY INVASIVE TREATMENT
Enoxaparin

Two pivotal clinical trials established that enoxaparin is at least as effective as UFH in the treatment of UA/NSTEMI. The A to Z trial compared enoxaparin with UFH in NSTEMI patients receiving tirofiban and aspirin. The primary endpoint (death, MI, or refractory ischemia at 7 days) for enoxaparin and UFH was 8.4% vs 9.4%, respectively, confirming the noninferiority of enoxaparin. Although clinically significant bleeding was slightly increased with enoxaparin (3.3% vs 2.0%, \( P=0.13 \)), a worst-case analysis for Thrombolysis in Myocardial Infarction (TIMI) major bleeding suggested an increased frequency of 1 event in 200 patients treated with enoxaparin.

The SYNERGY trial compared enoxaparin with UFH in high-risk NSTEMI patients treated with an early invasive strategy. The primary endpoint of death or MI at 30 days was similar in both treatment groups, although bleeding rates were elevated in enoxaparin-treated patients (Table 1). In a long-term follow-up of the SYNERGY trial, the results persisted at 6 months and 1 year, with similar death rates in the 2 treatment groups. Approximately 47% of SYNERGY patients underwent PCI during their initial hospitalization. No differences in ischemic events, such as abrupt closure, threatened abrupt closure, unsuccessful PCI, or emergency coronary artery bypass graft (CABG) surgery, were reported during PCI between patients treated with enoxaparin and UFH.

In a meta-analysis of the A to Z, SYNERGY, and 4 older trials (ESSENCE, TIMI 11B, ACUTE II, and INTERACT), enoxaparin was superior to UFH in the acute treatment of ACS patients. Overall, enoxaparin significantly reduced the composite endpoint of death or MI (OR=0.91; 95% CI, 0.83-0.99) without excessive risk of major bleeding or need for transfusion. The 2002 ACC/AHA guidelines provide a class Ia recommendation that enoxaparin is the preferred agent over UFH for the treatment of UA/NSTEMI when CABG is planned within 24 hours.

Fondaparinux

The OASIS-5 trial demonstrated that fondaparinux provides similar short-term efficacy compared with enoxaparin, but with a dramatic reduction in bleeding risk. A total of 20,078 UA/NSTEMI patients were randomized to fondaparinux or enoxaparin for a mean of 6 days. Patients also received background therapy, which could include aspirin, clopidogrel, glycoprotein (GP) IIb/IIIa inhibitors, and revascularization procedures.

The primary composite endpoint of death, MI, or refractory ischemia at 9 days occurred in 5.8% of fondaparinux recipients and 5.7% of enoxaparin recipients, demonstrating the noninferiority of fondaparinux. At 1 month, fondaparinux reduced mortality by 17% compared with enoxaparin \( P=0.02 \), a benefit that was maintained at 6 months \( P=0.05 \). Fondaparinux also reduced the risk of major bleeding at 9 days by 48% compared with enoxaparin (2.2% and 4.1%, respectively; \( P=0.001 \)). The composite of death, MI, refractory ischemia, and bleeding was 19% lower in the fondaparinux group compared with enoxaparin \( P<0.001 \) at 9 days and for the remainder of the study period.

In the OASIS-5 trial, 39.5% of patients in both treatment groups underwent PCI within the first 8 days of randomization. Outcomes for these patients demonstrated similar efficacy, but with a substantially lower rate of major bleeding, including significant reductions in pseudoaneurysms and large hematomas. Catheter-related thrombi were observed in both the enoxaparin and the fondaparinux groups; however, both groups had substantial reductions when open-label UFH was used, and showed no significant increase in bleeding in that scenario. In the enoxaparin group, UFH was given 6 hours after the last subcutaneous (SQ) dose, and there was only 1 catheter-related thrombus. In the

