

# Selecting the optimal antithrombotic regimen for patients with acute coronary syndromes undergoing percutaneous coronary intervention

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**Abstract:** The wide variety of anticoagulant and antiplatelet agents available for clinical use has made choosing the optimal antithrombotic regimen for patients with acute coronary syndromes undergoing percutaneous coronary intervention a complex task. While there is no single best regimen, from a risk-benefit ratio standpoint, particular regimens may be considered optimal for different patients. We review the mechanisms of action for the commonly prescribed antithrombotic medications, summarize pertinent data from randomized trials on their use in acute coronary syndromes, and provide an algorithm (incorporating data from these trials as well as risk assessment instruments) that will help guide the decision-making process.

**Keywords:** anticoagulant, antiplatelet, percutaneous coronary intervention

## Introduction

In the early days of percutaneous coronary intervention (PCI) the armamentarium of antithrombotic agents was limited; therefore, the decision on what agent(s) to administer was fairly straightforward. The wide variety of anticoagulant and antiplatelet agents available for clinical use now has made this decision-making process much more complex, and at times even confusing. While there is no single best choice for an antithrombotic regimen in patients with acute coronary syndromes (ACS) undergoing PCI, from a risk-benefit ratio standpoint, a particular regimen may be better for an individual patient. Because early invasive strategies with coronary angiography and PCI are preferred for certain patients with unstable angina, non-ST elevation myocardial infarction (STEMI),<sup>1-4</sup> and STEMI,<sup>5</sup> the scope of this issue is considerable. Nearly 8 million people are diagnosed with an ACS annually in the United States alone, and an estimated 1.3 million undergo a PCI procedure.<sup>6</sup> Importantly, up to 15% of patients undergoing PCI develop a major bleeding complication,<sup>7,8</sup> which results in higher rates of short- and long-term mortality.<sup>7,8</sup> The evidence supporting a causal relationship between major bleeding and excess mortality in patients undergoing PCI (including the potential mechanisms involved) has been recently reviewed.<sup>9</sup>

Decisions on the choice of antithrombotic regimen, therefore, should be individualized, and take into consideration both the risk of a recurrent cardiac event as well as the risk of a bleeding complication. We will review the mechanisms of action for the commonly prescribed antithrombotic medications, summarize pertinent data from randomized trials regarding their use in ACS, and provide an algorithm that will help physicians choose the most effective and safest regimen for an individual patient with an ACS undergoing PCI.

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## Antithrombotic agents – mechanisms of action

Patients presenting with ACS who undergo PCI benefit from a combination of antiplatelet and anticoagulant medications.<sup>10</sup> From a pathophysiologic standpoint, the inciting event for an ACS is endothelial injury (plaque rupture or erosion): subsequent activation of platelets and the coagulation cascade results in thrombus formation.<sup>11,12</sup> If this process is not interrupted, total occlusion of the coronary artery may occur, resulting in a myocardial infarction. Since platelet adhesion, activation, and aggregation comprise the initial stage in thrombus formation, antiplatelet agents (aspirin, thienopyridines, and platelet glycoprotein IIb/IIIa inhibitors) are critically important. Additionally, anticoagulant agents (indirect and direct thrombin inhibitors, and factor Xa inhibitor) also play a key role in the pathophysiologic process by limiting clot formation and propagation, particularly during the PCI procedure itself.

### Antiplatelet agents

Antiplatelet medications (aspirin, thienopyridines, and platelet glycoprotein IIb/IIIa inhibitors) are commonly used alone or in combination with other antithrombotic medications in patients with ACS undergoing PCI. We will briefly review their mechanisms of action.

#### Aspirin

Aspirin permanently and irreversibly blocks cyclooxygenase-1 for the lifespan of the platelet, inhibits the synthesis of thromboxane A<sub>2</sub>, and is a mainstay of therapy for patients with ACS. It has been shown to improve clinical outcomes<sup>13–16</sup> and unless contraindicated, should be administered to all patients with ACS, including those undergoing PCI.

#### Thienopyridines

Clopidogrel and ticlopidine are structurally related thienopyridines that selectively inhibit adenosine diphosphate (ADP)-induced platelet aggregation. They block the binding of ADP to the receptor P2Y<sub>12</sub>, thus inhibiting activation of the platelet glycoprotein IIb/IIIa complex and platelet activation.<sup>17</sup> A higher side effect profile of ticlopidine, including diarrhea, nausea, and vomiting in up to 50% of patients,<sup>18</sup> and serious hematologic complications such as neutropenia in 1.0% to 2.4% of patients,<sup>19</sup> and thrombotic thrombocytopenic purpura<sup>20</sup> has led to the primary use of clopidogrel in ACS. Prasugrel, a third generation thienopyridine recently approved by the United States Food and Drug Administration, is a more potent blocker of the platelet P2Y<sub>12</sub> receptor than

clopidogrel.<sup>21</sup> However, it has also been associated with increased risk of bleeding particularly in patients >75 years of age, in patients who weigh <60 kg, and in those with a history of transient ischemic attacks or strokes.<sup>22</sup>

#### Platelet glycoprotein IIb/IIIa inhibitors

Platelet activation leads to a conformational change in the glycoprotein IIb/IIIa receptor. Platelet glycoprotein IIb/IIIa inhibitors bind to and block the conformationally modified receptor, significantly blocking platelet aggregation. These agents can be divided into two groups:<sup>23</sup> (1) monoclonal antibodies that block the receptor (abciximab), and (2) natural or synthetic compounds that contain a sequence of amino acids recognized by the receptor that act as competitive inhibitors (tirofiban and eptifibatide). While all three agents are indicated as adjunctive agents in patients undergoing PCI, only eptifibatide and tirofiban are approved for use in patients presenting with a non-STEMI who do not undergo an early invasive strategy.

### Anticoagulant agents

Anticoagulant medications are also used alone or in combination with antiplatelet medications in patients with ACS undergoing PCI. These agents include indirect thrombin inhibitors (unfractionated and low-molecular-weight heparin), direct thrombin inhibitors (bivalirudin), and factor Xa inhibitor (fondaparinux).

#### Indirect thrombin inhibitors

The heparins, both unfractionated and low molecular weight, are indirect thrombin inhibitors. These agents complex with antithrombin and inhibit fibrin formation, as well as clot production and propagation. Unfractionated heparin has been the primary parenteral anticoagulant used in patients with ACS. It targets the coagulation factors IIa (thrombin) and Xa, with additional but less significant activity against factors IXa, XIa, and XIIa.<sup>24</sup> Unfractionated heparin inactivates thrombin by forming a complex with thrombin and antithrombin, and inactivates factor Xa through antithrombin. Limitations to unfractionated heparin use include the need for frequent laboratory monitoring, neutralization of heparin's activity by activated platelets,<sup>25</sup> thrombocytopenia,<sup>26</sup> platelet aggregation,<sup>26</sup> a dose-dependent risk of bleeding,<sup>27</sup> and rebound ischemia following its discontinuation.<sup>28–30</sup> Moreover, since unfractionated heparin is heterogeneous in structure (about one-third of heparin chains contain the high-affinity pentasaccharide required for anticoagulant activity) it is also heterogeneous in its pharmacologic activity.

