Mortality rates for acute ST-segment–elevation myocardial infarction (STEMI) have improved dramatically over the past 3 decades: effective reperfusion therapy has been the cornerstone of this improvement, with recent trends showing growth in primary percutaneous coronary intervention (PCI). Although mortality rates for routine risk STEMI patients are now ≤5%, process and procedure challenges remain prevalent. A key area of persistent controversy is optimal anticoagulation during the primary PCI procedure.

Four anticoagulant options are available for primary PCI: heparin, enoxaparin, fondaparinux, and bivalirudin. Clinical practice is heterogeneous in terms of anticoagulant choices, timing, and context of delivery. In a recent study of primary PCI for STEMI performed between 2007 and 2010, US practice reflected this heterogeneity—among over 66,000 primary PCI patients included in the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) registry, 80% received unfractionated heparin, 11% received low–molecular weight heparin, 23% received bivalirudin, and none received fondaparinux. Although glycoprotein inhibitors (GPI) are not anticoagulants, it is not possible to discuss primary PCI anticoagulant strategies without mentioning these potent antiplatelet agents—of note, the ACTION registry confirms the relevancy of this drug class, demonstrating that 79% of primary PCI patients in the United States received GPI agents in the first 24 hours of their hospitalization. This review will address the issues and controversy of anticoagulation for primary PCI in 4 sections: (1) thrombin generation during primary PCI and the individual characteristics of each anticoagulant, (2) the changing context of primary PCI anticoagulants with respect to other interventional approaches and therapies, (3) an overview of recent controversial trials, and (4) recommended anticoagulation for the clinical practice of primary PCI.

Antithrombins: Pathophysiology and Pharmacology

**Pathophysiology**

Anticoagulation for primary PCI addresses 2 pathophysiological processes: initial thrombin generation caused by spontaneous coronary plaque rupture and secondary thrombin generation caused by iatrogenic introduction of foreign bodies (stents) and arterial dissection (balloon angioplasty). The thrombotic process does not cease on successful implantation of a coronary stent: platelet activation in the setting of endothelial disruption continues and monocyte–platelet aggregates (a measure of platelet activation and inflammation) peak ≈2 hours after coronary intervention (Figure 1). This manifests itself clinically in studying peak time for acute stent thrombosis: in a large multicenter registry study (N=5842), the peak incidence of acute stent thrombosis occurs in the 2 to 3 hours after primary PCI. Thus, discussion of anticoagulation strategies involves not only type of anticoagulant but duration of effects. The relationship between an enhanced thrombotic potential and the underlying state of vascular inflammation is relevant to the topic of PCI during STEMI: the risk of stent thrombosis is proportional to the acuity of the coronary syndrome.

Thus, optimization of anticoagulation in the setting of primary PCI is of increased importance: the risk of acute (24 hour) stent thrombosis in the context of primary PCI may still be between 1% and 3%. In this context, 4 antithrombin agents have been studied in primary PCI: heparin, enoxaparin, fondaparinux, and bivalirudin. The role of these 4 anticoagulants in PCI in general has been the subject of prior reviews, and the comparative advantages/disadvantages of these agents in elective PCI is generally the same as for primary PCI. Additional data and pharmacology of specific importance to primary PCI will be reviewed below.

**Unfractionated Heparin**

Heparin was discovered in 1916 and works as an anticoagulant via the plasma cofactor, antithrombin. Heparin–antithrombin complexes inactivate multiple coagulation enzymes, with thrombin (and to a lesser degree, Factor Xa) receiving the most potent inhibitory effects from antithrombin. Although heparin can be administered intravenously or subcutaneously, only the intravenous form is relevant to primary PCI because subcutaneous delivery leads to delay in anticoagulant effects. The pharmacokinetics of unfractionated heparin are complex...
and nonlinear: the effective biological half-life of heparin increases from \( \approx 30 \) minutes after an IV bolus of 25 U/kg to 60 minutes with an IV bolus of 100 U/kg. Unfractionated heparin has heterogeneous anticoagulation effects and multiple limitations: inability to bind clot bound thrombin, inhibition by platelet factors, activation of platelets, and variable patient responses are all significant concerns. Despite the many limitations of unfractionated heparin, this anticoagulant has been extensively studied and is more widely used in primary PCI for STEMI than any other anticoagulant.

There are no placebo controlled trials of heparin in primary PCI. Furthermore, optimal dosing of heparin has varied dramatically over the past 2 decades of STEMI PCI. The earliest primary PCI experiences used not only high and fixed doses of heparin, but prolonged infusions lasting \( \leq 5 \) days. Some trials used activated clotting time to guide use of additional bolus heparin to achieve a variety of clotting time goals. Early studies in acute coronary syndrome patients suggested a relationship between activated clotting time (ACT) and risk of abrupt closure, and these findings were confirmed in the Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients (STEEPLE) trial: activated clotting times of \( <325 \) seconds were associated with increased ischemic events and ACT goals in early primary PCI trials like Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) were \( >325 \) seconds; the association between lower ACT values and ischemic risk has been controversial, but a narrow therapeutic window is clear—higher ACT values confer an enhanced risk of bleeding. More recent trials of heparin for primary PCI have used a weight-based dosing of 60 to 70 U/kg of heparin rather than fixed bolus or ACT-guided dosing.