### TABLE 1

<table>
<thead>
<tr>
<th>EVENT, % OF PATIENTS</th>
<th>UFH (N=4985)</th>
<th>ENOXAPARIN (N=4993)</th>
<th>( P ) VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or MI</td>
<td>14.5</td>
<td>14.0</td>
<td>.40</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>7.6</td>
<td>9.1</td>
<td>.008</td>
</tr>
<tr>
<td>GUSTO severe bleeding</td>
<td>2.2</td>
<td>2.7</td>
<td>.08</td>
</tr>
<tr>
<td>Transfusions</td>
<td>16.0</td>
<td>17.0</td>
<td>.16</td>
</tr>
</tbody>
</table>
fondaparinux group, when open-label UFH was given (mean dose >5000 U), only 1 case was reported.7 Thus, the use of UFH during PCI appeared safe, and largely avoided risk of catheter-related thrombus in subjects in the overall study group (Table 2).

It is therefore recommended that fondaparinux be used as upstream therapy, as it appears to be safer than enoxaparin.7 If PCI is performed, standard anticoagulation with UFH, a GP IIb/IIIa antagonist, or bivalirudin should be used according to current standard practice.

**Bivalirudin**

ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) is a prospective, randomized trial presented at the ACC (not yet published) of anticoagulation regimens in 13,819 patients with moderate- to high-risk UA or NSTEMI undergoing early invasive therapy. Patients were randomized to 1 of 3 treatment groups8:

- Heparin (UFH or enoxaparin) + GP IIb/IIa inhibitors9
- Bivalirudin + GP IIb/IIa inhibitors9
- Bivalirudin monotherapy9

All patients were to receive angiography within 72 hours of enrollment and additional therapy—medical management, PCI, or CABG—at the treating physician’s discretion. The primary endpoint was composite net clinical benefit at 30 days, which included an ischemic composite (death, MI, or unplanned revascularization for ischemia) and major bleeding. In 2 separate analyses, ACUITY compared bivalirudin with and without GP IIb/IIa inhibition with heparin + GP IIb/IIa inhibition.8 In the first comparison, there was no difference in ischemic events between patients managed with early invasive therapy. Costs of anticoagulation therapy include not only therapeutic agents, but also resource utilization and the procedural complications (eg, bleeding during hospital stays and follow-up care).10

The REPLACE-2 study highlighted the important cost implications of different treatment strategies in ACS patients managed with early invasive therapy. Costs of anticoagulation therapy include not only therapeutic agents, but also resource utilization and the procedural complications (eg, bleeding during hospital stays and follow-up care).10

**PUTTING EVIDENCE INTO PRACTICE**

**Cost Implications**

The REPLACE-2 study highlighted the important cost implications of different treatment strategies in ACS patients managed with early invasive therapy. Costs of anticoagulation therapy include not only therapeutic agents, but also resource utilization and the procedural complications (eg, bleeding during hospital stays and follow-up care).10

In the REPLACE-2 economic analysis, 4651 patients undergoing PCI were randomized to receive either bivalirudin + provisional GP IIb/IIa (n=2319) or heparin + routine GP IIb/IIa (n=2332).10 The total costs associated with the invasive procedure, hospital stay, and 30-day follow-up care were lower in the bivalirudin group ($10,561 ± $6267) vs the heparin group ($10,996 ± $6524; P<.001).10

The cost savings associated with bivalirudin therapy compared with heparin therapy were due mostly to the reduction in bleeding events. Approximately 60% of all complication-related costs in patients undergoing PCI were associated with hemorrhagic events and related outcomes, such as thrombocytopenia.10 Costs associated with each major and minor bleeding

**TABLE 2**

<table>
<thead>
<tr>
<th>OUTCOME, % OF PATIENTS</th>
<th>ENOXAPARIN (n=3104)</th>
<th>FONDAPARINUX (n=3135)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedural Complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Events at 9 Days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5.0</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Major bleed</td>
<td>5.1</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Death/MI/STROKE/major bleed</td>
<td>10.3</td>
<td>8.2</td>
<td>.003</td>
</tr>
<tr>
<td><strong>Any procedural complication, major bleeding, death, MI, or stroke</strong></td>
<td>20.6</td>
<td>16.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Clinical Events at 30 Days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2.1</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5.4</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Major bleed</td>
<td>5.4</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Death/MI/STROKE/major bleed</td>
<td>11.7</td>
<td>9.5</td>
<td>.004</td>
</tr>
</tbody>
</table>
Dosing Considerations

