

Value in Thrombosis Management

Advances in Anticoagulant Therapy to Support Primary PCI

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Introduction

ST-segment elevation myocardial infarction (STEMI) is the most severe form of acute coronary syndrome (ACS) and carries a substantial risk of death and disability.¹ Acute STEMI results from a severe and sudden cessation of myocardial blood flow, most commonly due to an atherosclerotic-thrombotic occlusion of a major coronary artery. The resulting myocardial injury is identified by a significant abnormality on the electrocardiogram (ECG), specifically ST-segment elevation.

Current American College of Cardiology and American Heart Association (ACC/AHA) practice guidelines recommend that STEMI patients receive rapid treatment to restore flow within the occluded coronary artery and prevent further heart damage.² The AHA estimates that 865,000 new and recurrent heart attacks occur every year, of which 400,000 are categorized as STEMI.³ STEMI is part of a spectrum of acute coronary syndromes (ACS) that also includes non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). Each year, approximately 5 million Americans require emergency care for chest pain, of which an estimated 1.4 million are diagnosed with ACS.

Advances in percutaneous coronary intervention (PCI) techniques and adjunctive pharmacologic therapy have improved outcomes in patients with STEMI. However, several areas for improvement remain.³ Hemorrhagic complications, which are relatively common in patients receiving intensive anticoagulant and antiplatelet therapy to suppress clot formation and ischemia during primary PCI, have been strongly associated with early and late mortality. Newer antithrombotic agents have been investigated with the intent to improve upon these outcomes.

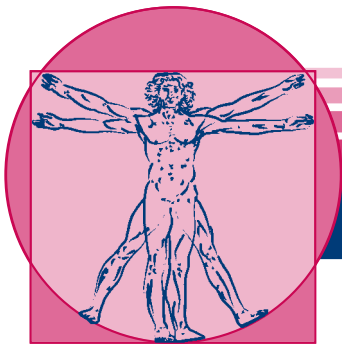
Primary PCI

Once again, the goals for the initial management of STEMI include rapid restoration of flow, prevention of early reinfarction, and avoidance of complications of reperfusion therapy.^{2,4}

The current standard of care for patients with STEMI involves urgent reperfusion of the infarct-related artery by either fibrinolysis or primary PCI. Survival depends on timely treatment with either modality. Although timely availability may be an issue in some cases, primary PCI has demonstrated a survival advantage when compared with fibrinolytic therapy alone and has the potential for fewer complications. Primary PCI in patients with evolving STEMI decreases infarct size and the rates of recurrent ischemia, reinfarction, and stroke and improves survival, as compared with pharmacologic (fibrinolytic) reperfusion therapy.

Fibrinolytic therapy, in comparison with conservative management (medical treatment without reperfusion therapy), leads to improved left ventricular systolic function and survival in patients with STEMI. In a pooled analysis of nine large trials, the rate of death at 35 days was 9.6% among patients receiving fibrinolytic therapy, as compared with 11.5% among control subjects.^{4,5} However, fibrinolytic therapy has several limitations.⁶ First, some patients may have a contraindication to fibrinolysis; second, in approximately 15% of patients given fibrinolytic therapy, thrombolysis does not occur; and third, approximately one-quarter of those receiving fibrinolytic therapy experience reocclusion of the infarct-related artery within three months post-MI with a resultant reinfarction.^{6,7-10}

These limitations are minimized with the use of primary PCI in acute STEMI that consists of urgent balloon angioplasty, with or without stenting, and without the previous



administration of fibrinolytic therapy or platelet glycoprotein IIb/IIIa inhibitors to open the infarct-related artery.⁶ In a meta-analysis of 23 randomized, controlled comparisons of primary PCI and fibrinolytic therapy, the rate of death at four to six weeks after treatment was significantly lower among those who underwent primary PCI [7% (n=270) vs. 9% (fibrinolytic therapy, n = 360); p=0.0002].⁴ Rates of nonfatal reinfarction and stroke were also significantly reduced. Similar results were found during long-term follow-up and were independent of both the type of fibrinolytic agent used and whether or not the patient was transferred for primary PCI.