In addition to bleeding risk and inconsistent anticoagulation, unfractionated heparin is limited by the complication of thrombocytopenia. Heparin-induced thrombocytopenia is an antibody-mediated reaction that may cause arterial or venous thrombosis. In addition to the heparin-induced thrombocytopenia syndrome, heparin-based regimens may be more likely to cause generalized thrombocytopenia: in the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS) trial, in hospital–acquired thrombocytopenia (platelet counts < 150000) occurred in 13.1% of primary PCI patients treated with heparin and GPI as compared with 10.4% patients treated with bivalirudin \( (P=0.004) \); new acquired thrombocytopenia demonstrated a potential association with mortality.

### Enoxaparin

Enoxaparin is the low–molecular weight heparin most studied in primary PCI. Low–molecular weight heparins are derived from unfractionated heparin and have greater activity against Factor Xa than thrombin. Enoxaparin has an ex vivo 4:1 ratio of Factor Xa: thrombin activity. As compared with unfractionated heparin, enoxaparin has reduced binding to plasma proteins and thus a more predictable anticoagulant effect. Furthermore, enoxaparin has a longer half-life than unfractionated heparin, with further delayed clearance in the setting of renal dysfunction. This combination of prolonged pharmacokinetic effects and more predictable anticoagulant effects led to comparisons of weight-based dosing of enoxaparin versus ACT-guided dosing of unfractionated heparin with clinical benefits seen for enoxaparin in the setting of acute coronary syndromes. Enoxaparin may be dosed by intravenous or subcutaneous routes with the intravenous route favored in primary PCI at the dose of 0.5 mg/kg bolus. The anti-Xa effects of enoxaparin become negligible 8 hours after initial dosing, and measurement of anti-Xa effects with ACT are not reliable.

Although there are many trials and analyses of enoxaparin in elective PCI, acute coronary syndrome PCI, and PCI in conjunction with fibrinolysis, there is limited randomized clinical trial data on enoxaparin efficacy and safety in the setting of primary PCI. Enoxaparin has clear pharmacological advantages over heparin, but the results of clinical trials in primary PCI have been mixed. The Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial was a large complex trial involving 3 randomized arms with upstream abciximab, upstream fibrinolysis, or no upstream agent in conjunction with STEMI PCI done with abciximab; the trial had a large prospective substudy of patients receiving enoxaparin versus unfractionated heparin in the setting of this abciximab-based STEMI PCI. FINESSE was a negative trial overall and failed to show superiority for aggressive upstream antiplatelet or fibrinolytic regimens, but the enoxaparin versus unfractionated heparin nonrandomized substudy generated a hypothesis of superiority for cardiac ischemic outcomes with enoxaparin-based STEMI PCI.

The STEMI Treated With Primary Angioplasty and Intravenous Lovenox or Unfractionated Heparin (ATOLL) trial was a large, international randomized trial and directly compared the superiority of these 2 heparin agents in the setting of primary PCI: 900 patients undergoing primary PCI were randomized to enoxaparin versus unfractionated heparin. Dosing of enoxaparin in ATOLL was 0.5 mg/kg intravenous bolus at time of PCI and was compared with unfractionated heparin dosing at 50 to 70 U/Kg (if GPI used) or 70 to 100 U/Kg (if no GPI used) with goal ACT of 200 to 300 seconds (if GPI used) or 300 to 350 seconds (if GPI not used). Of note, over 75% of patients in both arms received GPI agents at the time of PCI, and radial access was used in 2/3 of the patients. Bleeding complications were nearly identical in both arms of the trial. The trial did not meet its primary endpoint for demonstration of superiority of enoxaparin as compared with unfractionated heparin based on a composite end point involving both ischemic and bleeding end points: 28% event rate for enoxaparin versus 34% for unfractionated heparin, \( P=0.063 \); on the other hand, secondary end points and per protocol analyses did favor enoxaparin, and there was no suggestion of harm for any end point with the enoxaparin bolus strategy.