Thus, the efficacy and safety of low-molecular-weight heparin has been studied in patients with ACS as an alternative to unfractionated heparin.

Low-molecular-weight heparins are fragments of unfractionated heparin formed via depolymerization reactions that result in polysaccharides of smaller size. Low-molecular-weight heparin has greater anti-Xa than anti-IIa activity. Importantly, it does not require monitoring of clotting times, is less inhibited by activated platelets,<sup>25</sup> and is associated with a lower incidence of heparin-induced thrombocytopenia<sup>31</sup> and rebound ischemia following its discontinuation.<sup>29</sup> Since it binds less avidly to heparin-binding proteins than does unfractionated heparin, it has better bioavailability and a more predictable anticoagulant response. Of the low-molecular-weight heparins clinically available, enoxaparin is by far the most widely used. It has been shown to decrease ischemic complications in patients treated both conservatively and invasively.<sup>32</sup>

### Direct thrombin inhibitors

The direct thrombin inhibitors, hirudin, argatroban and bivalirudin directly bind to thrombin (factor IIa) without the need for antithrombin. Compared to indirect thrombin inhibitors, they have a more predictable anticoagulant response, do not require anticoagulant monitoring, and are able to inactivate fibrin-bound as well as fluid-phase thrombin.<sup>33,34</sup> Importantly, because they do not bind to platelet factor 4, they do not cause heparin-induced thrombocytopenia. Hirudin and argatroban are approved for the treatment of patients with heparin-induced thrombocytopenia;<sup>35,36</sup> bivalirudin is approved as an alternative to heparin in patients with ACS and in patients undergoing PCI.

### Factor Xa inhibitor

Fondaparinux is a synthetic analog of the antithrombin-binding pentasaccharide sequence found in heparin. It is the only selective factor Xa inhibitor available for clinical use. It binds to and produces a conformational change in antithrombin, markedly increasing its anti-factor Xa activity, but has no activity against thrombin. Fondaparinux does not require monitoring of coagulation, which results in more predictable and sustained anticoagulation compared to heparin. Additionally, since it does not bind to platelets or to platelet factor 4, it does not cause heparin-induced thrombocytopenia. Because it is cleared by the kidneys, it is contra-indicated in patients with a CrCl < 30 ml/min. The American College of Cardiology/American Heart Association (ACC/AHA) recommends its use for patients with ACS who

are undergoing an early invasive or conservative strategy.<sup>37</sup> However, in patients undergoing PCI its use has been associated with high rates of catheter thrombosis, making the addition of unfractionated heparin mandatory in this setting.<sup>38</sup>

## Reversal of agents

If a patient does experience a serious bleeding episode, in addition to discontinuation of antithrombotic agents, several antidotes are available for clinical use to help stop the bleeding and stabilize the patient. In patients in whom unfractionated heparin has been given protamine sulfate can be administered. Protamine sulfate is administered intravenously at a rate that should not exceed 50 mg over 10 minutes because of the risk of histamine release resulting in hypotension, bradycardia, and bronchospasm.<sup>39</sup> The newer agents including low-molecular-weight heparin, the factor Xa inhibitor, fondaparinux, and the direct thrombin inhibitors do not have specific antidotes. While protamine sulfate is a specific and effective antidote for unfractionated heparin, it only partially neutralizes the anticoagulant effect of low-molecular-weight heparin (approximately 60% of the anticoagulant effect), and therefore its use may result in failure to stop the bleeding.<sup>40</sup> Recombinant factor VIIa has been shown to reverse the anticoagulant effect of fondaparinux, however, one important caveat is that this reversal effect was shown in healthy volunteers, not in patients with ACS.<sup>41</sup> In experimental models, recombinant factor VIIa, prothrombin complex concentrates, and desmopressin acetate have all been studied as to their ability to reverse the anticoagulant effect of the direct thrombin inhibitors.<sup>39</sup> Lastly, hemodialysis, hemoperfusion, and plasmapheresis may be indicated in some cases of severe bleeding.<sup>42</sup>

## Data from the randomized trials

Over the last decade, many randomized trials have been performed to evaluate the efficacy and safety of antithrombotic therapies. We will summarize pertinent data regarding their use in patients with ACS undergoing PCI.

### Role of thienopyridines

In trials comparing ticlopidine to clopidogrel in combination with aspirin following intracoronary stent placement, clopidogrel was not only as effective as ticlopidine, but had a superior safety and tolerability profile.<sup>43-45</sup> These positive findings for clopidogrel, together with the serious risk of neutropenia with ticlopidine,<sup>46</sup> has led to the virtual discontinuation of ticlopidine administration: used only in the rare patient who is intolerant to clopidogrel.

It has become increasingly clear that, in addition to aspirin, the early administration of clopidogrel is key since optimal pretreatment with this medication has been shown to significantly influence clinical outcomes in patients with ACS treated both conservatively<sup>47</sup> and invasively.<sup>48,49</sup> Hence, clopidogrel carries a Class I (level of evidence: A) indication for all patients with ACS according to the ACC/AHA guidelines.<sup>37</sup> Moreover, pretreatment (or lack of pretreatment) with clopidogrel influences the decision as to which antithrombotic regimen to choose for patients undergoing PCI. The original study demonstrating the importance of clopidogrel therapy in patients with ACS undergoing PCI was the PCI-Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study.<sup>48</sup> Of the 2658 patients undergoing PCI in this study, those who were pre-treated with 300 mg of clopidogrel had a 31% relative risk reduction in cardiovascular death or myocardial infarction at long-term (8-month) follow-up compared to those treated with placebo (8.8% vs 12.6%,  $P = 0.002$ ). Importantly, there was no significant difference in rates of major bleeding between the two groups (2.7% vs 2.5%,  $P = 0.64$ ). The benefit of clopidogrel administration is also evident in ACS patients who require coronary artery bypass surgery (CABG) following diagnostic coronary angiography. An analysis from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) study showed that patients who received clopidogrel prior to CABG had lower rates of the composite endpoint of death, myocardial infarction, or unplanned revascularization at 30 days compared to those who did not receive clopidogrel (12.7% vs 17.3%,  $P = 0.01$ ).<sup>50</sup> Moreover, there was no difference in rates of post-surgical major bleeding (50.3% vs 50.9%,  $P = 0.83$ ).

