Use of Direct Thrombin Inhibitors for Treating Non-ST-Segment Elevation Acute Coronary Syndromes in Special Patient Groups: Women, Diabetics, the Elderly, and Chronic Renal Insufficiency

NEW CONCEPTS AND EMERGING TECHNOLOGIES FOR EMERGENCY PHYSICIANS

Dear Colleagues:

Antithrombin and antiplatelet therapies remain the foundation for the treatment of patients with NSTE ACS. Special groups including women, elderly, diabetics and those with chronic renal insufficiency represent a particular challenge for the clinician evaluating and treating these patients. These individuals are at high risk for ischemic complications including death, myocardial infarction, and unplanned intervention. Typically such patients are under-treated with antithrombins and antiplatelet agents because of an appropriate fear of bleeding complications, resulting in the significant proportion of these patients having ischemic adverse events.

The ACUITY trial was recently published and represents the evaluation of a direct thrombin inhibitor, bivalirudin, in patients with moderate to high risk NSTE ACS undergoing cardiac catheterization. Currently bivalirudin is the only direct thrombin inhibitor FDA approved for use in the cardiac catheterization laboratory. Dr. James Hoekstra, Professor and Chairman of the Department of Emergency Medicine at Wake Forest University, provides a targeted review of the results of the ACUITY trial with particular emphasis on the high risk populations – women, elderly, diabetics, and patients with chronic renal insufficiency. In addition, he describes the findings of ACUITY in relation to therapy “switch”, when patients were initially treated with heparins prior to randomization. Emergency physicians are increasingly becoming exposed to a greater variety of therapies for patients with acute coronary syndrome. It is our hope to provide you, the practicing clinician, with the educational tools to continue to give outstanding care to your patients.

Sincerely,

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Objectives:
1. Describe the mechanism of action of bivalirudin in non-ST-segment elevation acute coronary syndromes (NSTE ACS).
2. Describe the ACUITY trial, and the application of its results for the treatment of NSTE ACS
3. Discuss the increased risk of bleeding and ischemic adverse outcomes in high risk patients such as women, diabetics, the elderly, and patients with chronic renal insufficiency.
4. Discuss the effectiveness of bivalirudin in special high risk NSTE ACS populations.

Introduction

Antiplatelet and antithrombin therapies including aspirin, clopidogrel, unfractionated heparin (UFH), low molecular weight heparin (LMWH), and glycoprotein IIb/IIIa inhibitors (GPI) have been considered standard therapy in the emergency department (ED) for patients with high-risk non-ST-segment elevation acute coronary syndromes (NSTE ACS). The pharmacologic effects of these therapies increase the risk of bleeding, especially in the cardiac catheterization laboratory, and particularly in certain patient populations like women, the elderly, diabetics, and patients with chronic renal insufficiency (CRI). Because these same patient populations are also at high risk for adverse ischemic outcomes, antithrombotic treatments must be critically evaluated in these patients to assure a balance between efficacy and safety. Bivalirudin, a new direct thrombin inhibitor, has been shown to markedly reduce bleeding in NSTE ACS patients treated

Peer Reviewer for Industry Bias: W. Frank Peacock, MD, Associate Professor and Director of Research, The Cleveland Clinic Foundation, Department of Emergency Medicine, Cleveland, OH
with an invasive strategy.\textsuperscript{3} It has enjoyed relatively widespread use in the catheterization laboratory, and has been recently investigated in moderate to high risk NSTE ACS patients in the ACUITY trial.\textsuperscript{4,5} This review will discuss the pharmacology and clinical applicability of a direct thrombin inhibitor in high risk NSTE ACS, especially as it relates to the ED management of women, diabetics, the elderly, and patients with CRI.

