

Direct Thrombin Inhibitors in Non-ST-segment Elevation Acute Coronary Syndromes

Dear Colleagues,

For patients with non-ST-segment elevation acute coronary syndrome (NSTEMI/ACS) presenting to the emergency department, appropriate anti-thrombotic and anti-platelet therapy is critical to optimize outcome. Unfractionated heparin is often given as an anti-thrombin in this setting, however, it suffers from a number of pharmacologic limitations including non-specific binding, the requirement for frequent monitoring of its anti-coagulant effect, and the formation of antibodies to the heparin/platelet factor 4/platelet complex which can cause heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia thrombosis syndrome (HITS). Low molecular weight heparins, also an indirect thrombin inhibitor, can be used without monitoring their anti-thrombin effects. Ease of use and effectiveness makes them a popular choice in the emergency setting.

In this EMCREG-International Newsletter, Dr. James Hoekstra describes the pathophysiology of anti-thrombin agents and discusses a new class of drugs called direct thrombin inhibitors. This class, which includes bivalirudin, lepirudin, argatroban, ximelagatran, and desirudin, has been evaluated and used for a variety of conditions including HIT/HITS (argatroban and lepirudin), venous thromboembolism prophylaxis after hip replacement (desirudin), anticoagulation of patients with atrial fibrillation (ximelagatran), and NSTEMI/ACS (bivalirudin). In particular, the use of bivalirudin in NSTEMI/ACS trials such as REPLACE-2 and ACUITY evaluates the effectiveness of the direct thrombin inhibitor bivalirudin for the treatment of these high risk patients.

Through these EMCREG-International Newsletters, we hope to provide you with the most current data available to help with the care of your patients. In this particular disease process, NSTEMI/ACS, the evolution of novel approaches to improving care and optimizing outcomes requires vigilance on the part of the emergency physician and acute care physician to be aware of recent trials. We hope this continuing medical education monograph serves that purpose for you.

Sincerely,



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Objectives

1. Describe the pharmacology of direct thrombin inhibitors and how they differ from heparins.
2. Describe the pharmacologic advantages of bivalirudin in NSTEMI/ACS.
3. Describe the importance of catheter-related bleeding in the treatment of NSTEMI/ACS.
4. Describe the results of the ACUITY trial as it relates to the treatment of NSTEMI/ACS in the emergency department.

Introduction

Anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) has been considered standard therapy in the emergency department (ED) for patients with high-risk non-ST-segment elevation acute coronary syndromes (NSTEMI/ACS).¹ However, the pharmacologic limitations of UFH and LMWH therapy have prompted a search for new anticoagulants, including a class of drugs called direct thrombin inhibitors (DTIs). One of these DTIs, bivalirudin, has enjoyed relatively wide-spread use in the cardiac catheterization laboratory, and has been recently investigated in high risk NSTEMI/ACS patients in the ACUITY trial. This review will discuss the pharmacology and clinical applicability of DTIs in high risk NSTEMI/ACS, especially as it relates to the ED management of these patients.

Direct Thrombin Inhibitor Mechanisms of Action

Non-ST-segment elevation ACS is caused by coronary artery endothelial disruption 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. Factor Xa catalyzes the conversion of prothrombin to thrombin (Factor IIa), and thrombin catalyzes the conversion of fibrinogen to fibrin.² Simultaneously, activated platelets aggregate within a meshwork of cross-linked fibrin to form a thrombus that impedes epicardial coronary blood flow.³ Unfractionated heparin, LMWH, and DTIs each have unique pharmacologic properties (Table 1) and thus inhibit different factors involved with coagulation and thrombus formation. Briefly, UFH and LMWH are considered indirect thrombin inhibitors as they require binding with circulating anti-thrombin III to

Peer Reviewer for Industry Bias: Corey M. Slovis, MD, Professor and Chairman, Department of Emergency Medicine, Vanderbilt University, Nashville, TN

Table 1. Anticoagulant pharmacology summary for unfractionated heparin, low molecular weight heparin and direct thrombin inhibitors. IV, intravenous; SC, subcutaneous.