Appropriate dosing of antithrombotic therapy is critical to achieving optimal outcomes in patients with ACS (Table 3). A recent analysis of antithrombotic treatment practices showed that 42% of NSTEMI patients who were treated with at least 1 antithrombotic agent received a dose outside the recommended range.11 Excess doses were administered to 32.8% of patients treated with UFH, 13.8% treated with LMWH, and 26.8% treated with GP IIb/IIIa inhibitors.11

Compared with patients who did not receive excess doses, patients treated with extra UFH, LMWH, and GP IIb/IIIa inhibitors had elevated risks for major bleeding (8%, 39%, and 36%).11 Approximately 15% of major bleeding in this study was attributable to excess dosing.11 Mortality and length of stay were significantly higher among those patients administered excess dosing.11

Summary

Antithrombotic treatment options for patients with ACS are continuously evolving in patients with ACS. Compared with UFH, enoxaparin reduces the risk of death or MI while maintaining a similar risk of major bleeding or need for transfusion.5 Fondaparinux is similar to enoxaparin over the short term in preventing ischemic events among patients with NSTEMI, but is associated with even less bleeding—a benefit that translates into decreased long-term morbidity and mortality.7 Bivalirudin monotherapy is emerging as another alternative to heparin (UFH or enoxaparin) + GP IIb/IIIa inhibition. It produced a greater net clinical benefit with fewer adverse events,8 but the drug was not superior to treatment with heparin/enoxaparin in patients receiving IIb/IIIa inhibitors.8

Convenience should be balanced against the modest increase in major bleeding associated with current antithrombotic therapy. With more than 1 million patients hospitalized due to NSTEMI annually, minimizing bleeding events in this population would yield substantial health and cost benefits.11 As shown in REPLACE 2, a reduction in bleeding events translates to a reduction in costs.10 Careful attention to antithrombotic dosing may also prevent bleeding complications.

Table 3: Antithrombotic Dosing for Patients With NSTEMI

<table>
<thead>
<tr>
<th>AGENT</th>
<th>DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>• 1 mg/kg SC q12h</td>
</tr>
<tr>
<td></td>
<td>• Dose reduction by 50% if creatinine clearance is &lt;30 mL/min by increasing dosing interval to q24h</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>• 2.5 mg/kg OD until discharge from hospital, or up to 8 days, whichever occurs first</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>• 0.10 mg/kg bolus, then 0.25 mg/kg/h continued throughout angiography</td>
</tr>
<tr>
<td></td>
<td>• For PCI, give additional bolus of 0.50 mg/kg and increase the infusion to 1.75 mg/kg/h</td>
</tr>
<tr>
<td></td>
<td>• Post-PCI infusion: None recommended</td>
</tr>
<tr>
<td></td>
<td>• 0.25 mg/kg/h for 4–12 h at operator’s discretion in the absence of GP IIb/IIIa infusion</td>
</tr>
<tr>
<td></td>
<td>• Staged PCI procedure before discharge from hospital. If still on maintenance infusion of 0.25 mg/kg/h, dose additional bivalirudin as above</td>
</tr>
<tr>
<td></td>
<td>• If maintenance infusion discontinued, dose 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h IV infusion during PCI</td>
</tr>
<tr>
<td></td>
<td>• If medical treatment, either none or 0.25 mg/kg/h for up to 72 h (or longer if necessary) at physician’s discretion</td>
</tr>
</tbody>
</table>

Event were $6300 and $396, respectively.10 Although the cost of each minor bleeding event may be modest, additive costs were substantial; 25% of all heparin-treated patients experienced a minor bleeding event.10 Avoiding bleeding complications is therefore an important goal both for improving patient well-being and containing healthcare costs.