### Fondaparinux

Unlike unfractionated heparin that acts mainly on thrombin and enoxaparin, which acts partially on thrombin, fondaparinux is a synthetic pentasaccharide that acts entirely on Factor Xa. Like unfractionated heparin, it is an indirect inhibitor that
works through the antithrombin cofactor. The pharmacokinetics of fondaparinux are distinctly different than the other antithrombins. The half-life is \( \approx 18 \) hours and the anticoagulant effects are not reversible with protamine. Fondaparinux was compared with enoxaparin in the Organization for the Assessment of Strategies for Ischemic Syndromes-5 (OASIS-5) trial of patients with non-STEMI: fondaparinux was non-inferior for the primary efficacy end point and superior for the safety end point. But catheter-related thrombosis was significantly higher with fondaparinux (1.3% versus 0.5%, \( P \leq 0.001 \)), raising a safety concern.37,38 Fondaparinux was compared with unfractionated heparin or placebo in the large international randomized OASIS 6 trial: this is a complex trial, including both medically treated STEMI and primary PCI patients (31% of the total randomized sample), as well as 2 strata—fondaparinux versus placebo or fondaparinux versus unfractionated heparin. Fondaparinux was given at 2.5 mg/d subcutaneously for \( \leq 8 \) days; the primary PCI patients received a 2.5 mg IV bolus of fondaparinux compared with 60 U/kg bolus of unfractionated heparin followed by a 24 to 48 hour infusion of heparin. In stratum 2 (fondaparinux compared with unfractionated heparin), death or reinfarction occurred in 8.3% of fondaparinux patients as compared with 8.7% of the unfractionated heparin patients at 30 days follow up (\( P = \text{NS} \)). The results were less favorable for the newer, more predictable anticoagulant in the primary PCI substudy: death or MI occurred in 6.1% of the fondaparinux arm as compared with 5.1% of the control group (\( P = 0.19 \)). Concerns related to catheter-related thrombosis were apparent: 22 versus 0 catheter-related thromboses in the fondaparinux versus control arms (\( P < 0.001 \)).39,40 The pharmacokinetic properties and key clinical trials of the 4 potential anticoagulation regimens for primary PCI are summarized in Table 2. There is little controversy about the use of fondaparinux as an anticoagulant in primary PCI: both European and US guidelines contraindicate fondaparinux in primary PCI (Class III, level of evidence B34,35; Table 3).

**Bivalirudin**

Bivalirudin is a direct thrombin inhibitor and thus is the first anticoagulant discussed that is not dependent on plasma cofactors for inhibition of thrombin generation. Bivalirudin is an irreversible inhibitor of thrombin with a half-life of 25 minutes. There are multiple pharmacokinetic advantages to bivalirudin, including predictable anticoagulation effects, lack of platelet activation effects, short half-life, and ability to bind clot bound thrombin. Unlike unfractionated heparin, PCI dosing has been weight based, and monitoring with activated clotting times has not been required.19 Bivalirudin may be used after a bolus of unfractionated heparin with no clear adverse bleeding or thrombotic effects on switching between these 2 anticoagulants in the setting of primary PCI.16,40 On the other hand, bivalirudin has been studied in acute coronary syndrome PCI patient in conjunction with routine GPI utilization and showed no benefit compared with bivalirudin alone in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial: bleeding rates with bivalirudin and routine GPI were nearly identical to those of unfractionated heparin and GPI (5.3 versus 5.7%, \( P = \text{NS} \)), whereas the bivalirudin alone arm had significantly less bleeding compared with unfractionated heparin and GPI strategy (3.0 versus 5.7%, \( P < 0.001 \)).41 Based on ACUITY, a bivalirudin alone strategy (with bailout GPI only for large thrombus burden or slow flow) emerged as a potent bleeding avoidance strategy for acute coronary syndrome PCI, with little sign of increased thrombotic risk as compared with heparin and GPI.

Bivalirudin has been studied in 3 large randomized clinical trials of primary PCI: HORIZONS, European Ambulance Acute Coronary Syndrome Angiography Trial (EUROMAX), and How Effective Are Antithrombotic Therapies in Primary PCI (HEAT).16–18 Each trial has significant variation in both study arms—for example, although bivalirudin has been routinely dosed at 1.75 mg/kg/h at the time of primary PCI in all 3 trials, each study has varied the use of pre-PCI bivalirudin, the use of post-PCI bivalirudin, and the context of primary PCI. In addition, the comparator arms are significantly different as well—although all had an unfractionated heparin control arm, the frequency of use of GPI agents in each trial was variable. One can summarize the controversy engendered by the variable results of these 3 trials by making an analogy to the Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE 3) trial: BRAVE 3 compared an older standard of care (unfractionated heparin) to a strategy that was clearly pharmacologically superior with respect to antiplatelet inhibition (unfractionated heparin with routine GPI). BRAVE 3 failed to show a benefit of abciximab in primary PCI.42 (Figure 2). One could view the controversy regarding bivalirudin as similarly nihilistic—the newest trial shows no benefit of a pharmacologically superior thrombin inhibitor compared with unfractionated heparin in primary PCI and demonstrated potential harm (increased risk of acute stent thrombosis). These trial results are counterintuitive given the prior discussion of pharmacokinetics: before tackling this controversy, it is worth reviewing briefly the changing context of primary PCI anticoagulation over the past 2 decades.
Primary PCI Anticoagulation: A Changing Context

Primary PCI started as a risky procedure: “The role of coronary angioplasty relative to thrombolytic and conventional therapy of acute myocardial infarction has yet to be completely defined, but angioplasty will probably be most useful in patients who have contraindications to or have been unsuccessfully managed with thrombolytic therapies.” It is a remarkable tribute to PCI advances that such caution has been replaced by entire countries adopting primary PCI as the default or preferred strategy for STEMI reperfusion.