Drug	Factor inhibited	Anti-thrombin dependence	Dosing route	Duration of action	Antidote
Unfractionated heparin	Thrombin:Xa (1:1 ratio)	Indirect inhibitor via anti-thrombin	IV	T _{1/2} = 60 min.	Protamine
Low molecular weight heparin [enoxaparin, dalteparin]	Xa:Thrombin (3.8:1 ratio)	Indirect inhibitor via anti-thrombin	SC	Dosed every 12 hours	Protamine (partially)
Direct thrombin inhibitors [bivalirudin, argatroban, lepirudin, desirudin]	Thrombin	Direct inhibitor	IV	T _{1/2} = 25 min. [bivalirudin]	None

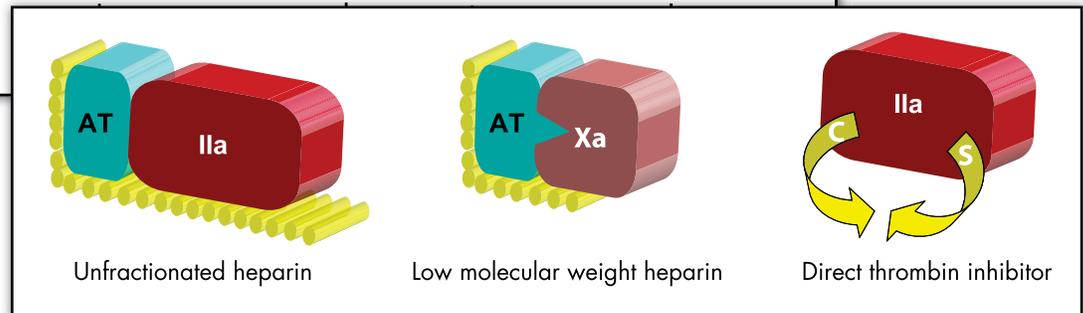
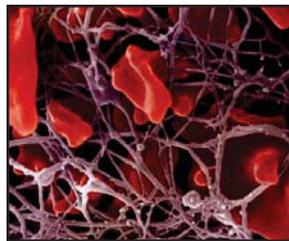


Figure 1. Schematic of anti-thrombin binding. Unfractionated heparin versus low molecular weight heparin versus direct thrombin inhibitor. IIa = thrombin. AT, anti-thrombin III; Xa, factor Xa; C and S; covalent binding sites on thrombin molecule.



Direct thrombin inhibitors can prolong activated clotting time (ACT) and aPTT to a variable degree, and some require monitoring while others do not.

exert their anticoagulant effect (Figure 1) on either thrombin (UFH>LMWH) or factor Xa (LMWH>UFH).⁴ Direct thrombin inhibitors, because of their molecular activity that is independent of anti-thrombin III, can inhibit both circulating and fibrin-bound thrombin.⁵ Direct thrombin inhibitors can prolong activated clotting time (ACT) and aPTT to a variable degree, and some require monitoring while others do not. Also, DTIs inhibit thrombin-mediated platelet activation, theoretically reducing the need for platelet inhibitors such as clopidogrel or glycoprotein IIb/IIIa inhibitors (GPI) during percutaneous coronary intervention (PCI). Finally, because DTIs do not bind to platelet-factor 4 (PF4), they do not stimulate the generation of antibodies to the heparin-PF4-platelet complex, thereby eliminating the possibility of developing heparin-induced thrombocytopenia. Conversely, DTIs are the preferred anticoagulant in patients with a history of heparin allergy, and are used in the treatment of heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia thrombosis syndrome (HITS).⁵



