

Value in Thrombosis Management

Anticoagulation in ACS: Emerging Therapeutic Options

ACS Management: A Continuing Challenge

More than 1.4 million persons are admitted to hospitals in the United States every year with non-ST elevation acute coronary syndromes (NSTEMI, e.g., unstable angina or myocardial infarction without ST-segment elevation).¹ Timely intervention with effective and safe antithrombotic therapy in acute coronary syndromes (ACS) is essential in minimizing cardiovascular risk and reducing the incidence of life-threatening events.

An early invasive strategy for patients with moderate or high-risk ACS, consisting of angiography followed by percutaneous coronary intervention (PCI), coronary-artery bypass grafting (CABG), or medical management, results in higher rates of event-free survival than does conservative care² and is recommended by the American Heart Association and the American College of Cardiology.^{3,4} Aspirin (ASA), clopidogrel, a platelet glycoprotein IIb/IIIa inhibitor, and an anticoagulant (either unfractionated heparin or low-molecular-weight heparin) are also recommended for patients for whom an invasive strategy is chosen.^{3,4} Although unfractionated heparin (UFH) has been used in clinical practice for over 60 years, multiple challenges have emerged regarding therapeutic dosing, monitoring, and safety. In addition, confusion continues regarding the comparative efficacies of UFH and low-molecular-weight heparins (LMWHs, e.g. enoxaparin) and the optimal use of these anticoagulants.

Nonetheless, the rates of death and myocardial infarction (MI) remain considerable in this patient population, and these intensive adjunctive pharmacologic regimens may result in major bleeding that has been associated with early and late mortality rates.

New Agents: Evolving Evidence

Fondaparinux: Evidence and Issues

Fondaparinux is a sulphated pentasaccharide containing the minimum antithrombin (AT) binding sites of UFH. This new agent's low molecular weight and small chain length allow it to be specific for Xa inhibition. Fondaparinux, like UFH and the LMWHs, must first bind with the intermediary, AT, prior to clotting factor inhibition. Fondaparinux has accumulated a significant body of evidence and is FDA-approved in VTE treatment and prevention.

More recently, it has been studied in ACS. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial was a head-to-head trial of over 20,000 patients with NSTEMI ACS.⁵ Patients were randomized to either enoxaparin or fondaparinux. The primary endpoint was D/MI/RI (death, myocardial infarction, recurrent ischemia) at day 9. The secondary safety endpoint was major bleeding at day 9. The findings were as follows:

- Primary endpoint (D/MI/RI at 9 days), 5.7% enoxaparin vs. 5.8% fondaparinux (p = NS)
- Death at 9 days, 1.9% enoxaparin vs. 1.8% fondaparinux (p = NS)
- Less major bleeding with fondaparinux compared to enoxaparin at 9 days, 2.2% vs. 4.1%, respectively (p < 0.0001)

Considering the study design and results of OASIS-5, some issues or unanswered questions have arisen:

- The mean duration of treatment with enoxaparin (e.g. 5.2 days) was longer than in current U.S. practice.
- Enoxaparin dosing may have been too high, particularly in patients greater than 65 years



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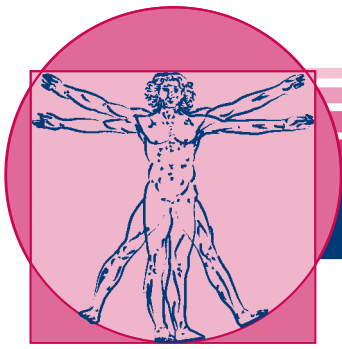
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of age and in patients with elevated serum creatinine (e.g. between 2-3 mg/dL)

- The study protocol changed for fondaparinux to permit open-label UFH during cardiac catheterization/PCI.
- Excessive catheter clots were seen with fondaparinux (0.9% vs. 0.4% with UFH). This adverse effect will likely prevent fondaparinux from being used in PCI.
 - The dose of UFH used in fondaparinux patients was less than that used in enoxaparin patients
 - Lower event rates for enoxaparin were demonstrated if no UFH therapy was used prior to enoxaparin therapy (as shown with consistent therapy in the SYNERGY trial).

Given the evidence and these potential issues, the hope is that future practice guidelines will provide clarification and make firm recommendations regarding the use of fondaparinux in NSTEMI ACS, including any caveats regarding its use in the setting of PCI.