Until the early 1990s, anticoagulation associated with PCI was complex, drug dosages were high, technology was mediocre (balloon angioplasty alone), and complications of dissection, thrombosis, and emergency bypass surgery rates were in excess of 5%. The utilization of unfractionated heparin in the initial primary PCI experience was strikingly different from current trials and clinical practice: patients received 3000 to 5000 U of heparin after femoral vascular access, followed by 5000 to 7000 additional units of heparin after coronary angiography. Patients were treated after balloon angioplasty with intravenous heparin for 3 to 10 days; some patients received additional anticoagulation with intravenous dextran. The vascular sheath was left in place for 24 hours with heparin interruption for 2 to 3 hours to allow sheath removal the day after percutaneous transluminal coronary angioplasty.

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Table 1. Selected Trials in the Evolution of Anticoagulation Strategies in Primary PCI

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Study design</th>
<th>Heparin strategy</th>
<th>Oral antithrombotic</th>
<th>Glycoprotein inhibitor strategy</th>
<th>Vascular access and sheath management</th>
<th>Thrombectomy</th>
<th>Bleeding, %</th>
<th>Stent thrombosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, N=395</td>
<td>Fibrinolysis vs primary angioplasty</td>
<td>Greater than 10,000 U of heparin with a 3−5 day infusion</td>
<td>Aspirin alone with balloon angioplasty alone</td>
<td>None</td>
<td>Femoral access with unspecified sheath management</td>
<td>None</td>
<td>2.6 (PTCA) vs 6.5% (Lytics), P=0.06</td>
<td></td>
</tr>
<tr>
<td>International, multicenter, N=2082</td>
<td>Heparin−abciximab vs heparin alone</td>
<td>ACT target over 350 s if heparin alone, 200−300 s if abciximab</td>
<td>Aspirin indefinitely and ticlopidine before PCI and continued for 30 days</td>
<td>Intravenous abciximab bolus−12 h infusion</td>
<td>Femoral access with unspecified sheath management</td>
<td>None</td>
<td>2.2 vs 1.9%, P=0.49</td>
<td></td>
</tr>
<tr>
<td>International, multicenter, N=3602</td>
<td>Heparin + routine GPI vs bivalirudin</td>
<td>60 U/kg bolus with target ACT of 200−250 s</td>
<td>Aspirin indefinitely and clopidogrel (with 300/600 mg load) followed by 6−12 months</td>
<td>Intravenous abciximab or eptifibatide bolus+12−18 h infusion</td>
<td>94% femoral access with unspecified sheath management</td>
<td>11%</td>
<td>3.1 vs 2.1%, P=0.05</td>
<td></td>
</tr>
<tr>
<td>International, multicenter, N=2198</td>
<td>Upstream heparin−frequent GPI vs upstream bivalirudin</td>
<td>60 U/kg as median dose; option for enoxaparin also</td>
<td>Aspirin indefinitely; P2Y12 antagonist before PCI (clopidogrel 50%, ticagrelor 50%, prasugrel 50%)</td>
<td>69% of heparin arm vs 11% of bivalirudin arm; bolus and infusion</td>
<td>47% radial access; 53% femoral access as per institutional preferences</td>
<td>32%</td>
<td>3.1 vs 2.9%, P=0.86</td>
<td></td>
</tr>
<tr>
<td>Single center, N=1829</td>
<td>Heparin with infrequent GPI vs bivalirudin</td>
<td>Aspirin indefinitely; 11% clopidogrel and 89% ticagrelor/ prasugrel</td>
<td>GPI in 14% and 16% of bivalirudin and heparin groups</td>
<td>GPI vs upstream bivalirudin</td>
<td>Radial artery access in 81% of patients; femoral access per operator preferences</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time; BARC, Bleeding Academic Research Consortium; CADILLAC, Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; EUROMAX, European Ambulance Acute Coronary Syndrom Angiography Trial; GPI, glycoprotein inhibitors; HEAT, How Effective Are Antithrombotic Therapies in Primary PCI; HORIZONS, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; PCI, percutaneous coronary intervention; and PTCA, percutaneous transluminal coronary angioplasty.