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The DTIs available and FDA-approved at this time include lepirudin, bivalirudin, argatroban, and desirudin. Argatroban and lepirudin are FDA-approved for the treatment of HIT/HITS, while desirudin is approved for venous thromboembolism prophylaxis after hip replacement. Ximelagatran was recently evaluated as an oral DTI for anticoagulation of patients with atrial fibrillation, but is not FDA-approved for this purpose.⁶ Bivalirudin has been evaluated in patients with NSTEMI ACS, but is FDA approved only for patients undergoing PCI. Bivalirudin has gained popularity in the cardiac catheterization laboratory due to its predictable dose-response anticoagulant effect, lack of need for monitoring, and lack of concern for HIT/HITS. Bivalirudin has a short half-life, with resolution of effects within one hour after drug discontinuation.⁶ This allows early removal of the catheter sheath in



the cardiac catheterization laboratory. Bivalirudin reduces bleeding complications compared to longer half-life anticoagulants. If bleeding complications occur with bivalirudin, they can effectively be treated by discontinuing the drug therapy and allowing its effects to dissipate. Fresh frozen plasma can be utilized to reverse bivalirudin, but it is rarely needed.

Bleeding Issues and Anticoagulants in the Cardiac Catheterization Laboratory

Given the overall improvement in reducing ischemic endpoints with an early-invasive strategy in the treatment of NSTEMI ACS, contemporary anticoagulant trials have begun to focus on safety. Thus, benefits of anti-thrombotic therapy must be balanced against the risks of bleeding complications, blood transfusions, and potential harm from improper dosing. The relationship between increased bleeding and adverse outcomes was noted in the REPLACE-2 trial, in which bleeding was a very strong predictor of 1-year mortality.⁶ The REPLACE-2 trial was also one of the first major trials to utilize bleeding as a portion of the primary endpoint, added to traditional ischemic endpoints to create "net clinical benefit" (efficacy plus safety). This net clinical benefit approach remains controversial, but the importance of catheter-related bleeding cannot be underestimated.⁷ The occurrence of bleeding in the setting of NSTEMI-ACS therapy is associated with worse clinical outcomes, regardless of which bleeding scale is used. Incorporation of bleeding into primary clinical outcomes raised the importance of the bleeding scales utilized in clinical trials.^{8,9} Using the TIMI definition of bleeding, PCI-related major bleeding is associated with higher in-hospital and 1-year mortality. Similarly, an

analysis with the GUSTO definition found that risk-adjusted 30-day and 6-month mortality rise in direct relation to bleeding severity (ie, mild, moderate and severe GUSTO bleeding increasingly effect long term mortality).¹⁰ Most recently, analysis of more than 34,000 NSTEMI 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).¹¹ Given the association of both bleeding and blood transfusions with increased 30-day mortality, prevention of bleeding episodes during NSTEMI ACS treatment is logical, and the definitions of bleeding in clinical trials becomes crucial (Table 2). Reduction of bleeding appears to be the most important advantage of bivalirudin over traditional anticoagulants in the setting of PCI. Its ease of use in the cardiac catheterization laboratory has been key to bivalirudin's popularity in lower risk NSTEMI ACS and elective PCI.

Bivalirudin in High Risk NSTEMI ACS: Results of the ACUITY Trial

In order to adequately review the ACUITY trial, the concept of non-inferiority warrants a brief description. Superiority occurs when patients receiving drug A have fewer adverse endpoints (e.g., death) than drug B, and analysis finds that both the odds ratio (OR) point estimates and the 95% confidence intervals (CI) are less than 1.0 (ie, do not cross the line of unity). With non-inferiority trials, OR point estimates can lie to either side of unity, but the upper boundary of the 95% CI must not exceed a pre-specified limit. If non-inferiority is observed, then the comparators can be considered "clinically similar" but not truly equivalent. If a new drug has certain unique practical advantages (i.e., dosing simplicity, cost, etc), then demonstrating non-inferiority to a standard drug is potentially sufficient to change clinical practice. In the case of bivalirudin, this practical advantage is a significant reduction in bleeding.¹¹