Regardless of the reperfusion method, the overriding factor in the management of acute STEMI is to minimize the time from symptom onset to initiation of reperfusion management. The 2007 ACC/AHA Focused Guideline Update for the Management of Patients with STEMI states the following:²

- If the patient arrives at a non-PCI-capable hospital, the **door-to-needle** (fibrinolytic administration) time should be within 30 minutes of arrival at the emergency department.
- If the patient arrives at a PCI-capable hospital, the **door-to-balloon** time should be within 90 minutes.
- If the patient presents to a non-PCI-capable hospital, it is appropriate to consider emergency *interhospital transfer* of the patient to a PCI-capable hospital if there is a contraindication to fibrinolysis or if PCI can be initiated within 90 minutes after the patient presented to the initial receiving hospital or within 60 minutes compared with when fibrinolysis could be initiated at the initial receiving hospital.

The “Door-to-Balloon (D2B)” is an Alliance for Quality campaign organized by the ACC in collaboration with many organizations to improve the timeliness of primary PCI.¹¹ The goal is to increase

the percentage of patients who receive timely primary PCI, with an emphasis on having at least 75% of patients treated within 90 minutes of presentation, with a recommendation for the use of evidence-based strategies to reduce needless delays.

Ancillary Therapy in Primary PCI

Anticoagulant and Antiplatelet Therapy

Anticoagulant therapy is indicated in STEMI patients regardless of reperfusion strategy. Unfractionated heparin (UFH) is the most commonly used anticoagulant in STEMI patients undergoing primary PCI, often with a glycoprotein (GP) IIb/IIIa inhibitor.² However, UFH has several well-known limitations, including an unpredictable anticoagulant effect necessitating careful laboratory monitoring, extensive protein binding, and inactivation by platelet factor⁴. In addition, the available data do not suggest a benefit of prolonging the duration of the UFH infusion beyond 48 hours in the absence of ongoing indications for anticoagulation; more prolonged infusions of UFH increase the risk of the development of heparin-induced thrombocytopenia (HIT).²

The GP IIb/IIIa inhibitors have been shown to decrease the short- and long-term risk of death in patients undergoing primary PCI and are used in more than 90% of patients who undergo this procedure in the United States.^{12–14} However, these agents have been shown to increase the risk of bleeding complications and thrombocytopenia, which are associated with early and late mortality.

The low-molecular-weight heparin, enoxaparin, can be prescribed as an alternative to UFH in patients presenting with STEMI who are receiving fibrinolytic therapy and are younger than 75 years without renal dysfunction.¹⁵ They are not indicated in primary PCI.

Recent Anticoagulant Evidence in Primary PCI

To overcome the many issues associated with the use of UFH, newer anticoagulants that possess more predictable and targeted anticoagulant effects have been investigated in patients with STEMI undergoing primary PCI.

Fondaparinux

Fondaparinux is a relatively new antithrombotic agent that selectively binds to antithrombin (AT) III, catalyzing the specific inhibition of factor Xa. Fondaparinux exhibits a prolonged elimination half-life of 17 to 21 hours and is predominately eliminated by the kidneys as an unchanged drug. The anticoagulant effects of fondaparinux are not reversible.¹⁶

The Sixth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-6) trial enrolled 12,092 patients with STEMI from 41 countries.¹⁷ Patients were randomized to fondaparinux (2.5 mg once daily given for up to eight days) or usual care consisting of placebo for those in whom UFH was not indicated (stratum 1) or UFH for up to 48 hours followed by placebo for up to eight days (stratum 2).

The composite endpoint of death or reinfarction at 30 days was significantly reduced in the fondaparinux group [9.7% vs. 11.2% (control), hazard ratio (HR) 0.86;95%CI,0.77-0.96; p = 0.008]. However, this benefit was lost in the 3,709 patients who underwent primary PCI (1,898 patients allocated to receive UFH or placebo and 1,890 patients allocated to receive fondaparinux). All patients in the control group received UFH during the procedure (per protocol), compared with 20.8% in the fondaparinux group. Although the combined rate of death and MI did not differ significantly between the two groups at 30 days [6.1% (fondaparinux) vs. 5.1% (control); p = 0.19], the use of fondaparinux compared to the control group was associated with a greater number of guiding catheter thrombosis

events (22 vs. 0, respectively; $p = 0.001$) and coronary complications (270 vs. 225, respectively; $p = .04$). The addition of UFH to the fondaparinux regimen during PCI largely avoided these complications, as demonstrated in 496 patients who received UFH prior to primary PCI.

In summary, the authors provide the following statement: "Given the very limited time for antithrombotic therapy prior to the procedure and the need for UFH during the procedure, there is probably little advantage in using fondaparinux as the initial treatment in patients in whom primary PCI is intended."