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Antiplalet therapy options were limited to aspirin alone, access was limited to large femoral sheaths, closure devices were nonexistent, and thrombus management with catheters and stents had yet to be developed. In this early experience, 20% of primary PCI patients failed to achieve either TIMI Grade 3 flow or a residual stenosis of <70%. Most sobering, 7% of patients required emergency bypass surgery because of failed angioplasty, and the hospital mortality rate was nearly 10%. In this context of frequent procedural failure and
thrombotic complications, it is not surprising that the impact of bleeding complications on primary PCI outcomes were not even considered.

The growth of primary PCI as the predominant reperfusion strategy for STEMI is not simply a story of advancing anticoagulation strategies; this can be symbolized by a triangle centered on technological achievement, namely routine stenting using strict door to reperfusion guidelines surrounded by the 3 sides representing advances in thrombus management,\textsuperscript{47–50} bleeding avoidance strategies,\textsuperscript{51,52} and time-based systems to reduce mortality\textsuperscript{53} (Figure 3). As we look at selected trials in the evolution of anticoagulation strategies (Table 1), progress from a balloon angioplasty–based procedure (Primary Angioplasty in Myocardial Infarction [PAMI], CADILLAC) to a routine and timely stent–based procedure (Primary Angioplasty in Myocardial Infarction; PAMI, Primary Angioplasty in Myocardial Infarction; and PCI, percutaneous coronary intervention).

Controversial Trials in Primary PCI

To address this controversy in context, each trial involving bivalirudin and primary PCI must be examined in detail. The large (N=3602) HORIZONS Acute Myocardial Infarction (AMI) trial examined a strategy of potent antithrombin alone (bivalirudin) compared with a combination of heparin with mandatory intravenous antiplatelet therapy (glycoprotein inhibition) in a large international trial (N=3602).\textsuperscript{16} The heparin arm of this trial is strikingly different from the antithrombin arms of PAMI and CADILLAC—heparin was weight-based, infusions were stopped after the PCI, sheaths were removed early, closure devices and radial access were possible, and all patients received dual oral antiplatelet therapy. In this context, bivalirudin provided similar ischemic outcomes to a heparin/GPI strategy and a marked reduction in bleeding complications. On the other hand, acute stent thrombosis rates clearly favored the heparin/GPI strategy: (0.3 versus 1.3%, \(P<0.001\)). Given the dichotomy of this trial’s findings, intense debate has continued over the relative value of preventing bleeding versus thrombotic events in primary PCI.\textsuperscript{6,8,57,58} A mortality reduction seen in the bivalirudin arm persisting out to 3 years suggested that bleeding benefits of bivalirudin outweighed the increased risk of acute stent thrombosis.\textsuperscript{59} This concept has been challenged by 2 recent findings: (1) the mortality benefit of bivalirudin is seen independent of the bleeding reduction\textsuperscript{60} and (2) the mortality benefit of bivalirudin was not reproduced in the subsequent EUROMAX trial, despite reproducing the bleeding benefit of the bivalirudin strategy.\textsuperscript{17}

### Table 2. Anticoagulation Options for Primary PCI

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Mechanism of Action</th>
<th>Pharmacokinetics</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Key Primary PCI Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>Activation of antithrombin: Indirect antithrombin</td>
<td>Half Life: (\approx) 60 min but depends on bolus amount</td>
<td>Inexpensive and extensively studied; reversible; easily measurable anticoagulant effects</td>
<td>Heparin-induced thrombocytopenia (rare); platelet activation; inactive against clot bound thrombin; optimal dosing unclear</td>
<td>PAMI (23); CADILLAC (26); HORIZONS (16); ATOLL (30)</td>
</tr>
<tr>
<td>Low molecular weight heparin: enoxaparin</td>
<td>Inhibition of Factor Xa and IIa; 4:1 ratio of effect, predominantly acting on Factor Xa</td>
<td>Anti-Xa effects negligible after 8 h</td>
<td>More reliable thrombin inhibitory effect than heparin; Partially reversible</td>
<td>Heparin-induced thrombocytopenia (rare); Difficult to measure anticoagulant effect</td>
<td>ATOLL (30)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Indirect inhibitor of factor Xa</td>
<td>Half life: (\approx) 20 h</td>
<td>Daily dosing</td>
<td>Heparin-induced thrombocytopenia (rare); difficult to measure anticoagulant effect; catheter-related thrombosis</td>
<td>OASIS 6 (39)</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Direct antithrombin</td>
<td>Half life: 25 min</td>
<td>More reliable thrombin inhibitory effect than heparin; does not activate platelets; short half-life; no associated thrombocytopenia</td>
<td>Expensive; of reversible; short half-life; acute stent thrombosis risk</td>
<td>HORIZONS (16); EUROMAX (17); HEAT (18)</td>
</tr>
</tbody>
</table>