In addition to the length of time prior to PCI the loading dose of clopidogrel is administered, the dosage (conventional 300 mg or high dose 600 mg) is also important. It has been shown that some patients exhibit incomplete inhibition of ADP-induced platelet aggregation within 24 hours of a 300 mg loading dose of clopidogrel.<sup>51</sup> Thus, the risks and benefits of administering a higher loading dose of clopidogrel (600 mg) have been examined. In one study, 292 patients were randomized to either a 300 mg or 600 mg loading dose of clopidogrel at least 12 hours prior to PCI.<sup>52</sup> ADP-induced platelet aggregation was significantly lower in patients who received 600 mg of clopidogrel compared to those who received 300 mg of clopidogrel. Moreover, there were significantly fewer cardiovascular events in the group that received the 600 mg loading dose of clopidogrel compared to the 300 mg loading dose (5.0% vs 12.0%,  $P = 0.02$ ).

The benefit of a higher loading dose of clopidogrel was also seen in the Platelet Responsiveness to Aspirin and Clopidogrel and Troponin Increment after Coronary Intervention in Acute Coronary Lesions (PRACTICAL) trial.<sup>53</sup> In this trial patients who were randomized to 600 mg of clopidogrel had significantly reduced ADP-induced platelet aggregation compared to those who were randomized to 300 mg. However, there was no difference in clinical outcomes at 6 months – the high rate (69%) of concomitant platelet glycoprotein IIb/IIIa inhibitor use may have attenuated the effect of the higher loading dose of clopidogrel. The Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)-2 trial randomized 255 patients undergoing PCI to either a 600 mg loading dose or a 300 mg loading dose of clopidogrel 4 to 8 hours prior to the procedure.<sup>54</sup> The primary endpoint (a 30-day composite of death, myocardial infarction, or target vessel revascularization) was significantly lower in patients who received the high loading dose of clopidogrel compared to those who received the conventional loading dose (4% vs 12%,  $P = 0.041$ ), and was driven by a significantly lower rate of myocardial infarction: on multivariate analysis the high loading dose of clopidogrel was associated with a 50% risk reduction of infarction (odds ratio [OR] 0.48, 95% confidence interval [CI] 0.15–0.97,  $P = 0.044$ ).

Prasugrel, a third generation thienopyridine, has been recently studied in patients with acute coronary syndromes in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI)-38 trial.<sup>22</sup> In this trial, 13,608 patients with moderate to high risk acute coronary syndromes scheduled to undergo PCI were randomized to prasugrel (60 mg loading dose and a 10 mg daily maintenance dose) or to clopidogrel (300 mg loading dose and a 75 mg daily maintenance dose) for 6 to 15 months. Patients who were randomized to prasugrel were less likely to experience the primary endpoint (a combined endpoint of death, nonfatal myocardial infarction, or nonfatal stroke; 9.9% vs 12.1%,  $P < 0.001$ ). However, major bleeding (including fatal bleeding) was significantly increased in patients who received prasugrel compared to clopidogrel (2.4% vs 1.8%,  $P = 0.03$ ). In a prespecified subgroup analysis of patients presenting with STEMI,<sup>55</sup> prasugrel treatment again was associated with a significant decrease in the primary endpoint (6.5% vs 9.5%,  $P = 0.0017$ ), however, there was no difference in rates of major bleeding between patients randomized to prasugrel vs clopidogrel (1.0% vs 1.3%,  $P = 0.34$ ). Lastly, in a separate substudy of patients who underwent coronary artery stenting, patients who were randomized to prasugrel had significant

decreases not only in the primary endpoint (9.7% vs 11.9%,  $P = 0.0001$ ), but also the rate of stent thrombosis (1.13% vs 2.35%,  $P < 0.0001$ ).<sup>56</sup> The TRITON-TIMI 38 trial is a perfect example of the balancing act between achieving improved ischemic outcomes and decreasing bleeding complications, and underscores the importance of patient selection and individualizing antithrombotic therapy.

### Role of platelet glycoprotein IIb/IIIa inhibitors

Abciximab was the first platelet glycoprotein IIb/IIIa inhibitor available for clinical use. Several trials showed improved clinical outcomes in patients with ACS undergoing PCI who were treated with abciximab vs control;<sup>57–62</sup> however, its use was associated with significant bleeding complications in many of these trials.<sup>57,60</sup> Trials assessing the safety and efficacy of tirofiban and integrilin have shown mixed results with no significant differences in clinical outcomes in some,<sup>63,64</sup> and improved clinical outcomes in others.<sup>65–67</sup>

An important complication of platelet glycoprotein IIb/IIIa inhibitors that limits widespread use of these agents is the increased risk of bleeding.<sup>68</sup> Although a meta-analysis of 6 trials, enrolling 31,402 patients with ACS who were not routinely scheduled for early revascularization showed a 9% reduction in the rate of death or myocardial infarction at 30-day follow-up in patients randomized to platelet glycoprotein IIb/IIIa inhibitors compared with placebo (10.8% vs 11.8%, OR 0.91, 95% CI 0.84–0.98,  $P = 0.015$ ), major bleeding complications were increased in patients who received them (2.4% vs 1.4%,  $P < 0.0001$ ).<sup>69</sup> One caveat regarding these results is that the improved clinical outcomes provided by these agents were confined to ACS patients with elevated troponin levels.

Questions remain about the choice of platelet glycoprotein IIb/IIIa inhibitor due to conflicting results from comparative studies. In the Tirofiban and Reopro Give Similar Efficacy Outcomes (TARGET) trial<sup>70</sup> the primary endpoint (a composite of death, myocardial infarction, or target vessel revascularization at 30 days) occurred more frequently in the patients randomized to tirofiban compared to those randomized to abciximab (7.6% vs 6.0%,  $P = 0.038$ ). However, in the Multicentre Evaluation of Single High Dose Bolus Tirofiban vs Abciximab with Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction (MULTISTRATEGY) trial,<sup>71</sup> there was no difference in ST segment resolution between patients treated with abciximab or tirofiban (Relative Risk [RR] 1.02, 97.5% CI 0.958–1.086,  $P < 0.001$  for noninferiority). Moreover, ischemic and bleeding complications were similar between

the groups. Lastly, a recent meta-analysis of randomized trials comparing abciximab vs eptifibatid and tirofiban in primary PCI found no significant differences in angiographic, electrocardiographic or clinical outcomes (including bleeding complications) between abciximab and the use of either eptifibatid or tirofiban.<sup>72</sup>