Bivalirudin: From Theory to Practice

There are a number of theoretical advantages of direct thrombin inhibitors (DTIs) such as bivalirudin over indirect thrombin inhibitors (e.g. UFH and LMWH). DTIs are not dependent on antithrombin (AT, formerly known as AT III). They are active against clot-bound as well as circulating thrombin. Because the heparin-anti-thrombin complex is so large, it cannot penetrate into the interstices of a clot to inhibit clot-bound thrombin. DTIs also block other important effects of thrombin such as its ability to stimulate platelet aggregation. Furthermore, DTIs do not interact with platelet-factor 4 as heparin does; consequently they do not carry the risk of heparin-induced thrombocytopenia (HIT). Bivalirudin has a relatively short half-life of approximately 25 minutes, and its effects dissipate rapidly once it is

discontinued. Bivalirudin also does not need to be routinely monitored, adjusted, and titrated as UFH does in NSTEMI ACS.

Bivalirudin (Angiomax™, the Medicines Company), a synthetic direct-thrombin inhibitor, has been approved by the FDA as an anticoagulant alternative to UFH for patients with ACS who are undergoing PCI. In the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2 (REPLACE-2) trial, bivalirudin monotherapy, as compared with UFH plus a glycoprotein IIb/IIIa inhibitor, resulted in a significant reduction in rates of major and minor bleeding, with similar rates of ischemic events and death among patients with stable or unstable angina who were undergoing PCI.⁶

The ACUTY Trial: Comparable Efficacy, Superior Safety

The usefulness of bivalirudin, as part of an early invasive strategy with optimal antiplatelet therapy in patients with NSTEMI ACS, has recently been investigated in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUTY) trial.⁷

There were two primary questions to be answered in ACUTY:

1. When given with a glycoprotein IIb/IIIa inhibitor (e.g. abciximab, eptifibatid), does bivalirudin provide benefit over UFH/enoxaparin in moderate and high risk ACS patients treated with an invasive management strategy?
2. When given by itself (with provisional glycoprotein IIb/IIIa inhibitor usage), is a strategy of bivalirudin alone comparable to UFH/enoxaparin plus a glycoprotein IIb/IIIa inhibitor in moderate and high risk ACS patients treated with an invasive management strategy?

The ACUTY trial was a prospective, open-label, randomized, multicenter trial in which UFH or a LMWH plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, and bivalirudin alone were compared in patients with moderate- or high-risk ACS undergoing an early invasive strategy. Patients went on to angiography within 72 hours and were then treated with medical management, PCI, or CABG. The primary endpoints at 30 days were composite net clinical benefit, composite ischemia, and major bleeding.

Bivalirudin plus a glycoprotein IIb/IIIa inhibitor, as compared with UFH or a LMWH plus a glycoprotein IIb/IIIa inhibitor, was associated with noninferior 30-day rates of the composite ischemia endpoint

Figure 1

UFH/Enox + GPB vs. Bivalirudin + GPB (ITT)

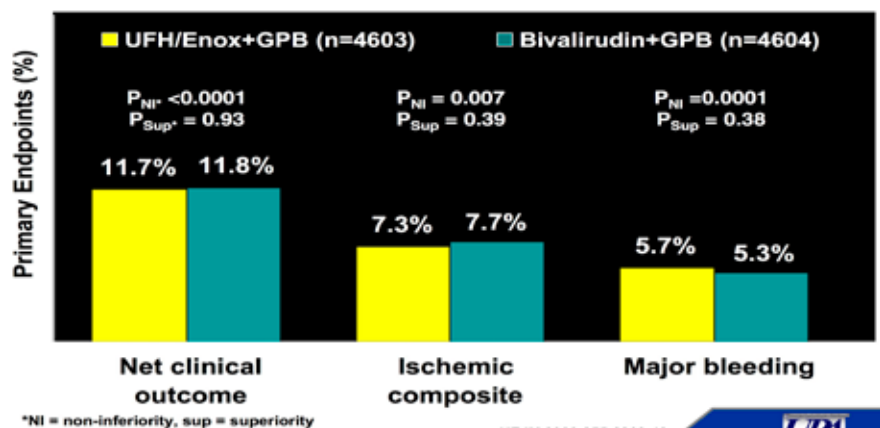
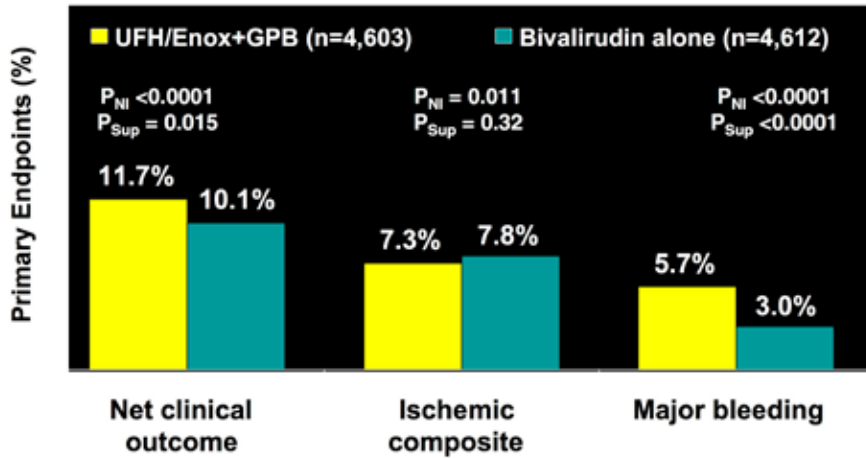