CADILLAC indicates Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; EUROMAX, European Ambulance Acute Coronary Syndrome Angiography Trial; HEAT, How Effective Are Antithrombotic Therapies in Primary PCI; HORIZONS, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; PAMI, Primary Angioplasty in Myocardial Infarction; and PCI, percutaneous coronary intervention.
Over the last decade, bivalirudin’s strength as a pharmacological approach to bleeding reduction has been challenged with nonpharmacological approaches to reducing bleeding.51,52 With the growth of radial artery-based primary PCI, it is possible that access site–related bleeding would become minimal and pharmacological-based bleeding avoidance strategies were irrelevant. On the other hand, use of more potent oral antiplatelet therapy was absent from HORIZONS and some argued that the bivalirudin’s stent thrombosis risk outcomes could be ameliorated with better oral P2Y12 receptor antagonists.60 The large (N=2198), multicenter EUROMAX trial provides clinicians with

Table 3. European and US Recommendations for Anticoagulation in Primary PCI

<table>
<thead>
<tr>
<th>2013 ACC-AHA STEMI guidelines34</th>
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<tbody>
<tr>
<td><strong>Unfractionated heparin</strong>—Class I recommended, level of evidence C</td>
</tr>
<tr>
<td>With GP IIb/IIIa receptor antagonist planned: 50 to 70 U/kg IV bolus to achieve therapeutic ACT</td>
</tr>
<tr>
<td>With no GP IIb/IIIa receptor antagonist planned: 70 to 100 U/kg bolus to achieve therapeutic ACT</td>
</tr>
<tr>
<td><strong>Bivalirudin</strong>—Class I recommended, level of evidence B</td>
</tr>
<tr>
<td>Bivalirudin: 0.75 mg/kg IV bolus, then 1.75 mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg can be given if needed</td>
</tr>
<tr>
<td>Reduce infusion to 1 mg/kg/h with estimated CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td>Preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high risk of bleeding Class IIA, level of evidence B</td>
</tr>
<tr>
<td><strong>Fondaparinux</strong>: Not recommended as sole anticoagulant for primary PCI Class III: Harm, B</td>
</tr>
<tr>
<td><strong>Enoxaparin</strong>: Not mentioned; no recommendation level given</td>
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</tbody>
</table>

<table>
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<tr>
<th>2012 ESC STEMI guidelines35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bivalirudin</strong>—Class I recommended, level of evidence B</td>
</tr>
<tr>
<td>With use of GP IIb/IIIa blocker restricted to bailout</td>
</tr>
<tr>
<td>Recommended over unfractionated heparin and a GP IIb/IIIa blocker</td>
</tr>
<tr>
<td>Bivalirudin 0.75 mg/kg IV bolus followed by IV infusion of 1.75 mg/kg/h for ≤4 h after the procedure as clinically warranted. After cessation of the 1.75 mg/kg/h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4–12 h as clinically necessary</td>
</tr>
<tr>
<td><strong>Enoxaparin</strong>—Class IIB, level of evidence B</td>
</tr>
<tr>
<td>With or without routine GP IIb/IIIa blocker</td>
</tr>
<tr>
<td>May be preferred over unfractionated heparin</td>
</tr>
<tr>
<td>Enoxaparin 0.5 mg/kg IV bolus</td>
</tr>
<tr>
<td><strong>Unfractionated heparin</strong>—Class I recommended, level of evidence C</td>
</tr>
<tr>
<td>With or without routine GP IIb/IIIa blocker</td>
</tr>
<tr>
<td>Must be used in patients not receiving bivalirudin or enoxaparin</td>
</tr>
<tr>
<td>Unfractionated heparin 70–100 U/kg IV bolus when no GP IIb/IIIa inhibitor is planned</td>
</tr>
<tr>
<td>50–60 U/kg IV bolus with GP IIb/IIIa inhibitors</td>
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<td><strong>Fondaparinux</strong> is not recommended for Primary PCI; Class III, level of evidence B</td>
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ACC-AHA indicates American College of Cardiology–American Heart Association; ACT, activated clotting time; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and UFH, unfractionated heparin.

Figure 2. Progress in primary percutaneous coronary intervention (PCI) pharmacology has occurred in the context of 3 moving pieces during the stent era: improved antithrombin strategies, improved antiplatelet therapy options, and a focus on access site management.
some answers to this controversy.\textsuperscript{17} Although this trial did not mandate GPI use in the heparin arm, GPI utilization was permitted. Over 2/3 of all heparin-based PCI was performed with a GPI strategy (69%). This trial has many unique features, including ambulance-based administration of bivalirudin, prolonged 4 hour infusions of bivalirudin predominantly at the 0.25/mg/kg/h dose post PCI, incorporation of radial access in 47% of primary PCI patients, and use of second generation P2Y12 antagonists in half of the population. But, it remains still a trial of largely bivalirudin versus heparin+prasugrel predominant GPI strategy and should be interpreted in that context.