Because clopidogrel therapy plays a critical therapeutic role in patients with ACS, some investigators have asked whether platelet glycoprotein IIb/IIIa inhibitors add sufficient clinical benefit when superimposed upon a background of aspirin, heparin, and clopidogrel. One of the first studies to examine this question was the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT)-2 study.<sup>73</sup> This study randomized 2022 high-risk patients with ACS undergoing PCI to either abciximab therapy (bolus + 12-hour infusion) or placebo. Importantly, all patients were optimally pretreated with 600 mg of clopidogrel (at least 2 hours prior to the procedure) in addition to aspirin and unfractionated heparin. There was a 25% relative risk reduction in the primary endpoint (a composite of death, myocardial infarction, or urgent target vessel revascularization occurring within 30 days) in the patients treated with abciximab (8.9% vs 11.9%; RR 0.75, 95% CI 0.58–0.97,  $P = 0.03$ ). Moreover, there were no differences in rates of major or minor bleeding, or in the need for blood transfusion. However, at 30 days a pre-specified analysis showed that the significant benefit was confined to the patients who had elevated troponin levels, a finding consistent with a previously published meta-analysis.<sup>69</sup>

In the Early or Late Intervention in Unstable Angina (ELISA)-2 trial, 328 consecutive patients with ACS were randomized to pretreatment with dual antiplatelet therapy (aspirin and clopidogrel 600 mg) or triple antiplatelet therapy (aspirin, clopidogrel 300 mg, and tirofiban).<sup>74</sup> The primary endpoint was enzymatic infarct size, with a prespecified secondary endpoint of Thrombolysis in Myocardial Infarction (TIMI) flow on the initial angiogram. Although rates of TIMI 3 flow on the initial angiogram were significantly higher in patients who were treated with triple antiplatelet therapy (67 vs 47%,  $P = 0.002$ ), there was no difference in the primary endpoint of enzymatic infarct size (median, interquartile range): 166 IU/L (60–349) in the triple antiplatelet group vs 193 IU/L (75–466) in the dual antiplatelet group,  $P = 0.2$ . Additionally, there was no significant difference in bleeding rates between the groups.

More recently, the Early Versus Delayed, Provisional Eptifibatid in Acute Coronary Syndromes (EARLY-ACS) trial compared the safety and efficacy of early, routine

administration of eptifibatide (2 boluses and a 12-hour infusion prior to angiography) to delayed, provisional administration of eptifibatide in 9492 patients with unstable angina or non-STEMI who were undergoing PCI.<sup>75</sup> Importantly, 75% of the patients were pretreated with 300 mg of clopidogrel. There was no difference in the primary endpoint (a composite of death, myocardial infarction, recurrent ischemia requiring urgent revascularization, or the occurrence of a thrombotic complication during PCI that required bolus therapy opposite to the initial study group assignment at 96 hours) between the groups (9.3% in the early eptifibatide group, and 10.0% in the delayed eptifibatide group, OR 0.92, 95% CI 0.80–1.06,  $P = 0.23$ ). Moreover, there was no difference in the rate of death or myocardial infarction at 30 days between the early and delayed eptifibatide groups, with or without the presence of troponin elevation. However, patients randomized to early eptifibatide had a statistically significant increase in TIMI major hemorrhage (2.6% vs 1.8%,  $P = 0.02$ ), and an increased need for blood transfusions (8.6% vs 6.7%,  $P = 0.001$ ). Thus, these results indicate that the routine early administration of platelet glycoprotein IIb/IIIa inhibitors in patients with unstable angina and non-STEMI prior to PCI is not recommended. Moreover, in non-STEMI patients who are optimally pre-treated with clopidogrel, the addition of platelet glycoprotein IIb/IIIa inhibitors is unlikely to add significant clinical benefit. Hence, the ACC/AHA guidelines state that for non-STEMI patients in whom an initial invasive approach is selected, it is reasonable to omit the upstream use of a platelet glycoprotein IIb/IIIa inhibitor if bivalirudin is used and if at least 300 mg of clopidogrel was administered at least 6 hours prior to the planned procedure (Class IIa, level of evidence: B).<sup>37</sup>

The data supporting the addition of upstream platelet glycoprotein IIb/IIIa inhibitors to high dose clopidogrel in patients presenting with STEMI is conflicting. In the Bavarian Reperfusion Alternatives Evaluation (BRAVE) 3 trial,<sup>76</sup> 8000 patients with STEMI received a 600 mg loading dose of clopidogrel and were then randomized to upstream abciximab or placebo prior to PCI. There was no difference in the primary endpoint of infarct size between the two groups. Moreover, there was no difference in the composite endpoint of death, recurrent infarction, stroke, or urgent revascularization between those randomized to abciximab compared to placebo (5.0% vs 3.8%,  $P = 0.40$ ). In the Ongoing Tirofiban in Myocardial Evaluation (On-TIME) 2 trial,<sup>65</sup> 984 patients with STEMI were randomized to either a high-dose bolus of tirofiban or placebo in addition to high dose clopidogrel (600 mg), aspirin, and heparin. Patients who were pretreated with tirofiban had significantly better ST segment resolution

compared to those who received placebo. The combined endpoint of death, recurrent infarction, urgent target vessel revascularization, or blinded bail-out use of tirofiban was significantly decreased in those who received tirofiban compared to placebo (26.0% vs 32.9%,  $P = 0.020$ ), suggesting that further platelet inhibition in addition to high dose clopidogrel is important in patients with STEMI undergoing PCI.

In order to decrease the rates of bleeding complications while still benefiting from their use, several studies have evaluated alternate ways to administer platelet glycoprotein IIb/IIIa inhibitors. One such study called the Brief Infusion of Eptifibatide Following Percutaneous Coronary Intervention (BRIEF-PCI) trial examined whether an abbreviated infusion of eptifibatide was safe following a successful, non-emergent PCI.<sup>77</sup> A total of 624 patients with stable angina, unstable angina, or recent STEMI who underwent successful stenting were randomized to either the standard 18-hour infusion of eptifibatide following the procedure, or an abbreviated infusion of <2 hours. The primary endpoint (the incidence of peri-procedural myonecrosis defined as troponin I elevation  $>0.26 \mu\text{g/L}$ ) was similar between the groups (30.1% in the <2-hour group vs 28.3% in the 18-hour group,  $P < 0.012$  for noninferiority). Moreover, the secondary endpoint (30 day incidence of myocardial infarction, death, and target vessel revascularization) was similar between the two groups (4.5% vs 4.8%,  $P = 1.0$ ). Importantly, from a risk-benefit ratio standpoint, the abbreviated infusion (<2-hour) resulted in significantly decreased rates of major bleeding complications compared to the standard 18-hour infusion (1.0% vs 4.2%,  $P = 0.02$ ).