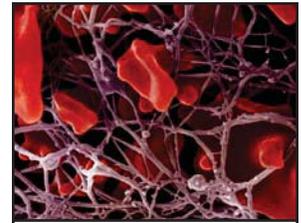
Table 2. Bleeding definitions for non-ST-segment elevation acute coronary syndrome trials. Hgb, hemoglobin; g, gram; dl, deciliter

Trial	Bleed Definitions		
TIMI (Chesebro Circ 1987)	MAJOR Intracranial hemorrhage (or) $\geq 5\text{g/dl}$ \downarrow in Hgb	MINOR <u>Observed blood loss</u> (and) $\geq 3\text{g/dl}$ \downarrow in Hgb <u>No observed blood loss</u> (and) $\geq 4\text{g/dl}$ \downarrow in Hgb	MINIMAL Any overt sign of hemorrhage that is associated with $\leq 3\text{g/dl}$ \downarrow in Hgb
GUSTO (NEJM 1993)	SEVERE OR LIFE THREATENING Intracranial hemorrhage (or) Bleeding that causes hemodynamic compromise and requires intervention	MODERATE Bleeding that requires transfusion but no hemodynamic compromise	MILD Bleeding that does not meet criteria for severe or moderate.
ACUITY (Stone AHJ 2004)	MAJOR Intracranial, intraocular or retroperitoneal bleeding. Access site: Requiring intervention or hematoma $\geq 5\text{cm}$ Hgb $\downarrow \geq 3\text{g/dl}$ with overt source Hgb $\downarrow \geq 4\text{g/dl}$ without overt source. Any blood transfusion Re-operation for bleeding	MINOR Ecchymosis Epistaxis Gastrointestinal bleeding Genitourinary bleeding Puncture site Hemopericardium Pulmonary	

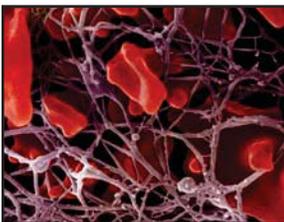
In the Acute Catheterization and Urgent Intervention and Triage Strategy Trial (ACUITY), NSTEMI ACS patients were assigned in an open-label, randomized fashion to one of three treatment arms: "heparins" (either UFH or enoxaparin) + GPI, bivalirudin + GPI, or bivalirudin alone (with provisional GPI use). The ACUITY arms are illustrated in Figure 2.¹² Patients in the ACUITY trial were considered "moderate to high risk" for adverse outcomes, with inclusion criteria including elevated troponin or CKMB, ischemic ECG changes (ST depression or transient elevation), TIMI score ≥ 4 , or known coronary artery disease. Randomization and initiation of study drug occurred within 24 hours of ischemic symptoms, either in the ED, CCU, or cardiac catheterization laboratory. After randomization, at a time of cardiologist discretion, patients were taken to cardiac catheterization for elucidation of coronary anatomy as per study protocol. Median time from admission to angiography was approximately 20 hours, which is very consistent with practice patterns noted in CRUSADE for high risk NSTEMI ACS. Prior to catheterization, patients in the bivalirudin only arms received a bivalirudin infusion as their sole anti-thrombin. Ninety-nine percent of patients in the ACUITY trial underwent cardiac catheterization, and the majority were treated

with a reperfusion strategy including PCI 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.

Prespecified sequential non-inferiority and superiority analyses were performed on all three treatment arms with regard to efficacy (death, MI, or unplanned revascularization), safety, and net clinical benefit. Of particular interest is the finding that the efficacy of bivalirudin alone at reducing ischemic events (death, MI, unplanned revascularization) was non-inferior to the combination of "heparins" + GPI (7.8% vs. 7.3%, OR = 1.08, 95% CI = 0.93-1.24) (Figures 3 and 4). 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) (Figures 3 and 4). The authors concluded that bivalirudin alone was superior to "heparins" + GPI in the treatment of moderate to high risk NSTEMI ACS.¹³