EUROMAX, like HORIZONS AMI, shows a 40% to 50% reduction in major bleeding with the bivalirudin strategy as compared with the heparin+frequent GPI strategy.\textsuperscript{17} The benefit is strikingly similar in patients undergoing radial or femoral procedures (P int = 0.97), thus demonstrating that reduced access site bleeding with the radial approach is not the sole factor in overall bleeding complication rates. The acute stent thrombosis rate was once again 5-fold higher in the bivalirudin arm, despite 4 hours of low dose bivalirudin and frequent use of prasugrel or ticagrelor.\textsuperscript{4} Thus, EUROMAX primarily confirms and extends the prior observations of HORIZONS to the current era of oral antiplatelet therapy and optimized vascular access: compared with a frequent GPI+heparin strategy, bivalirudin maintains its bleeding benefit at the expense of increased risk of acute stent thrombosis.\textsuperscript{7} Notably, the mortality benefit of bivalirudin was not seen despite the bleeding benefit, although the low mortality rate in the trial makes this comparison underpowered.

The superiority of bivalirudin as compared with heparin with routine GPI for reduction of bleeding complications is clear and consistent; the increased risk of acute stent thrombosis with a bivalirudin strategy is similarly clear and generally consistent.\textsuperscript{5,7} This increased risk of acute stent thrombosis may be related to the short half-life of bivalirudin—a 25 minute half-life confers little or no antithrombin activity 2 hours after primary PCI is completed. As mentioned earlier in this review, PCI-related platelet activation and inflammation does not cease at the end of the PCI and may peak 2 hours later, which is associated with clinical consequence.\textsuperscript{3,14} Given the lack of consistent oral antiplatelet effects this early after primary PCI,\textsuperscript{6} this may make the bivalirudin strategy vulnerable to early thrombotic events (although GPI strategies that used 12–24 hour infusions would provide extended antiplatelet effects in this time window for acute stent thrombosis risk). Some data exists that ischemic outcomes could be improved with a 2 to 4 hour continuation of the bivalirudin infusion at the PCI dose.\textsuperscript{4,5} Of note, EUROMAX predominantly used a routine 0.25 mg/kg/h infusion for 4 hours after primary PCI, and this dosing did not prevent the acute stent thrombosis risk. Our group and a smaller sample from EUROMAX have proposed that continuing bivalirudin for 2 to 4 hours at 1.75 mg/kg/h might counteract the platelet activation and thrombosis risk after primary PCI, but this has not been proven in a randomized clinical trial.\textsuperscript{3,6,2}

In this context of persistent increased risk of acute stent thrombosis with bivalirudin, the large (N=1829) single-center HEAT trial generates even more controversy: this trial returns to the CADILLAC era question of the role of heparin alone in primary PCI (Table 1 and Figure 2).\textsuperscript{18,65} Unlike CADILLAC, HEAT randomized patients treated with heparin alone against patients treated with bivalirudin alone (as opposed to heparin/GPI).\textsuperscript{19} Heparin alone has a contemporary context in HEAT: multiple changes have occurred to minimize bleeding and thrombosis in primary PCI. Notably, stenting was used routinely, the dosing of heparin is lower (70 U/kg) with no post PCI infusion, access site management is 81% radial, and nearly 90% of patients receiving ticagrelor or prasugrel. Finally, selected patients in both the bivalirudin and heparin arms did have access to GPI as a bailout strategy (=15% of patients in each arm). The results of the study may not be nearly as shocking in this context of modernized heparin, vascular access, and PCI technologies: bleeding rates were =3.0% in both arms of the study; unlike EUROMAX and HORIZONS trials, which used routine/predominant GPI strategies, a bleeding benefit of bivalirudin could not be demonstrated. Like EUROMAX, mortality was similar in both arms. As with EUROMAX, more potent oral antiplatelet therapy did not eliminate the increased risk of acute stent thrombosis with bivalirudin: 0.9% versus 2.9%, P=0.007.

There are 2 possible analogies to understanding the HEAT challenge to routine use of bivalirudin in primary PCI: (1) HEAT is to potent antithrombins what Thrombus Aspiration during Percutaneous Coronary Intervention In Acute Myocardial Infarction is to thrombectomy—it is a single-center trial and no matter how well it is done, it cannot be acted on until multicenter trials (ie, for thrombectomy, TASTE [Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia], and TOTAL [Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With ST-Elevation Myocardial Infarction Undergoing Primary PCI]) adequately test these controversial single-center findings or (2) HEAT is to antithrombins what BRAVE-3 is to glycoprotein inhibition in primary PCI: a demonstration...
that rapid stenting, improved vascular access, and potent oral antiplatelet therapy (Figure 2) reduces the reliance on pharmacologically superior intravenous agents for excellent outcomes. Thus, clinicians are left with doubt regarding the optimal antithrombin strategy for primary PCI. New trial data will inform this debate, and further insights into the role of anticoagulant choices on the risk of early stent thrombosis may come from optical coherence tomography analyses. For now, the following is somewhat clear:

- **HEAT** primarily applies to the radialist using a modernized lower dose heparin strategy. For those clinicians performing primary PCI via the femoral approach or using larger doses of heparin, there is less data to support or refute the claim that a heparin strategy provides similar bleeding outcomes to the bivalirudin strategy.