REFERENCES

FUTURE PROSPECTS IN THE MANAGEMENT OF ACUTE CORONARY SYNDROME AND THROMBOSIS

POSTTEST

1. In a meta-analysis of UA/NSTEMI trials, early invasive therapy reduced the risk of death or MI compared with conservative therapy. A. True B. False

2. A meta-analysis of the A to Z, SYNERGY, and other trials found which of the following benefits of enoxaparin compared with UFH in patients with UA/NSTEMI: A. Reduction in death or MI B. No elevated risk of bleeding C. No elevated transfusion rate D. All of the above

3. In the 2002 ACC/AHA guidelines, enoxaparin is listed as the preferred agent over UFH for patients with UA/NSTEMI, with the exception of those who are scheduled to undergo CABG therapy within 24 hours. A. True B. False

4. The OASIS-5 trial demonstrated which of the following benefits of fondaparinux compared with enoxaparin in patients with UA/NSTEMI: A. A nearly 50% reduction in the risk of bleeding at 9 days B. A reduction in mortality at 1 month

5. In patients undergoing PCI during the study treatment period in OASIS-5: A. There was a nearly 50% reduction in major bleeding with fondaparinux B. Fondaparinux significantly reduced pseudoaneurysms C. Fondaparinux significantly reduced large hematomas D. Fondaparinux was superior to enoxaparin in reducing any PCI-related complication, death, MI, or stroke compared with enoxaparin

6. In the ACUITY trial, which of the following treatments was shown to have the least net clinical benefit in patients with high-risk UA/NSTEMI: A. Heparin (UFH or enoxaparin) + GP IIb/IIIa inhibitors B. Bivalirudin + GP IIb/IIIa inhibitors C. Bivalirudin monotherapy

7. In the REPLACE-2 trial, 60% of all complication-related costs in patients undergoing PCI were associated with bleeding events and related outcomes, such as thrombocytopenia. A. True B. False

8. In the REPLACE-2 trial, the average cost related to a major bleeding event was: A. $63 B. $630 C. $6300 D. None of the above

9. Excessive dosing of UFH, LMWH, and GP IIb/IIIa inhibitors can lead to which of the following adverse outcomes in patients with NSTEMI: A. Increased bleeding B. Increased mortality C. Increased length of stay D. All of the above

10. Which of the following is an inappropriate dose for antithrombotic therapy in patients with NSTEMI? A. Enoxaparin 1 mg/kg SC q12h B. Fondaparinux 2.5 mg, OID until discharge from hospital, or for up to 8 days C. Bivalirudin 0.10 mg/kg bolus, then 0.25 mg/kg/h continued throughout angiography D. All of the above are appropriate

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2. Upon completion of this activity, participants should be better able to:
   a. List the cornerstones of current treatment and the recommended use of antithrombotic therapies for UA/NSTEMI
   b. Discuss the treatment recommendations from the ACC/AHA guidelines on UA/NSTEMI
   c. Discuss recent clinical trials, ongoing studies and their impact on clinical practice in patients with UA/NSTEMI
   d. Identify strategies for preventing bleeding events to maximize the substantial health and cost benefits of antithrombin therapy

3. Overall Effectiveness of the Activity.
   a. Was timely and will influence how I practice
   b. Will assist me in improving patient care
   c. Fulfilled my educational needs
   d. Avoided commercial bias or influence

4. Impact of the Activity.
   a. The information presented… (select all that apply)
   b. Will the information presented cause you to make any changes in your practice?

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   YES, I would be interested in participating in a follow-up survey
   NO, I'm not interested in participating in a follow-up survey

Additional comments about this activity:

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1: [ ] 2: [ ] 3: [ ] 4: [ ] 5: [ ] 6: [ ] 7: [ ] 8: [ ] 9: [ ] 10: [ ]

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