The short-term effects of bolus-only administration of abciximab, tirofiban, and eptifibatide have also been studied.<sup>78–82</sup> These studies have suggested that bolus-only platelet glycoprotein IIb/IIIa inhibitors are as effective as the standard bolus and infusion protocol, but are associated with better clinical outcomes. Additional trials assessing the role (and perhaps length of administration) of platelet glycoprotein IIb/IIIa inhibitors in ACS patients undergoing PCI in the setting of clopidogrel pretreatment are needed.

## Role of heparin

The benefit of using unfractionated heparin in the treatment of ACS was first documented more than 20 years ago,<sup>83</sup> and subsequently, its use has been shown to result in a 33% relative risk reduction in death or myocardial infarction when prescribed in addition to aspirin.<sup>84</sup> In patients with ACS undergoing an initial invasive strategy, both unfractionated

heparin and low-molecular-weight heparin carry a Class I indication (level of evidence: A).<sup>37</sup> However, the limitations of unfractionated heparin as described above have led investigators to explore the use of low-molecular-weight heparin instead. One of the first studies to evaluate low-molecular-weight heparin in patients with ACS was the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events Study Group (ESSENCE) trial.<sup>85</sup> The ESSENCE trial compared the use of the low-molecular-weight heparin, enoxaparin, to unfractionated heparin in patients with ACS undergoing PCI. Patients randomized to enoxaparin had lower rates of the composite endpoint of death, myocardial infarction, or recurrent angina compared to patients treated with unfractionated heparin at 14 days (16.6% vs 19.8%,  $P = 0.019$ ), and at 30 days (27.9% vs 32.2%,  $P = 0.001$ ). Moreover, this benefit was maintained at 1-year follow-up (32.0% vs 35.7%,  $P = 0.002$ ).<sup>29</sup> The TIMI-IIb trial confirmed the benefit of enoxaparin in patients with ACS.<sup>86</sup> There was a significant reduction in the primary endpoint (a composite of death, myocardial infarction, or urgent revascularization at 8 days and at 43 days) in patients treated with enoxaparin versus unfractionated heparin (12.4% vs 14.5%,  $P = 0.048$ ). A meta-analysis combining data from both the ESSENCE and TIMI-IIb trials showed a reduction in death and ischemic events for patients receiving enoxaparin at day 8 (OR 0.77, 95% CI 0.62–0.95,  $P = 0.02$ ), which persisted through follow-up at 14 days (OR 0.79, 95% CI 0.65–0.96,  $P = 0.02$ ) and at 43 days (OR 0.82, 95% CI 0.69–0.97,  $P = 0.02$ ).<sup>87</sup>

The more recent Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial which randomized 10,027 high-risk patients with non-STEMI to either enoxaparin or unfractionated heparin prior to an early invasive approach, found no significant difference in the primary endpoint of all-cause death or nonfatal myocardial infarction during the first 30 days after randomization between the groups (14.0% vs 14.5%,  $P = \text{NS}$ ).<sup>88</sup> While no differences in the rates of bleeding have been reported in patients receiving unfractionated vs enoxaparin who undergo an initial conservative approach,<sup>89,90</sup> the SYNERGY trial reported an increase in TIMI major bleeding in patients receiving enoxaparin (9.1% vs 7.6%,  $P = 0.008$ ).<sup>88</sup> A meta-analysis comparing unfractionated heparin to low-molecular-weight heparin in patients with ACS revealed no significant difference in the risk of major bleeding with the *short-term* use of both unfractionated heparin vs placebo (OR 1.88, 95% CI 0.60–5.87,  $P = 0.28$ ) and low molecular weight vs placebo (OR 1.41, 95% CI 0.62–3.23). However, *long-term* use of unfractionated heparin was associated

with a significant increase in major bleeding (OR 2.26, 95% CI 1.63–3.14,  $P < 0.0001$ ) which was equivalent to an excess of 12 major bleeds for every 1000 patients treated.<sup>90</sup> Pooled data from 21,946 patients in 6 trials comparing unfractionated heparin to low-molecular-weight heparin in patients with ACS showed no significant difference in death at 30 days for enoxaparin vs unfractionated heparin (3.0% vs 3.0%, OR 1.00, 95% CI 0.85–1.17).<sup>91</sup> However, the combined endpoint of death or nonfatal infarction at 30 days was significantly lower for patients treated with enoxaparin rather than unfractionated heparin (10.1% vs 11.0%, OR 0.91, 95% CI 0.83–0.99). Importantly, there was no significant difference in rates of blood transfusions (OR 1.01, 95% CI 0.89–1.14) or major bleeding (OR 1.04, 95% CI 0.83–1.30) at 7 days after randomization.

Nonetheless, the inability to measure the level of anticoagulant therapy with the activated clotting time in patients receiving low-molecular weight-heparin generates reluctance by interventional cardiologists to use it during PCI. The widespread use of low-molecular-weight heparin in ACS patients *before* angiography, however, makes this issue unavoidable. Guidelines for the use of enoxaparin in the peri-PCI period have been proposed.<sup>37,92</sup> These guidelines state that if enoxaparin is to be used as the antithrombotic agent during the PCI procedure, no additional amount should be given if the last dose was administered within 8 hours. If the last subcutaneous dose was administered at least 8 to 12 hours earlier, an intravenous dose of 0.3 mg/kg of enoxaparin should be given. An 8-hour window after the last dose of low-molecular-weight heparin is preferred prior to switching to unfractionated heparin.<sup>93</sup>

A unique treatment strategy using low dose enoxaparin (0.50 mg/kg every 12 hours) prior to PCI in conjunction with dual antiplatelet therapy (aspirin and clopidogrel) followed by triple antiplatelet therapy (aspirin, clopidogrel and eptifibatide) during the PCI has been evaluated in a large, single center study.<sup>94</sup> The analysis included 1400 consecutive patients and found that this treatment strategy was associated with low rates of acute ischemic events (1.8%), minor bleeding complications (2.1%), major bleeding complications (0.1%), thrombocytopenia (1.3%), and major adverse clinical events (0.4%); suggesting the need for a randomized clinical trial to further evaluate this approach.<sup>94</sup>

Despite improved bioavailability and predictable weight-based dosing, there are several patient populations where pharmacologic parameters for low-molecular-weight heparin are altered including patients with renal insufficiency, the elderly, and the obese.<sup>95</sup> Patients who are obese have less lean body mass as a percentage of total body weight, so dosing

low-molecular-weight heparin according to total body weight can cause supra-therapeutic anticoagulation. A similar problem arises in the elderly who also have less lean body mass (in addition to other complicating factors such as renal insufficiency). Since the kidneys are the primary route of elimination for low-molecular-weight heparin, patients with impaired renal function, particularly with CrCl < 30 ml/min are at risk for accumulation of the drug, increased levels of anti-Xa, and increased risk of major bleeding complications.<sup>96,97</sup> In general, the use of low-molecular-weight heparin should be avoided in patients with CrCl < 30 ml/min.