Figure 2

UFH/Enox + GPB vs. Bivalirudin Alone (ITT)

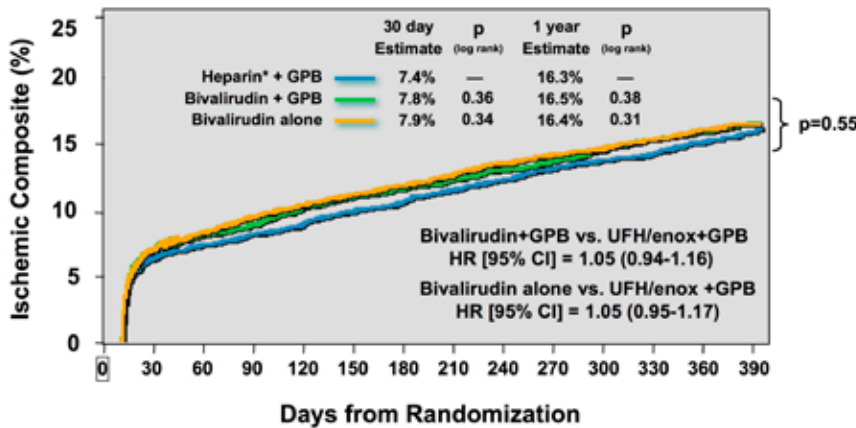


Circulation 2006;114:551. NEJM 2006;355:2203-16.



Figure 3

Ischemia Composite



*Heparin=unfractionated or enoxaparin

ACC, New Orleans, March, 2007.



(7.7% and 7.3%, respectively), major bleeding (5.3% and 5.7%, respectively), and the net clinical outcome endpoint (11.8% and 11.7%, respectively) (Figure 1). Bivalirudin alone, as compared with UFH or a LMWH plus a glycoprotein IIb/IIIa inhibitor, was associated with a noninferior rate of the composite ischemia endpoint (7.8% and 7.3%, respectively, $p = 0.32$); and significantly reduced rates of major bleeding (3.0% vs. 5.7%, respectively; $p < 0.001$); and the net clinical outcome endpoint (10.1% vs. 11.7%, respectively; $p = 0.02$) (Figure 2).

The one-year ACUTY results were presented at the Annual American College of Cardiology Meeting in New Orleans in March, 2007. The Kaplan-Meier curves for the ischemic composite endpoint for all three arms at one year were essentially superimposable (Figure 3). Thus, consistent with the 30-day data, there was no statistically significant difference in composite ischemia between the three treatment arms at 1 year.

One of the most hotly debated aspects of the ACUTY trial was the potential interaction with clopidogrel. In patients who were not exposed to clopidogrel before PCI (defined as any pre-procedural exposure, regardless of dose or timing), there was a significantly higher incidence of ischemic composite events in patients in the bivalirudin monotherapy group in contrast to patients who had been exposed to clopidogrel where no such difference existed.

Mechanistically, this could relate to the fact that patients undergoing PCI may benefit from more than just ASA as an antiplatelet foundation. In addition, for patients not pre-loaded with clopidogrel, a critical time window may not be covered when glycoprotein IIb/IIIa inhibitor treatment is omitted. What is really being compared may be potent early platelet inhibition versus no potent early platelet inhibition, emphasizing the need for clopidogrel pretreatment in ACS patients moving forward to intervention.