Bilvalirudin

Bilvalirudin, a synthetic direct thrombin inhibitor (DTI), has been approved by the U.S. Food and Drug Administration as an antithrombotic alternative to UFH for patients with UA/NSTEMI undergoing PCI, including those with a history of HIT. Bivalirudin exhibits predictable, linear pharmacokinetics allowing for a simplified dosing regimen and limited monitoring. Because of a relatively short half-life of approximately 25 minutes, bivalirudin's effects dissipate rapidly once discontinued, permitting early sheath removal two hours after the infusion is stopped without checking the activated clotting time (ACT).^{18, 19}

When bivalirudin is used in place of UFH plus a GP IIIa/IIb inhibitor in patients with stable/unstable angina and NSTEMI, it has been shown to reduce rates of major and minor bleeding and thrombocytopenia while producing similar rates of ischemia after PCI.^{21, 22} Prior to the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) study, the safety and efficacy of bivalirudin in patients with STEMI undergoing primary PCI had not been evaluated.²³

The HORIZONS AMI trial enrolled 3,602 patients from 123 centers in 11 countries. All patients had STEMI with a symptom onset of less than 12 hours and were randomized in a 1:1 ratio to UFH [60 U/kg IV, with subsequent boluses titrated per protocol to achieve an activated clotting time (ACT) of 200 to 250 seconds] plus a GP IIb/IIIa inhibitor (abciximab or eptifibatide), or to bivalirudin monotherapy (0.75 mg/kg bolus; infusion 1.75 mg/kg per hour), or bivalirudin plus a provisional GP IIb/IIIa inhibitor for large thrombus or refractory no-flow.²³ (Figure 1.) After randomization, emergency coronary angiography was completed followed by PCI, coronary artery bypass graft (CABG) surgery, or medical management as determined by the cardiologist. Once vessel patency was restored, eligible patients were then randomly assigned, in a 3:1 ratio, to either paclitaxel-eluting

Figure 1: Initial Invasive Strategy with Bivalirudin in STEMI: HORIZONS AMI

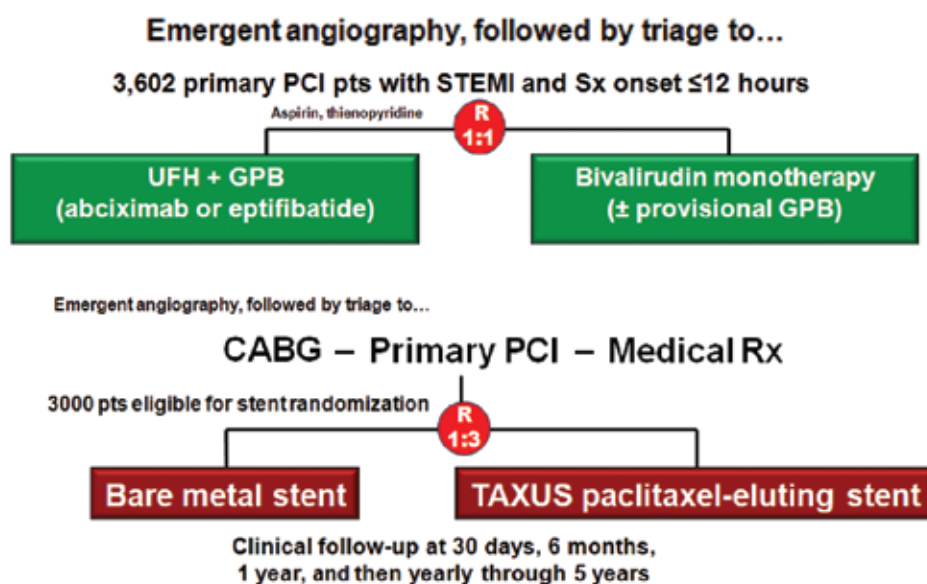
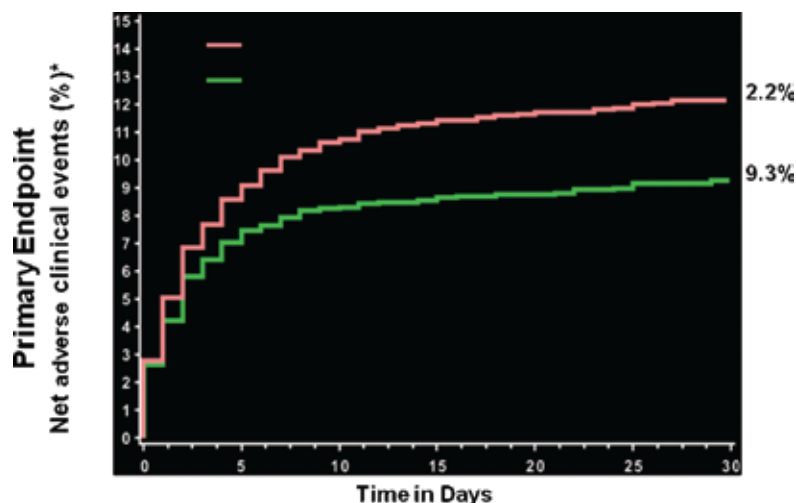