### Role of factor Xa inhibitor

The safety and efficacy of the novel factor Xa inhibitor, fondaparinux, was evaluated in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial.<sup>38</sup> In this trial 20,078 patients with unstable angina or non-STEMI were randomized to enoxaparin 1.0 mg/kg every 12 hours or to fondaparinux 2.5 mg daily. The primary outcome (a composite of death, myocardial infarction, or refractory ischemia at 9 days) occurred in 5.7% of those randomized to enoxaparin and 5.8% of those randomized to fondaparinux (hazard ratio 1.01, 95% CI 0.90–1.13,  $P = 0.007$  for noninferiority). Moreover, major bleeding complications were significantly less in the patients receiving fondaparinux (2.2% vs 4.1%,  $P < 0.001$ ). However, in the patients who underwent PCI, those who were treated with fondaparinux had a significant increase in rates of catheter thrombosis compared to those treated with enoxaparin (0.9% vs 0.4%,  $P = 0.001$ ) which was believed to be from the inability of fondaparinux to block pre-existing thrombin. Therefore, because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant during PCI in patients with STEMI (Class III indication, level of evidence: C); unfractionated heparin should be concomitantly administered.<sup>98</sup>

The use of fondaparinux in patients with non-STEMI and unstable angina who undergo both an initial conservative or invasive management strategy carries a Class I indication (level of evidence: B) according to the ACC/AHA guidelines.<sup>37</sup> Similar to low-molecular-weight heparin, fondaparinux is excreted by the kidneys and therefore is contraindicated in patients with a CrCl < 30 ml/min.<sup>37</sup>

### Role of bivalirudin

In addition to low-molecular-weight heparin, bivalirudin has also been studied as a replacement for unfractionated heparin in patients with ACS undergoing PCI and carries a Class I (level of evidence: B) indication for use in these patients.<sup>37</sup>

One of the first studies to evaluate the use of bivalirudin in PCI randomized 4098 patients to receive either unfractionated heparin or bivalirudin during the procedure.<sup>99</sup> While there was no difference in the primary endpoint (a composite of death, myocardial infarction, abrupt vessel closure, or rapid clinical deterioration of cardiac origin), patients randomized to bivalirudin had significantly lower rates of bleeding compared to patients randomized to unfractionated heparin (3.8% vs 9.8%,  $P < 0.001$ ).

With the introduction of more potent antiplatelet agents like clopidogrel and platelet glycoprotein IIb/IIIa inhibitors, several trials have examined the safety and efficacy of bivalirudin in conjunction with these medications. In a pilot trial called the Comparison of Abciximab Complications with Hirulog for Ischemic Events (CACHET) trial, 268 patients were randomized to receive bivalirudin (with or without abciximab) or abciximab with low-dose weight-adjusted heparin during PCI.<sup>100</sup> In this study, bivalirudin with planned or provisional abciximab was as safe and effective as low-dose heparin plus abciximab. In a separate trial called the Protection against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents-Thrombolysis in Myocardial Infarction (PROTECT-TIMI)-30 trial, 857 patients with non-STEMI were randomized to one of three regimens following angiography: eptifibatide + reduced-dose unfractionated heparin, eptifibatide + reduced dose low-molecular-weight heparin, or bivalirudin monotherapy.<sup>101</sup> The primary endpoint, coronary flow reserve, was greater in the bivalirudin arm compared to pooled data from the two different eptifibatide arms (1.43 vs 1.33,  $P = 0.036$ ). However, TIMI myocardial perfusion grade was more often normal in patients treated with eptifibatide compared to bivalirudin (57.9% vs 50.9%,  $P = 0.048$ ), and the duration of ischemia on Holter monitoring after PCI was significantly longer in patients treated with bivalirudin (169 min vs 36 min,  $P = 0.013$ ). Although there was no excess of TIMI major bleeding in patients treated with eptifibatide compared with bivalirudin (0.7% vs 0%,  $P = \text{NS}$ ), TIMI minor bleeding was increased (2.5% vs 0.4%,  $P = 0.027$ ) as well as blood transfusion requirements (4.4% vs 0.5%,  $P < 0.001$ ).

The ACUITY study examined the use of bivalirudin in 13,819 moderate-risk and high-risk patients with ACS undergoing an early invasive strategy.<sup>102</sup> Patients were randomized to one of three regimens: platelet glycoprotein IIb/IIIa inhibitor + unfractionated heparin or low-molecular-weight heparin; platelet glycoprotein IIb/IIIa + bivalirudin; or bivalirudin alone. Bivalirudin + platelet glycoprotein IIb/IIIa inhibitor, as compared to heparin + platelet glycoprotein IIb/IIIa,



was associated with similar rates of the composite ischemic endpoint of death, myocardial infarction, or unplanned revascularization (7.7% vs 7.3%,  $P = \text{NS}$ ); major bleeding (5.3% vs 5.7%,  $P = \text{NS}$ ); and the net clinical endpoint of ischemia or major bleeding (11.8% vs 11.7%,  $P = \text{NS}$ ). In addition, bivalirudin alone, as compared to heparin + platelet glycoprotein IIb/IIIa inhibitor, was associated with similar rates of the composite ischemic endpoint (7.8% vs 7.3%,  $P = 0.32$ ), and significantly reduced rates of major bleeding (3.0% vs 5.7%,  $P < 0.001$ ), and the net clinical endpoint (10.1% vs 11.7%,  $P = 0.02$ ). In a subgroup analysis of this trial that evaluated 7789 patients who underwent PCI, there were no differences in the composite endpoint of death, myocardial infarction, unplanned revascularization, or death at one year.<sup>103</sup> However, there was a significant reduction in major bleeding in those patients who received bivalirudin alone compared to those who received heparin + platelet glycoprotein IIb/IIIa inhibitors (4.0% vs 7.0%,  $P < 0.001$ ). In a separate analysis of the ACUTY trial, patients who were switched to bivalirudin from either unfractionated or low-molecular-weight heparin had similar rates of ischemia (6.9% vs 7.4%,  $P = 0.52$ ), but less major bleeding complications (2.8% vs 5.8%,  $P < 0.01$ ), which resulted in improved net clinical outcomes (9.2% vs 11.9%,  $P < 0.01$ ) compared to those who remained on unfractionated heparin or low-molecular-weight heparin + platelet glycoprotein IIb/IIIa inhibitors.<sup>104</sup>

