INTRODUCTION

Unfractionated heparin (UFH), low molecular weight heparin (LMWH), thienopyridines (clopidogrel), and glycoprotein (GP) IIb/IIIa inhibitors are class I guideline recommendations from the most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with non-ST-segment elevation acute coronary syndromes (ACS).1 The use of enoxaparin (a LMWH), rather than UFH, has decreased ischemic complications in patients with ACS who are treated conservatively.2,3 Reductions in both early and late composite of death and myocardial infarction (MI) are enhanced with early addition of clopidogrel4-6 and a GP IIb/IIIa inhibitor7-9 to unfractionated heparin (UFH) and aspirin in patients with ACS. Several trials10-12 have established early invasive management as the optimal treatment for patients with moderate-to high-risk ACS and the guidelines have endorsed this approach.1 An early invasive strategy consists of early initiation of anti-thrombotic and anti-platelet therapy, angiographic assessment within 48 hours, followed by definitive therapy tailored to each patient’s coronary anatomy.

The ideal anti-thrombotic regimen for patients with ACS should facilitate an early invasive strategy (including percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery, if appropriate); should provide maximal protection from adverse ischemic events; should minimize the risk of hemorrhagic complications; enable more simplified (or emergency department [ED] friendly) treatment pathways; and should be cost-effective.

New considerations in trial design: Inclusion of Bleeding Parameters

Traditionally, hard outcomes, such as death were considered the ideal outcome parameter for large scale clinical trials. However, improved treatment modalities have resulted in improved outcomes and a reduction in the frequency of death,
such that it is no longer practical as a sole outcome measurement, even in clinical trials with over 10,000 patients. The incremental improvement in mortality is too small to be detected, even with these large trials. Therefore, contemporary studies have used composite efficacy endpoints, comprised of patients that attain any of a combination of outcomes, typically, mortality, myocardial infarction and refractory ischemia (possibly defined by urgent target vessel revascularization). Recently, a new composite has been defined: net clinical benefit, which includes a triple composite efficacy parameter as well as major bleeding complications. The rationale is that short term bleeding complications are associated with worse long term outcomes.\textsuperscript{13} Likewise, the need for blood transfusions is associated with increased 30 day mortality even after adjustment for risk factors.\textsuperscript{14} It makes sense that the ideal anti-thrombotic therapy should minimize short term bleeding risk to optimize long term outcome.

**Anti-thrombins**

Thrombin is the most potent natural platelet activator.\textsuperscript{15} Thrombin converts fibrinogen to fibrin, activates coagulation factors V and VIII, accelerates coagulation, stimulates its own generation, and interacts with endothelial cells to upregulate tissue factor.\textsuperscript{15-19} Thrombin is pivotal link in the process of tissue injury, coagulation, and the platelet response (Figure 1).

Unfractionated heparin, enoxaparin, and fondaparinux are considered indirect thrombin inhibitors because they require binding with circulating anti-thrombin III (an endogenous circulating alpha-globulin) to exert their anticoagulant affect. In contrast to UFH and LMWH, direct thrombin inhibitors interact with circulating and clot-bound thrombin.\textsuperscript{20}

Bivalirudin, a direct thrombin inhibitor, binds specifically to thrombin at its active catalytic site and at the exosite-1 docking locus.\textsuperscript{21} Bivalirudin competitively inhibits thrombin with high affinity but is a short-acting agent, with a half-life of only 25 minutes (compared with 60 to 90 minutes with UFH).\textsuperscript{20,22} It does not require laboratory monitoring due to predictable linear pharmacokinetics.

**New Clinical Data**

Since the publication of the 2002 AHA/ACC guidelines for the management of patients with NSTEMI, there have been 3 large pivotal trials regarding anti-thrombin therapy: SYNERGY, OASIS-5, and ACUITY.\textsuperscript{23-25} SYNERGY demonstrated that enoxaparin was non-inferior to UFH, with death and MI occurring in 14.0% (n = 696) and 14.5% (n = 722), respectively (hazard ratio 0.96; 95% CI = 0.86-1.06). There was a slight excess in bleeding in the enoxaparin group.\textsuperscript{23} In OASIS-5 (The Organization
NOVEL ANTI-THROMBOTIC THERAPIES FOR ACUTE CORONARY SYNDROME: DIRECT THROMBIN INHIBITORS

to Assess Strategies in Acute Ischemic Syndromes) fondaparinux (2.5mg SQ qd) was compared to enoxaparin (1 mg/kg SQ BID) in 20,078 unstable angina or NSTEMI patients with respect to a primary endpoint representing net clinical benefit. This net clinical endpoint was a composite of death, myocardial infarction, and refractory ischemia combined with major bleeding. OASIS-5 found no difference in the efficacy endpoint (fondaparinux, 5.8% versus enoxaparin, 5.9%), however the net clinical benefit outcome favored fondaparinux (hazard ratio, 0.81 (95% CI 0.74-0.90). This benefit was due to reduced major bleeding.