**High Risk NSTE ACS Patient Populations and Bleeding in the Catheterization Laboratory**

Given the overall improvement in reducing ischemic endpoints with an early invasive strategy in the treatment of NSTE ACS, contemporary anticoagulant trials have begun to focus on efficacy versus safety issues.\textsuperscript{6} Benefits of antithrombotic therapy in reducing death and recurrent myocardial infarction (MI) must be balanced against the risks of bleeding complications, blood transfusions, and potential harm from improper dosing. Special populations such as women, diabetics, the elderly, and patients with CRI have been shown to have worse ischemic outcomes as well as higher bleeding rates in numerous clinical trials and in the CRUSADE registry.\textsuperscript{7,12} Antithrombotic therapy places these patients at risk from both under-treatment, as well as overtreatment. A recent analysis of more than 34,000 NSTE ACS patients in the Population Health Research Institute database demonstrated that major bleeding was associated with an increase in risk-adjusted 30-day mortality (HR = 5.37, 95\% CI 3.9-7.3, p<0.0001). Similarly, an analysis of the GUSTO 2, PURSUIT, and PARAGON trial populations by Rao identified transfusions as an independent predictor of mortality (OR 3.94, 95\% CI 3.26-4.75).\textsuperscript{7,8} Finally, the CRUSADE registry identified that overdosing of antithrombin and antiplatelet agents is significantly more common in elderly patients and those with CRI, and that overdosed patients had significantly higher rates of transfusions and ischemic adverse outcomes.\textsuperscript{11} These data illustrate the need to identify antithrombotic regimens which reduce bleeding and transfusion rates while maintaining ischemic efficacy in the treatment of NSTE ACS.

**Bivalirudin in Moderate to High Risk NSTE ACS**

NSTE ACS is caused by coronary artery endothelial disruption, typically from a ruptured atheromatous plaque, triggering activation of both platelets and the coagulation cascade. Multiple interactions between the coagulation proteins, cellular components, and the vessel wall result in a series of reactions leading to the production of Factor Xa and eventually thrombin. Simultaneously, activated platelets aggregate within a meshwork of cross-linked fibrin to form a thrombus that impedes epicardial coronary blood flow. Bivalirudin inhibits both circulating and fibrin-bound thrombin, resulting in inhibition of the coagulation process and platelet activation. Bivalirudin has gained increased use in the cardiac catheterization laboratory due to its predictable dose-response anticoagulant effect, lack of need for monitoring, and lack of concern for heparin-induced thrombocytopenia (HIT) and heparin-induced thrombosis syndrome (HITTS), as platelet antibodies are not formed. Bivalirudin has a short half-life, with diminution of effects within one hour after drug discontinuation. This characteristic allows early removal of the catheter sheath in the cardiac catheterization laboratory, and reduced bleeding complications compared to longer half-life anticoagulants.

In the Acute Catheterization and Urgent Intervention Triage Strategy Trial (ACUITY), NSTE ACS patients were assigned in an open-label, randomized fashion to one of three treatment arms: “heparin” (either UFH or enoxaparin) + GPI, bivalirudin + GPI, or bivalirudin alone (with provisional GPI use). The ACUITY arms are illustrated in Figure 1.\textsuperscript{4} Patients in the ACUITY trial were considered “moderate to high risk” for adverse outcomes, with inclusion criteria including elevated troponin or CK-MB, ischemic electrocardiographic changes (ST-segment depression or transient ST-segment elevation), TIMI score ≥4, or known coronary artery disease. Ninety-nine percent of patients in the ACUITY trial underwent cardiac catheterization, and the majority were treated with a reperfusion strategy including percutaneous coronary intervention or coronary artery bypass grafting. The primary outcome of the trial was the “net clinical benefit” (death, MI, unplanned revascularization, and major bleeding) at 30 days.\textsuperscript{5}
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The overall results of the ACUITY trial demonstrated the efficacy of bivalirudin alone in reducing ischemic events (death, MI, unplanned revascularization) and bivalirudin was non-inferior to the combination of “heparins” + GPI (7.8% vs. 7.3%, OR = 1.08, 95% CI = 0.93-1.24) (Figure 2). With almost 50% less bleeding in patients treated with bivalirudin alone, the net clinical benefit (efficacy + safety) was found to be superior in the bivalirudin monotherapy cohort compared to “heparins” + GPI (10.1% vs 11.7%, OR = 0.86, 95%CI 0.77-0.97) (Figure 2). The authors concluded that bivalirudin alone was superior to “heparins” + GPI in the treatment of moderate to high risk NSTE ACS.