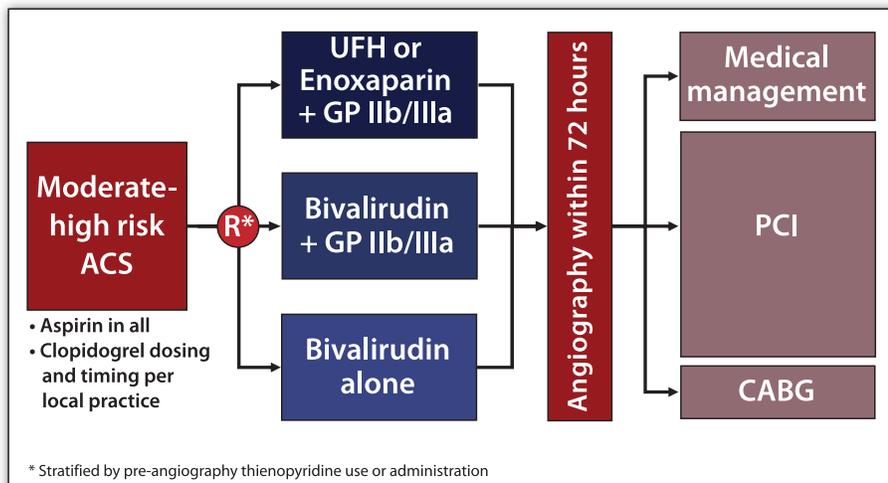


The emergency physician is concerned with minimizing the risk of early adverse ischemic outcomes (the pre-catheterization period), the cardiologist is focused on outcomes in the catheterization laboratory and prior to hospital discharge.



The optimal anticoagulant should reduce ischemic endpoints while maintaining safety, and allow for a seamless transition between ED-initiated medical management of NSTEMI ACS and cardiology-based PCI therapy.

Figure 2: ACUITY trial study design.





Choosing the Optimal Anticoagulant for NSTEMI ACS:

Although the choice of anticoagulant in the ED begins with consideration of efficacy and safety issues, practical concerns regarding cardiac catheterization laboratory compatibility, dosing simplicity, 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 NSTEMI ACS and cardiology-based PCI therapy. Herein lies the difficulty with choosing the optimum ED anticoagulant: while the emergency physician is concerned with minimizing the risk of early adverse ischemic outcomes (the pre-catheterization period), the cardiologist is focused on outcomes in the catheterization laboratory and prior to hospital discharge. Peri- or post-procedural thrombotic or bleeding complications, unseen by the emergency physician, are of critical importance to the cardiologist. This conflict of priorities has led to the phenomenon of anti-thrombotic switching, such as a periprocedural switch from enoxaparin to UFH. Switching or stacking anticoagulants prior to cardiac catheterization was shown to result in an increase in both catheter-related bleeding and adverse ischemic outcomes in the SYNERGY trial.¹⁴ With bivalirudin, however, this may not be the case. A recent subanalysis of patients in the ACUITY trial showed that patients who were initially started on a "heparin" and then switched during pre-randomization to bivalirudin did not demonstrate any deleterious bleeding affects.¹⁵

In order for the bivalirudin to be routinely initiated in the ED, as accomplished in a portion of the patients in the ACUITY trial, compatibility between the pre-catheterization medical management needs of the emergency physician with the needs of downstream interventional cardiologists must be demonstrated. At this time, bivalirudin is not FDA approved for pre-angiography medical management of NSTEMI ACS, and medical management experience with this drug is limited. In the ACUITY trial, the pre-catheterization medical management interval was relatively short (median 4 hours), limiting the applicability of the ACUITY data to ED-initiated pre-catheterization medical management, except in short trips to the cath lab. A recent subanalysis of ACUITY patients with prolonged pre-cath drug infusions >24 hours did demonstrate improved net clinical benefit to bivalirudin versus heparins plus a GPI, but the patient numbers were small, and pre-catheterization events were uncommon.¹⁶ Cost concerns regarding medical management with

Figure 3: ACUITY trial primary outcome.