Figure 2: 30-day Net Adverse Clinical Events (HORIZONS AMI)



*NACE (All cause death, reinfarction, ischemic target vessel revascularization or stroke) or non-CABG major bleeding

stents (Taxus Express) or uncoated bare-metal stents. Aspirin (324 mg orally or 500 mg intravenously) was given in the emergency room, followed by 300–325 mg daily during hospitalization and 75–81 mg daily thereafter, indefinitely. A loading dose of clopidogrel (either 300 mg or 600 mg), according to the physician, or ticlopidine 500 mg (if allergic to clopidogrel) was administered before catheterization followed by 75 mg daily for at least six months.

The investigators prespecified two primary endpoints, including major bleeding (not related to CABG surgery) and/or net adverse clinical events (NACE) defined as the combination of bleeding or a composite of major adverse cardiovascular events (MACE), including all-cause death, reinfarction, target vessel revascularization for ischemia, and stroke. The trial was powered to test for noninferiority and superiority, with noninferiority margins for major bleeding and net adverse clinical events prespecified at 1% and 3.2%, respectively.

At 30 days, the bivalirudin alone group had a significantly reduced rate of net adverse clinical events compared to UFH plus a GP IIb/IIIa inhibitor. (Figure 2, Table 1.) The rate of major adverse cardiovascular events was similar between the two groups (5.4% vs. 5.5%, $p = 0.95$). (Table 1.) Thus, the benefit of bivalirudin was driven by the 40% reduction in non-CABG-related major bleeding. (Figure 3, Table 1.)

In addition, treatment with bivalirudin resulted in significantly lower 30-day rates of death from cardiac causes and all-cause death. (Table 2.) The authors suggested that the reduction in bleeding could account for the mortality benefit. There were no significant differences between groups in the rates of reinfarction, target-vessel revascularization, and stroke.

Among 3,124 patients in whom stents were successfully implanted, the overall rate of stent thrombosis at 30 days did not differ significantly between the groups. However, in a prespecified

Figure 2: 30-day Non-CABG Major Bleeding Events (HORIZONS AMI)

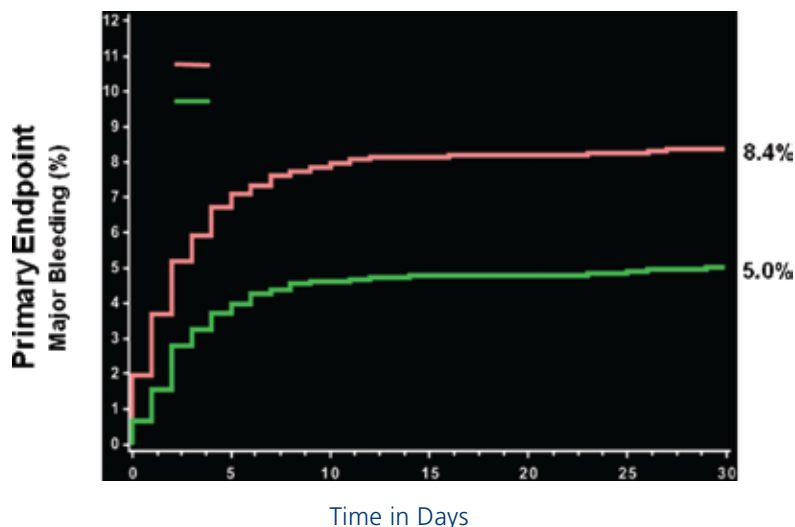


Table 1. Major Outcomes in HORIZONS AMI

Endpoint	UFH-GP IIb/IIIa inhibitors (%)	Bivalirudin (%)	Absolute difference (%)	RRR (%)	p: noninferiority	p: superiority
NACE	12.1	9.2	-2.9	24	<0.0001	0.006
Major bleeding	8.3	4.9	-3.3	40	<0.0001	<0.0001
MACE	5.5	5.4	—	—	—	NS