The ACUITY Trial: Key Findings

Important findings from the ACUITY trial which are likely to impact practice include:

- ACUITY compared a new anticoagulant strategy against the currently defined standard of care in NSTEMI ACS patients managed with an early invasive strategy.
- Bivalirudin plus a glycoprotein IIb/IIIa inhibitor had similar ischemic outcomes, similar bleeding, and similar net clinical benefit to heparin/LMWH plus a glycoprotein IIb/IIIa inhibitor.
- Bivalirudin alone had similar ischemic outcomes, less major bleeding, and superior net clinical benefit compared to UFH or LMWH plus a glycoprotein IIb/IIIa inhibitor. Whether or not reductions in major bleeding will translate into longer-term reductions in mortality has yet to be determined.
- When bivalirudin is administered alone, patients should be pre-treated with clopidogrel.

Comparable "Real-World" Patient Outcomes Demonstrated

A recent retrospective cohort analysis was conducted at the University of Pittsburgh Medical Center.⁸ Data for all patients undergoing PCI during a 12 month interval and receiving either UFH or bivalirudin during or on the day of PCI were included. Clinical outcomes evaluated included bleeding episodes, in-hospital mortality, MI after the initial intervention, need for surgical or repeat revascularization, and length of stay (LOS). These outcomes, not including LOS, were

evaluated for up to 30 days or to hospital discharge, whichever came first. One-thousand seventy-five adult patients were identified: 536 received UFH and 539 received bivalirudin. The patient characteristics were well-matched. A total of 97.4% underwent PCI with stent implementation, and the remaining 2.6% underwent angioplasty without stent implementation. Drug-eluting stents were used in 50% of all patients, and were commonly used in the bivalirudin group (58.8% vs. 41.2%, $p < 0.0001$). Glycoprotein IIb/IIIa inhibitors were used in more than twice as many patients in the UFH group compared to the bivalirudin group. Table 1 shows the bleeding rates and individual components of this end point. It is clear from the data that the use of bivalirudin alone was associated with a significant reduction in major bleeding when compared with UFH. Patients who received UFH were approximately twice as likely to bleed.

The all-cause in-hospital mortality was 3.9% in the UFH group versus 1.3% in the bivalirudin group ($p = 0.01$). Myocardial infarction after catheterization occurred in 18% of UFH-treated patients versus 10.7% of the bivalirudin-treated patients whose catheterization was not related to an MI ($p = 0.007$). The LOS was longer in the patients who received UFH [3.5 ± 4.1 days (mean \pm SD)] than in those who received bivalirudin [2.8 ± 2.9 days), $p < 0.001$].

This large comparative analysis of the clinical outcomes of UFH versus biva-

lirudin, with provisional glycoprotein IIb/IIIa inhibition, in a setting which included high-risk patients, correlates with the findings in clinical studies such as REPLACE-2 and the ACUITY trial. Bivalirudin was shown, in these trials, to be an attractive alternative to UFH/LMWH due to decreased major bleeding without compromising efficacy.

Economic Assessment

Traditionally, the economic emphasis of the Pharmacy Department, as well as the hospital's perspective, has been only on the drug acquisition cost. A new paradigm or shift in our thinking should place emphasis on the total cost analysis of treating the patient. We should ask ourselves, "can we lower overall costs while still achieving comparable or superior outcomes of efficacy and safety?"

The economic substudy of the ACUITY trial included all U.S. patients ($n = 7,851$).⁹