- The **HEAT** bleeding results are seen only in the context of a 14% GPI bailout rate. If GPI bailout is used routinely in clinical practice, the results of EUROMAX more closely apply, and enhanced bleeding should be expected for both femoral and radial operators with non-bivalirudin strategies.

- The risk of acute stent thrombosis (within 24 hours of PCI) is generally higher with bivalirudin, regardless of the type of oral antiplatelet therapy and comparator drug; clinicians should be aware of this risk if bivalirudin is chosen—whether a 2 to 4 hour post PCI bivalirudin infusion (specifically at the PCI dose) obviates this risk remains to be determined.

**Recommended Anticoagulation for Primary PCI**

The European and US guidelines for primary PCI anticoagulation are summarized in Table 3. Both guidelines reach consensus on 2 guidelines—(1) both unfractionated heparin and bivalirudin receive strong Class I recommendations and (2) unfractionated heparin may be used either with or without GPI agents. These guideline statements were published before the HEAT trial publication, and whether they will be revised based on this single trial is unclear. The European guidelines do recommend continuing a 0.25 mg/kg/h bivalirudin infusion post STEMI PCI, and this will likely be revised given the lack of benefit of this approach seen in the EUROMAX trial. Both guidelines recommend bivalirudin over a strategy of heparin with routine GPI in patients at high risk for bleeding (American Heart Association–American College of Cardiology Guidelines) or all primary PCI patients (European Society of Cardiology guidelines) based on superior bleeding outcomes in HORIZONS and EUROMAX for bivalirudin. But, whether bivalirudin is superior to heparin with infrequent GPI (HEAT trial) is not addressed. Enoxaparin is mentioned in the European Society of Cardiology guidelines only (Class IIB) and both guidelines contraindicate fondaparinux.

The current guidelines give clinicians 3 viable options for primary PCI anticoagulation—(1) heparin with GPI routinely (less preferred), (2) bivalirudin alone with bailout GPI, or (3) heparin alone—all as Class I or Class II A recommendations. The controversies over anticoagulation for primary PCI provide clinicians with multiple reasonable choices. On the other hand, timely stent-based PCI is not optional. To perform primary PCI in a timely fashion, each institution or region must have an algorithm for care that eliminates delays and
errors. Each institution’s primary PCI pharmacology algorithm can be approached in 3 stages:

1. Standardize the upward medications for patients undergoing STEMI PCI to eliminate delays. Aspirin and ticagrelor can both be administered upstream in conjunction with bolus heparin.34,35 Whether ticagrelor administration provides substantial benefit upstream is controversial,54 but earlier dosing may be practical as it avoids swallowing pills after narcotics and sedation ensue. Notably, bolus heparin is not a commitment to any PCI anticoagulation strategy; the bivalirudin strategy was used after bolus heparin in nearly 2/3 of bivalirudin patients in the HORIZONS study.16

2. Anticoagulation at the time of the primary PCI procedure can begin with a bivalirudin or heparin alone strategy. The bivalirudin strategy is more expensive: it may still be strongly considered if (1) frequent GPI utilization is documented (>15% of patients),18 (2) the access is routinely femoral,16 or (3) heparin dosing exceeds 100 U/kg.75 But the risk of acute stent thrombosis with bivalirudin for primary PCI is real: a prolonged PCI dose of bivalirudin,62 optimization of stent implantation techniques, and close monitoring for 6 hours after PCI are all to be considered.

3. Catheterization laboratory nurses, emergency medical services personnel, and emergency department staff need timely feedback on all critical aspects of primary PCI, including first medical contact to device times, adjunctive medical therapies, and PCI outcomes (Figure 4). Delays and dosing errors associated with primary PCI anticoagulation are not rare and formal feedback may be helpful.9 Such feedback can improve both anticoagulation and overall processes across regional networks53,67 and, thus, allow continued evolution of the primary PCI process. And, feedback provides a path forward for the most certain aspect of primary PCI anticoagulation—a mechanism to change and update the regional pharmacological approach as we perform new trials, inevitably incorporating new anticoagulation strategies into the ever changing context of primary PCI delivery.

Disclosures

Dr Dauerman is currently a consultant to Medtronic, Abbott Vascular, Boston Scientific, Daichi Sankyo, and The Medicines Company and have research grants from Medinol, Medtronic, and Abbott Vascular.

References


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