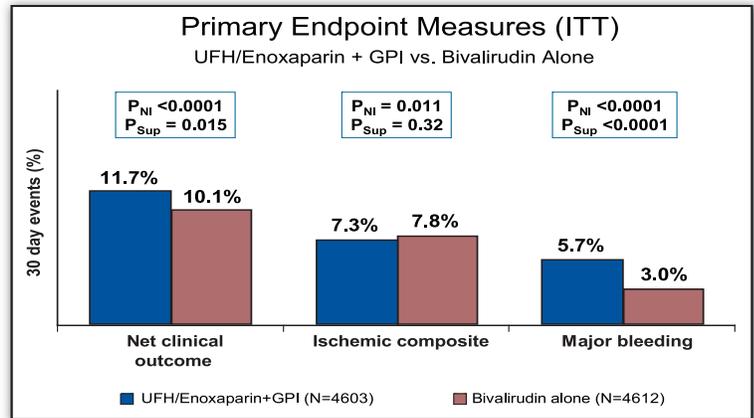
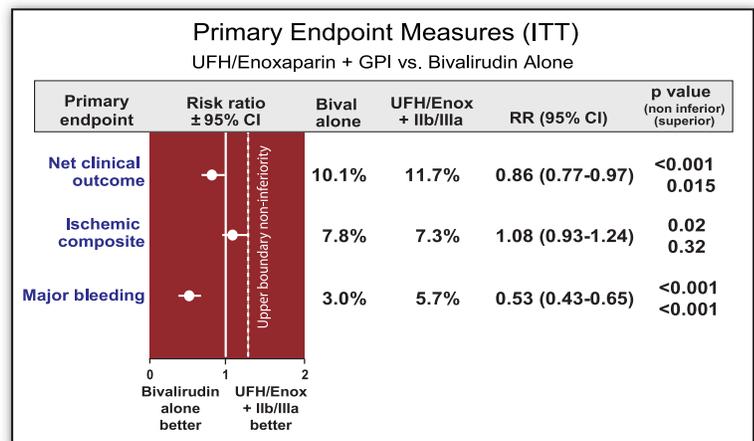


Figure 4: ACUITY Trial Results: ischemia versus bleeding risk plot



bivalirudin versus UFH are also important especially when compared to heparins alone. Conversely, bivalirudin has high potential to be accepted "inside" the cardiac catheterization laboratory in the treatment of high risk NSTEMI ACS. Bivalirudin has already become familiar to many interventionalists for urgent and elective PCI based upon the REPLACE-2 trial, and the ACUITY study of NSTEMI ACS now demonstrates that bivalirudin monotherapy is a reasonable substitute for the combination of either heparin or enoxaparin, and a platelet GPI, within the context of an early-invasive strategy for NSTEMI ACS.

In conclusion, the DTI bivalirudin has the potential to improve the care of NSTEMI ACS patients. Favorable pharmacokinetic properties, a short half-life, and lack of heparin-induced antibody formation make bivalirudin an important anti-thrombin for NSTEMI ACS care. Bivalirudin has been investigated in urgent and elective PCI in the REPLACE-2 trial, and high risk NSTEMI ACS in the ACUITY trial, with promising results. Applicability of bivalirudin in the emergency setting demonstrates promise, but it remains to be seen whether bivalirudin will gain acceptance in the pre-catheterization medical management of patients with high risk NSTEMI ACS.