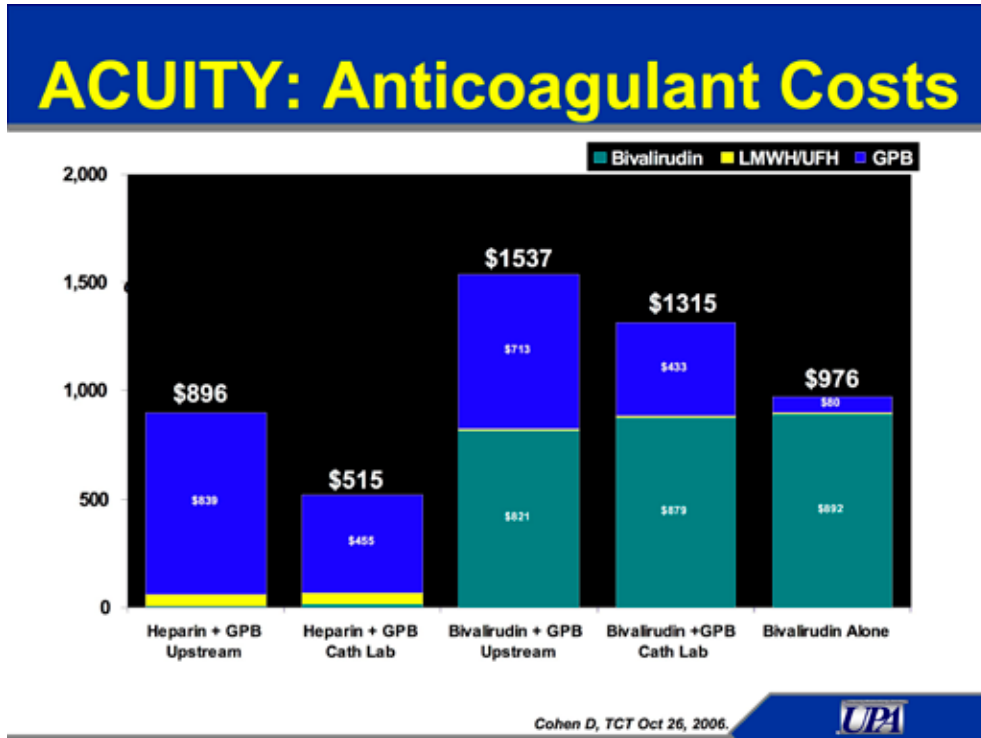
Hospital costs were determined by standard methods as follows:

- **Anticoagulants:** Number of vials and average wholesale costs (assumed any unused drug would be discarded)
- **Cath Lab Procedures:** Resource utilization and current unit cost

Table 1. Bleeding End Points

| End Point | UFH Group (n = 536) No. (%) of patients | Bivalirudin Group (n = 539) No. (%) of patients | p Value |
|----------------------|--|--|---------|
| TIMI criteria | | | |
| Major | 52 (9.7) | 27 (5.0) | 0.003 |
| Minor | 32 (6.0) | 9 (1.7) | <0.001 |
| REPLACE criteria | | | |
| Major | 69 (12.9) | 29 (5.4) | <0.001 |
| Minor | 33 (6.2) | 32 (5.9) | 0.880 |
| Received Transfusion | 48 (9.0) | 24 (4.5) | 0.003 |

Figure 4

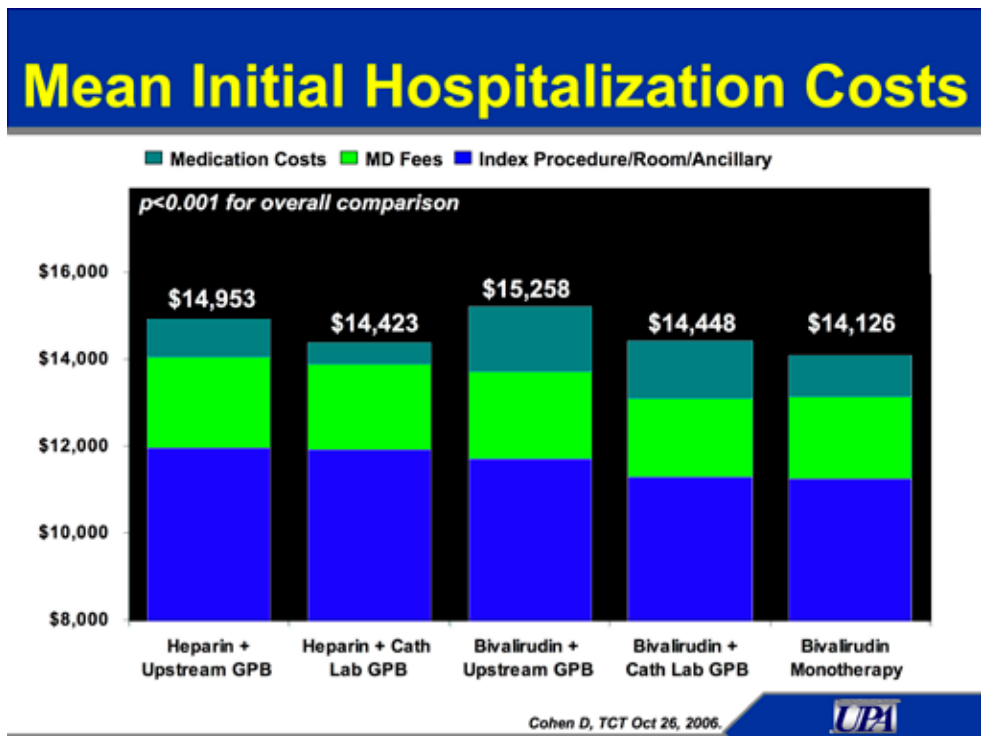


- **Hospital care:** Hospital charges converted to costs based on department level cost to charge ratios (>3000 bills collected); regression approach for patients without billing data

The comparative anticoagulant costs in ACUITY are compared in Figure 4. Obviously, the use of a glycoprotein IIb/IIIa inhibitor significantly increased the cost of the various regimens. In comparing the UFH plus a glycoprotein IIb/IIIa inhibitor in the cath lab (second bar) to the cost of bivalirudin alone (last bar), it can be seen that when comparing only the drug costs, the cost of bivalirudin alone was over \$400 greater.