The ACUITY trial has been criticized because of its fairly liberal definition of bleeding. The ACUITY trial used its own pre-specified definition of bleeding, rather than the traditional TIMI or GUSTO bleeding scales (Table 1). Most notably, this included the presence of a 5 cm hematoma at the catheterization site as a “major bleed.” There was uniformly less bleeding with bivalirudin in ACUITY regardless of the bleeding definition, but the degree of reduction in bleeding with bivalirudin may have been overstated with the use of this bleeding definition.

Bivalirudin in NSTE ACS Special Populations

While the primary results of ACUITY were promising, questions remained regarding the efficacy versus safety of bivalirudin in NSTE ACS special populations. In the overall ACUITY trial, consistent with other NSTE ACS trials, women, diabetics, the elderly, and patients with CRI all had higher incidences of ischemic adverse outcomes (death, MI, unplanned intervention). Similarly, female sex, diabetes, advanced age (≥75 years of age) and CRI (creatinine clearance <60 ml/min) were found to be independent predictors of major bleeding (Figure 3), and advanced age (OR 2.55, 95% CI 1.68-3.87) and major bleeding (OR 7.55, 95% CI 4.68-12.18) were found to be independent predictors of mortality in the PCI population of the ACUITY trial.
When special populations of the ACUITY trial are analyzed separately, the advantages of bivalirudin therapy, especially as it relates to decreasing bleeding, are evident (Figure 4). These results have been presented at national meetings, and in the cardiology literature. In ACUITY, 4157 (30.1%) of the patients enrolled were women, and in these patients, despite higher overall rates of ischemia and bleeding, bivalirudin resulted in a significant decrease in major hemorrhage, with no increase in ischemic outcomes, when compared to heparin plus GPI. The resulting net clinical benefit (ischemia plus bleeding) of bivalirudin in women was improved, although not to a statistically significant level (11.6% versus 13.5% (p= 0.12)) (Figure 4). In 2137 diabetics in ACUITY who underwent PCI, major hemorrhage was reduced from 7.1% with heparin + GPI to 3.7% with bivalirudin alone (p<0.001), while ischemic outcomes were sustained at an equivalent rate (9.5% with hep + GPI versus 8.3% with bivalirudin (p=0.42)). With regard to the elderly, in 1376 ACUITY patients 75 years or older who underwent PCI, bivalirudin resulted in a significant reduction in bleeding (6.1% versus 12.3% (p,0.001)) and equivalent ischemic outcomes (12.2% versus 11.0% (p=0.56)) when compared to heparin + GPI. In 2,468 ACUITY patients with CRI, treatment with bivalirudin resulted in a significant reduction in major bleeding (6.2% versus 9.8% (p<0.001)), and equivalent ischemic outcomes (11.1% versus 9.2% (p= 0.425)) (Figure 5). In each of these high risk patient groups, the pattern of benefit of bivalirudin over heparins plus GPI remained consistent - bivalirudin reduced bleeding while maintaining ischemic efficacy. Given the high incidence of catheter-related bleeding in these high risk groups, and the association of bleeding to mortality, the use of bivalirudin in the cardiac catheterization laboratory for NSTE ACS has increased.

Choosing the Optimum Anticoagulant Regimen for NSTE ACS Special Populations: Can a Switch in Therapy at the Time of Catheterization be Performed?