Lastly, the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial randomized 3602 patients with STEMI to heparin + platelet glycoprotein IIb/IIIa or bivalirudin alone.<sup>105</sup> Anticoagulation with bivalirudin was associated with a 24% absolute risk reduction in the net adverse clinical events (major bleeding or major adverse cardiac events including death, re-infarction, target vessel revascularization for ischemia, and stroke) at 30 days (9.2% vs 12.1%, RR 0.76, 95% CI 0.63–0.92,  $P = 0.0005$ ) with a 40% absolute reduction in major bleeding (4.9% vs 8.3%, RR 0.60, 95% CI 0.46–0.77,  $P < 0.001$ ). One important caveat regarding the results of this trial is that there was an increased risk of acute stent thrombosis within 24 hours in patients treated with bivalirudin (0.3% vs 1.3%,  $P < 0.001$ ). It has been suggested that one contributing factor could have been inadequate pretreatment with clopidogrel. This concern was addressed in a post-hoc analysis of the 7789 patients in the ACUTY trial that underwent PCI:<sup>106</sup> when clopidogrel was administered prior to the PCI or within 30 minutes after the PCI, bivalirudin therapy alone was associated with similar ischemic outcomes compared to placebo (8.2% vs 8.3%,

RR 0.98, 95% CL 0.81–1.20,  $P = 0.88$ ). However, in patients who received clopidogrel either  $>30$  minutes after the PCI or not at all, there was a significant increase in ischemic events in patients randomized to bivalirudin compared to placebo (14.1% vs 8.5%, RR 1.66, 95% CI 1.05–2.63,  $P = 0.03$ ).

The prevailing theme of the importance of optimal clopidogrel pretreatment is also evident in trials assessing the safety and efficacy of bivalirudin in patients with ACS undergoing PCI.<sup>107,108</sup> In the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 3 study,<sup>107</sup> the use of bivalirudin in patients with stable or unstable angina undergoing PCI was evaluated. In this trial 4570 patients who were optimally pretreated with 600 mg of clopidogrel were randomized to either bivalirudin or unfractionated heparin at the time of the PCI procedure. While there was no difference in the primary endpoint (a composite of death, myocardial infarction, and target vessel revascularization due to myocardial ischemia at 30 days), there was a lower incidence of major bleeding in the bivalirudin group (4.6% vs 3.1%,  $P = 0.0008$ ). In the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial 6010 patients undergoing elective or urgent PCI were randomized to bivalirudin with provisional platelet glycoprotein IIb/IIIa inhibitor, or to heparin with planned platelet glycoprotein IIb/IIIa inhibitor.<sup>108</sup> Importantly, greater than 84.9% of patients received pre-treatment with clopidogrel (26.6% received clopidogrel  $<2$  hours prior to PCI and 56.7% received it between 2–48 hours prior of PCI). Similar to the ISAR-REACT 3 study, there was no difference in the primary endpoint of death, myocardial infarction, or urgent repeat revascularization at 30 days, and in-hospital major bleeding rates were significantly less with bivalirudin than the combination of heparin and platelet glycoprotein IIb/IIIa inhibitor (2.4% vs 4.1%,  $P < 0.001$ ).

## What agents should be used?

The combination of a large variety of antithrombotic medications available (Table 1), and the lack of consensus regarding the optimal regimen for any given patient, has resulted in a long list of potential regimens. There must be a balance between choosing the regimen that will minimize the risk of recurrent ischemic events, and one that will minimize the risk of bleeding.<sup>9</sup> Considering the overall risk-benefit ratio, therefore, is important in the decision-making process since it may guide the physician to choose one particular antithrombotic regimen over another for any given patient.<sup>109</sup> Several risk assessment algorithms are available to help the physician gauge whether the patient is at high- or low-risk for

**Table I** Antithrombotic agents commonly administered to patients with acute coronary syndrome undergoing percutaneous coronary intervention

**Antiplatelet**

- Aspirin
- Thienopyridine (clopidogrel)
- Platelet glycoprotein IIb/IIIa inhibitors

**Anticoagulant**

- Indirect thrombin inhibitors
  - Unfractionated heparin
  - Low molecular weight heparin
- Direct thrombin inhibitor (bivalirudin)
- Factor Xa inhibitor (fondaparinux)

a recurrent cardiac event including the TIMI risk score,<sup>110</sup> the Global Registry of Acute Coronary Events (GRACE) score,<sup>111</sup> and the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT)<sup>112</sup> (Figure 1). In addition to the risk of a recurrent ischemic

event, there are other important factors that should be taken into consideration (Table 2): (1) the risk of bleeding, (2) the timing and dose of clopidogrel prior to PCI (if administered), (3) the timing and dose of low-molecular-weight heparin prior to PCI (if administered), (4) the patient’s renal function, and (5) whether the patient has a history of heparin-induced thrombocytopenia, or previous drug reactions.

Recently, the Can Rapid Risk stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) bleeding score has been developed and validated.<sup>113</sup> This score predicts the baseline risk of in-hospital major bleeding and incorporates patient information that is readily available upon admission: patient factors predictive of in-hospital major bleeding are female gender, diabetes, a history of vascular disease, high or low systolic blood pressure, tachycardia, hematocrit <36%, and renal insufficiency. Advanced age has also been shown to be a risk factor for major bleeding complications.<sup>114</sup> However, since no current algorithm

TIMI risk score		GRACE risk score	
Factors	Points	Factors	Points
Age ≥ 65	1	Age ≤29	0
≥3 CAD risk factors	1	30–39	0
Known CAD (stenosis ≥ 50%)	1	40–49	18
Aspirin use in past 7 days	1	50–59	36
>1 episode of rest pain in <24 hours	1	60–69	55
Elevated cardiac enzymes	1	70–79	73
ST deviation ≥0.5 mm	1	80–89	91
		≥90	100
		History of CHF	24
		History of MI	12
		Resting heart rate (bpm)	
		≤49.9	0
		50–69.9	3
		70–89.9	9
		90–109.9	14
		110–149.9	23
		150–199.9	35
		>200	43
		Systolic blood pressure (mm Hg)	
		≤79.9	24
		90–99.9	22
		100–119.9	18
		120–139.9	14
		140–159.9	10
		160–199.9	4
		≥200	0
		ST segment depression	11
		Initial serum creatinine (mg/dl)	
		0–0.39	1
		0.4–0.79	3
		0.8–1.19	5
		1.2–1.59	7
		1.6–1.99	9
		2–3.99	15
		≥4	20
		Elevated cardiac enzymes	15
		No in-hospital PCI	14