Again, with the shifting paradigm, total hospital costs should be assessed to more fully evaluate the total cost to the health system. Figure 5 compares the total hospitalization costs of the different regimens. If the second bar, which is the total cost of using UFH plus a glycoprotein IIb/IIIa inhibitor in the cath lab, is compared to the last bar, which is the total cost of using bivalirudin alone, the overall cost for bivalirudin is now about \$300 less. Thus, despite higher drug acquisition costs, aggregate hospital costs were lowest with bivalirudin monotherapy. Thus, bivalirudin is positioned favorably in terms of net cost to the health system.

Figure 5



As Evidence Evolves, Guidelines Evolve

As alluded to earlier, the American College of Cardiology and American Heart Association (ACC/AHA) periodically define practice guidelines and recommendations for the management of NSTEMI ACS that are dependent on the relative risk of the patient at the time of presentation.^{3,4} Briefly, the 2002 NSTEMI ACS guidelines for antithrombotic therapy in the hospital setting include a Class Ia recommendation for immediate therapy with aspirin or clopidogrel (if aspirin is contraindicated), dual therapy with both of these agents

for up to 1 month if medical therapy or PCI is planned, and for treatment with a heparin (either intravenous parenteral UFH or LMWH).

Class IIa recommendations, based on grade A evidence, state that enoxaparin should be used over UFH unless CABG is planned within 24 hours. The reason for this is that the LMWH has a longer half-life than UFH. Patients may experience an increase in bleeding if the LMWH has not been adequately cleared from their systems before CABG.

These 2002 guidelines are somewhat outdated at this point in that they do not reflect the latest clinical evidence and the role of new agents such as fondaparinux and bivalirudin. The revised NSTEMI ACC/AHA practice guidelines will be published in 2007. Some of the specific aspects which will be addressed or expanded upon in the new guidelines will include:

- A re-emphasis on early risk stratification and an early invasive approach in higher risk patients as per the TIMI 18 trial and meta-analyses
- Emphasis on combination oral anti-platelet therapy (ASA + clopidogrel), with an appropriate loading dose of clopidogrel and a lowering of ASA dose as per the CURE, CURE-PCI, ARMYDA-2, ISAR-REACT and CREDO trials
- Expanding the duration of treatment with clopidogrel to one year as per the CURE and CREDO trials
- The question as to whether a glycoprotein IIb/IIIa inhibitor should be used in higher-risk patients as per the ISAR-REACT 2 and ACUITY trials
- The use of enoxaparin, UFH, or fondaparinux for medical stabilization as per the ESSENCE, TIMI 11B, and OASIS-5 trials
- The use of enoxaparin, UFH, or bivalirudin with an early invasive approach as per the SYNERGY and ACUITY trials

Anticoagulation in ACS: A Shifting Paradigm

Considering the outcomes of recent trials such as the REPLACE-2, OASIS-5 and ACUITY trials, the optimal use of anticoagulant therapy in NSTEMI ACS has been further elucidated. The findings can be summarized as follows:

- NSTEMI-ACS is common and associated with high morbidity and mortality.
- Early invasive strategy is preferred in higher-risk individuals.
- Early initiation of appropriate anti-platelet and anticoagulant therapy is important for reduction of ischemic events.
- Balancing the risk of ischemic and bleeding complications is essential to maximize clinical benefit in individual patients.
- Fondaparinux has demonstrated comparable efficacy to LMWH in NSTEMI ACS and less major bleeding. However, the increased incidence of catheter clot formation in the setting of PCI is a significant concern.
- The direct thrombin inhibitor, bivalirudin, has been evaluated in NSTEMI ACS and has demonstrated noninferiority to traditional UFH or LMWH therapy in preventing ischemic events and superior outcomes in terms of major bleeding and patient safety.
- The evidence base and strategies for optimal management of NSTEMI-ACS continue to evolve.

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