Although the choice of anticoagulant in the ED begins with consideration of efficacy and safety issues as discussed above, practical concerns regarding cardiac catheterization laboratory compatibility, dosing simplicity, switching anticoagulants, and cost also merit evaluation. The optimal anticoagulant should reduce ischemic endpoints while maintaining safety, and allow for a seamless transition between ED-initiated medical management of NSTE ACS and cardiology-based PCI therapy. Often this therapeutic approach is not possible, however, due to differing antithrombotic choices pre-catheterization versus during PCI. At present, bivalirudin is not FDA approved for pre-catheterization medical management, and experience with bivalirudin in the ED is minimal. In the ACUITY trial, the majority of high risk NSTE ACS patients were treated in the ED or CCU with heparin or enoxaparin prior to randomization to study drug. In CRUSADE, approximately 83% of patients with high risk NSTE ACS were treated with either UFH or enoxaparin in the first 24 hours. For a patient who has been started on UFH or enoxaparin in the ED, is it safe to switch to bivalirudin in the cardiac catheterization laboratory? Given the bleeding reduction advantages of bivalirudin in high risk patients noted above, this strategy may have significant advantages.
With enoxaparin or UFH, switching or stacking anticoagulants was shown in the SYNERGY trial to result in an increase in both catheter-related bleeding and adverse ischemic outcomes. With bivalirudin, however, this may not be the case. A recent subanalysis of patients in the ACUITY trial showed that patients who were begun on a “heparin”, and then switched at randomization to bivalirudin, did not demonstrate any deleterious bleeding effects. As can be seen in Figure 6, patients who were switched from UFH or enoxaparin to bivalirudin at the time of randomization did not experience an increase in either bleeding or ischemic events. In fact, they experienced less bleeding, with sustained ischemic outcomes. In a similar analysis, the group that had the best results with the ACUITY randomization switches was the consistent therapy group, who were started on bivalirudin as their initial antithrombin, and did not have to be switched from another antithrombin to bivalirudin. It appears from these data that switching from UFH or enoxaparin to bivalirudin is a viable option in the care of NSTE ACS patients.

Conclusions

The direct thrombin inhibitor bivalirudin has the potential to significantly improve the care of patients with NSTE ACS. The major benefit of bivalirudin in NSTE ACS is a reduction in bleeding, especially in the cardiac catheterization laboratory, where bleeding has been strongly associated with mortality. Women, diabetics, the elderly, and patients with chronic renal failure are at risk for high rates of ischemia as well as bleeding during the course of NSTE ACS. Tailoring antithrombin agents in the cardiac catheterization laboratory as well as “upstream” in the ED may reduce the risk of bleeding, while maintaining ischemic efficacy. For patients at high risk for bleeding, bivalirudin may be the prudent choice as an antithrombin agent in these high risk patients, where bleeding is an issue. Emergency physicians should familiarize themselves with this drug, and its applicability in high risk patients, when developing protocols for the treatment of NSTE ACS patients in their institutions.

REFERENCES


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CME Post Test

After you have read the monograph carefully, record your answers by circling the appropriate letter answer for each question.

1. Which of the following patient populations is at increased risk of adverse outcomes with NSTE ACS?
   a. Male sex     d. a and c
   b. Female sex   e. b and c
   c. Diabetics

2. Which of the following NSTE ACS adverse outcomes are increased in patients with chronic renal insufficiency?
   a. Recurrent myocardial infarction
   b. Cardiovascular death
   c. Major Bleeding
   d. All of the above

3. According to the CRUSADE Initiative, which of the following patient groups is not typically at risk for overdosing of antithrombin and antiplatelet agents in NSTE ACS?
   a. Male sex     c. Female sex
   b. Age > 75      d. Diabetics

4. Which of the following pharmacologic properties of bivalirudin is advantageous in the cardiac catheterization laboratory for the treatment of NSTE ACS?
   a. Short half-life
   b. Lack of formation of heparin-induced platelet antibodies
   c. Predictable dose response
   d. All of the above

5. Which of the following statements is true regarding catheter-related bleeding in patients with NSTE-ACS?
   a. Catheter-related bleeding is not associated with long term mortality
   b. Catheter-related bleeding is more common in young patients.
   c. Catheter-related bleeding is not related to appropriate dosing of antithrombins
   d. Catheter-related bleeding is associated with mortality

6. Based on the ACUITY trial, which of the following is the major advantage of bivalirudin compared to heparin plus GPI in women, diabetics, the elderly, and patients with CRI?
   a. Bivalirudin is associated with more bleeding than heparin + GPI
   b. Bivalirudin is superior to heparin + GPI at reducing ischemic outcomes
   c. Bivalirudin reduces bleeding while maintaining ischemic efficacy compared to heparin + GPI
   d. Bivalirudin is less expensive than heparin.

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