UFH: unfractionated heparin
GP IIb/IIIa inhibitor: glycoprotein IIb/IIIa inhibitor
RRR: relative risk reduction

NACE: net adverse clinical events
MACE: major adverse cardiovascular events

Table 2. Death at 30 Days in HORIZONS AMI

Endpoint	UFH-GP IIb/IIIa inhibitors (%)	Bivalirudin (%)	p
All death	3.1	2.1	0.058
Cardiac death	2.9	1.8	0.035

UFH: unfractionated heparin
GP IIb/IIIa inhibitor: glycoprotein IIb/IIIa inhibitor

analysis, within the first 24 hours, stent thrombosis occurred in 17 more patients in the bivalirudin vs. the UFH + GP IIb/IIIa inhibitor (1.3% vs. 0.3%, $p < 0.001$). This outcome did not increase the rate of reinfarction or death at 30 days. In addition, between 24 hours and 30 days, stent thrombosis occurred in seven fewer patients in the bivalirudin group (1.2% vs. 1.7%, $p = 0.28$).

It should be noted that the results of this study are similar to those of the ACUITY trial, which showed a significant reduction in major bleeding and net adverse cardiac events with bivalirudin alone among patients with UA/NSTEMI²². This outcome in HORIZONS AMI also was driven by a significant reduction in major bleeding with no real difference between groups for cardiac events. One limitation of the HORIZONS AMI trial is that a large majority of patients received UFH prior to randomization. This makes extrapolation of bivalirudin monotherapy to clinical practice somewhat less clear. Another trial limitation was the open-label design, with physicians aware of which study drug the patient had received.

ACC 2007 PCI Guideline Update: Ancillary Therapy (Antithrombotic Agents)

The following updated practice guidelines reflect recent clinical evidence for the use of anticoagulant therapy in PCI:

- For prior treatment with UFH: Administer additional boluses of UFH as needed to support the procedure, taking into account whether GP IIb/IIIa inhibitors have been administered. (Level of Evidence: 1C.) Bivalirudin also may be used in patients treated previously with UFH. (Level of Evidence: 1C, HORIZONS AMI.)
- For prior treatment with enoxaparin: If the last subcutaneous dose was administered within the prior eight hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered at least eight to 12 hours earlier, an IV dose

of 0.3 mg/kg of enoxaparin should be given. (Level of evidence 1B.)

- For prior treatment with fondaparinux: Administer additional intravenous treatment with an anticoagulant possessing anti-IIa activity, taking into account whether GP IIb/IIIa receptor antagonists have been administered. (Level of Evidence: 1C, OASIS-6.)
- Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered. (Level of Evidence: 3C, OASIS-6.)

Conclusion

ST-segment elevation myocardial infarction is the most severe form of ACS and carries a substantial risk of death and disability. The ACC/AHA practice guidelines recommend that STEMI patients be treated rapidly to prevent further heart damage leading to increased morbidity and mortality. Advances in techniques and pharmacologic management have improved patient outcomes after primary PCI in STEMI. However, hemorrhagic complications are relatively common in patients receiving intensive anticoagulant and antiplatelet regimens. Clinical trials have evaluated newer antithrombotic agents in this patient population. In review of the OASIS-6 trial, the composite endpoint of death or reinfarction at 30 days was significantly reduced in the fondaparinux group compared to UFH. However, this benefit was lost in the patients who underwent primary PCI due to a greater number of guiding catheter thrombosis events and coronary complications. The HORIZONS AMI trial was the first large-scale study to evaluate the clinical value of bivalirudin in patients with STEMI. This well-designed trial shows that the administration of bivalirudin alone in patients with acute

STEMI undergoing primary PCI is safe and even superior when compared with UFH in combination with a GP IIb/IIIa inhibitor. Major and minor bleeding complications were significantly less in patients treated with bivalirudin. Bivalirudin warrants consideration among the alternatives for ancillary anticoagulant therapy in patients undergoing primary PCI.

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