The Path to ACUITY: bivalirudin
Bivalirudin has been extensively investigated in patients undergoing PCI. In the Bivalirudin Angioplasty Trial, 4312 patients receiving PCI were randomized to bivalirudin or UFH without GP IIb/IIIa inhibitor use. The bivalirudin-treated patients showed lower rates of ischemic events and hemorrhage. A 30% to 60% reduction in ischemic complications (P < .01) and 60% to 80% reduction in bleeding (P < .001) were noted in the 1006 unstable angina patients and the 741 patients following acute myocardial infarction. This trial predated the use of stents, GP IIb/IIIa inhibitors, and thienopyridines, and relatively high UFH doses were used in the control arm.

A more contemporary study was performed in the Randomized Evaluation of PCI Linking Bivalirudin to Reduce Clinical Events (REPLACE)-2 trial. REPLACE-2 randomized 6010 patients undergoing stent implantation to UFH and planned GP IIb/IIIa inhibition versus bivalirudin and provisional GP IIb/IIIa inhibition (which was used in only 7.2% of patients). The 30-day composite net clinical benefit (death, MI, urgent repeat revascularization, and major bleeding) was similar between the two groups (10.0% with UFH + routine GP IIb/IIIa inhibition vs 9.2% with bivalirudin and provisional GP IIb/IIIa inhibition, P = .32), as was the rate of death, MI, and urgent revascularization (7.1% vs 7.6%, respectively, P = .40). Major bleeding was less common in the bivalirudin patients (4.1% vs 2.4%, P < .001). These studies demonstrated the utility of bivalirudin in the cardiac catheterization laboratory during angioplasty. It should be noted that the results were similar in the most ED relevant group: the 1340 REPLACE-2 patients who presented with ACS.

The Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial was a large-scale, prospective, multicenter, randomized study designed to determine the optimal anticoagulation regimen in patients with moderate to high-risk ACS undergoing an early invasive strategy. In ACUITY, heparin (either UFH or enoxaparin) and bivalirudin, with or without an upstream GP IIb/IIIa inhibition, was compared to bivalirudin alone in high-risk NSTEMI ACS patients.
treated with a planned early interventional strategy (Figure 2). An important secondary objective was to examine clinical outcomes after GP IIb/IIIa inhibition given upstream (before angiography) versus selective use of GP IIb/IIIa inhibition in patients undergoing PCI only.

The results of ACUITY, which were released at the American College of Cardiology Late Breaking Clinical Trials session in March of 2006, demonstrate the beneficial effects of bivalirudin on net clinical benefit (composite of death, AMI, urgent revascularization and major bleeding), predominantly due to reduction in major bleeding. The net clinical benefit endpoint favored bivalirudin monotherapy (10.1%) over heparin with or without upstream GP IIb/IIIa inhibition (11.7%), and bivalirudin with or without upstream GP IIb/IIIa inhibition (11.8%). The precise role of bivalirudin in the ED will be defined, as ACUITY is further analyzed to determine if ED administration is associated with improved outcomes.

The View From the Emergency Department

Most emergency physicians are primarily concerned with minimizing the risk of early adverse ischemic outcomes and are inherently less likely to be concerned about procedural complications. On the other hand, interventional cardiologists are also concerned about procedure complications and post-procedure bleeding. Therefore, it is not surprising that emergency physicians and cardiologists might choose different therapies given the same patient. The SYNERGY trial demonstrated that consistent therapy (not changing between UFH and LMWH in either direction) is associated with an improved outcome. The optimum anti-thrombin should enable a seamless transition from the ED to the cardiac catheterization laboratory. It should minimize pre-procedural ischemia and both peri- and post-procedural ischemic and bleeding outcomes, be easy to administer, require no monitoring, and be cost effective. The preliminary data from ACUITY suggest that bivalirudin has improved net clinical benefit. However, several questions remain unanswered: (1) Does starting bivalirudin in the ED, when a patient may or may not receive cardiac catheterization, improve outcomes? (2) In patients who will receive an intervention, is there additional benefit to beginning upstream bivalirudin in the ED or should administration wait until catheterization? Further analysis of the ACUITY trial might help answer these and other questions, was well as determine whether patients benefit from having this therapy initiated in the ED.
REFERENCES


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