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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 drugs is a direct thrombin inhibitor?
 - a. Enoxaparin
 - b. Fondaparinux
 - c. Unfractionated heparin
 - d. Bivalirudin

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

3. High risk NSTEMI ACS patients (troponin positive or ECG changes) in the U.S. are usually treated by which of the following strategies?
 - a. Medical management, with selective catheterization based on stress testing results
 - b. Short term medical management, followed by catheterization within 48 hours
 - c. Medical management, followed by catheterization within 5-7 days
 - d. Immediate catheterization within 90 minutes from door to needle

4. Which of the following statements is true regarding catheter-related bleeding in patients with NSTEMI 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 anti-thrombins
 - d. TIMI bleeding, GUSTO bleeding, and transfusions are all related to mortality in NSTEMI ACS.

5. Based on the ACUITY trial, which of the following is true regarding the bivalirudin alone arm in patients with NSTEMI ACS?
 - a. Bivalirudin is associated with more bleeding than heparin + GPI
 - b. Bivalirudin is superior to heparin + GPI at reducing ischemic outcomes
 - c. Bivalirudin is superior to heparin + GPI with net clinical benefit as an outcome
 - d. Bivalirudin is non-inferior to heparin + GPI with net clinical benefit as an outcome.

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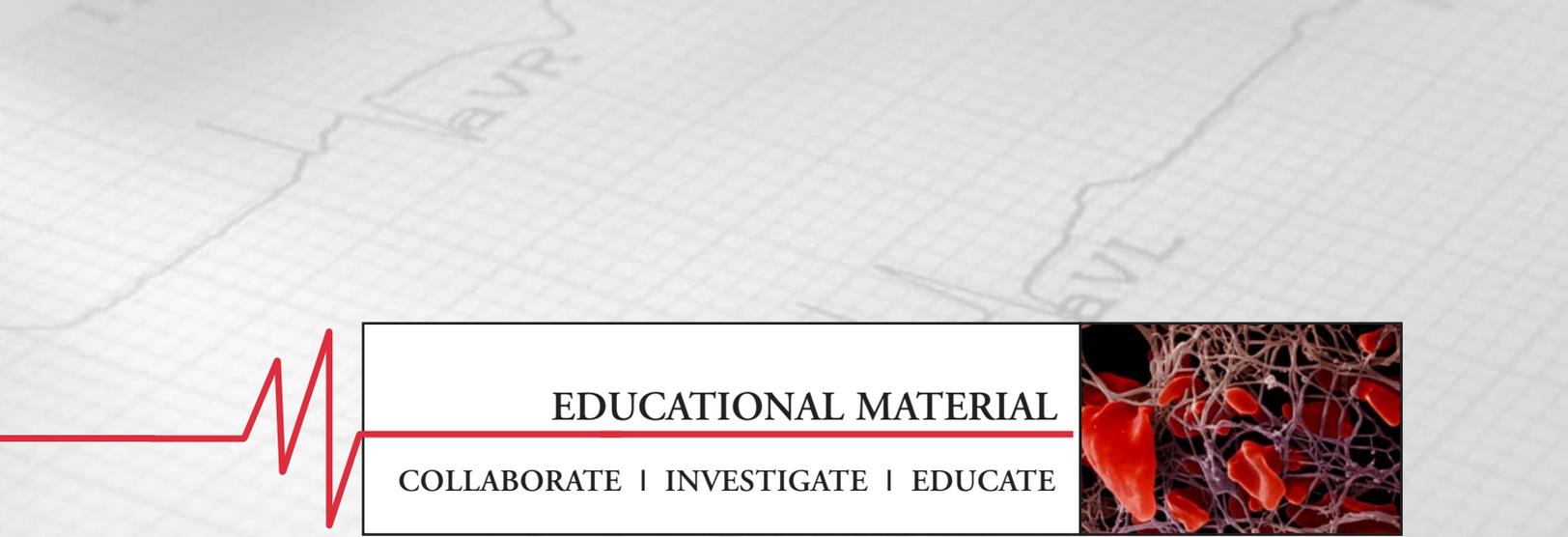
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Direct Thrombin Inhibitors in Non-ST-segment Elevation Acute Coronary Syndromes

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**Direct Thrombin Inhibitors in Non-ST-segment Elevation
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