PURSUIT risk score	
Factors	Points
Age (decade) UA and (MI)	
50	8 (11)
60	9 (12)
70	11 (13)
80	12 (14)
Gender	
Male	1
Female	0
Worst CCS class	
No angina or CCS class I/II	0
CCS class III/IV	2
Heart rate (bpm)	
80	0
100	0
120	0
Systolic blood pressure (mm Hg)	
120	0
100	0
80	0
Signs of heart failure	2
ST depression	1

**Figure 1** The TIMI, PURSUIT, and GRACE risk scores.

**Abbreviations:** CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

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**Table 2** Key considerations in selecting the optimal antithrombotic regimen for an individual patient

<b>Risk of recurrent ischemic event</b>	<b>Consider</b> TIMI risk score GRACE risk score PURSUIT risk score
<b>Risk of major bleeding</b>	<b>Consider</b> CRUSADE bleeding score
<b>Clopidogrel pretreatment</b>	<b>Yes or no</b> If yes, determine timing and dose of administration prior to PCI procedure
<b>Enoxaparin pretreatment</b>	<b>Yes or no</b> If yes, determine timing and dose of administration prior to PCI procedure
<b>Renal insufficiency</b>	<b>Yes or no</b> If yes, follow recommended renal dosing <sup>a</sup>
<b>Heparin-induced thrombocytopenia</b>	<b>Yes or no</b> If yes, tailor regimen accordingly, use bivalirudin in place of heparin

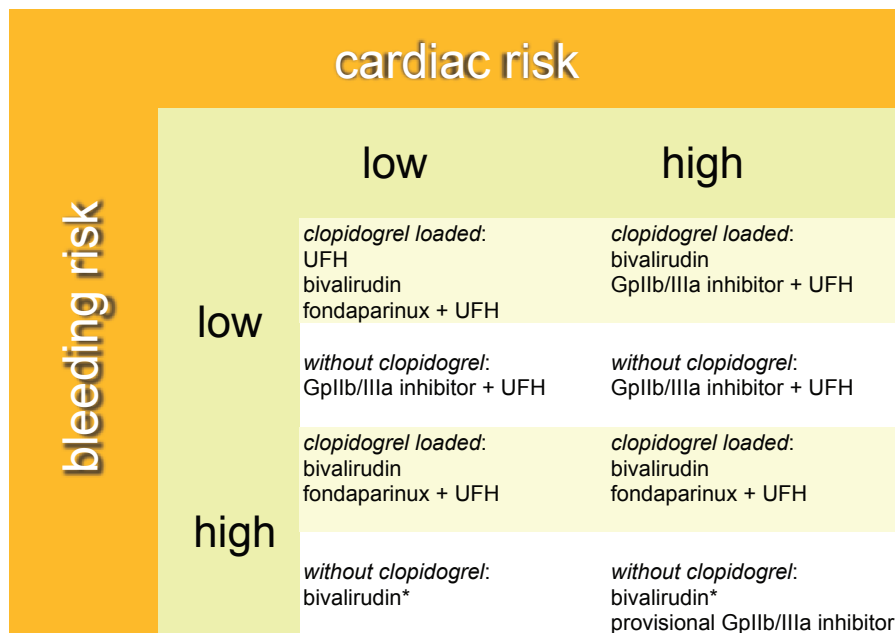
<sup>a</sup>integrilin, fondaparinux and enoxaparin should be avoided in patients with severe renal insufficiency (creatinine-clearance  $\leq 30$  mL/min).

**Abbreviations:** CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines;<sup>112</sup> GRACE, Global Registry of Acute Coronary Events;<sup>110</sup> PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy;<sup>111</sup> TIMI, Thrombolysis in Myocardial Infarction.<sup>109</sup>

incorporates both ischemic and bleeding risk, creation of a “bleeding risk subscale” has been proposed.<sup>115</sup> Moreover, these investigators recommend particular antithrombotic agents by integrating bleeding risk with specified ranges of the TIMI, PURSUIT, and GRACE risk scores that define patients at low (defined as TIMI 0–2, PURSUIT 0–8, GRACE 0–124); moderate (defined as TIMI 3–4, PURSUIT 9–16, GRACE 125–248); and high (defined as TIMI 5–7, PURSUIT 17–25, GRACE 249–372) ischemic risk. We similarly propose an algorithm, but include not only cardiac and bleeding risk, but also whether the patient has been pretreated with clopidogrel (Figure 2). In patients who are pretreated with clopidogrel, there are many acceptable choices for an antithrombotic regimen during PCI, especially when the bleeding risk is low. The more difficult scenario, however, is when the patient has not been pretreated with clopidogrel, and is at high risk for a bleeding complication: in this case, if bivalirudin is used, a loading dose of clopidogrel should be administered as soon as possible in the cardiac catheterization laboratory to decrease the risk of subacute stent thrombosis. Moreover, if a platelet glycoprotein IIb/IIIa inhibitor is needed on a provisional basis, a short-acting agent would be preferable.

## Future prospects

Novel agents primarily used for prevention of venous thromboembolism are currently being investigated for



**Figure 2** Algorithm for selecting the optimal antithrombotic regimen incorporating cardiac risk, bleeding risk, and clopidogrel pretreatment. In this algorithm it is assumed that all patients have received aspirin.

\*If bivalirudin is used, a loading dose of clopidogrel should be given as soon as possible in the cardiac catheterization laboratory to decrease the risk of subacute stent thrombosis.

use in patients with ACS.<sup>116</sup> In the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction (ATLAS ACS-TIMI) 46 trial, rivaroxaban (an oral direct factor Xa inhibitor) was associated with a dose-dependent increase in clinically significant bleeding events, with a trend towards a reduction in the primary efficacy endpoint of death, myocardial infarction, stroke, or severe recurrent ischemia requiring revascularization.<sup>117</sup> Similar findings have been published regarding apixaban, also an oral direct factor Xa inhibitor evaluated in the Apixaban for Prevention of Acute Ischemic Events (APPRAISE) trial.<sup>118</sup> Lastly, dabigatran, an oral direct thrombin inhibitor is being studied in the context of secondary prophylaxis after myocardial infarction in the placebo-controlled phase II Randomized Dabigatran Dose Finding Study in Patients with Acute Coronary Syndromes Post Index Event with Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel: Multi-Centre, Prospective, Placebo Controlled, Cohort Dose Escalation (RE-DEEM) trial.<sup>119</sup>

## Conclusion

Selecting the appropriate antithrombotic regimen for patients with ACS undergoing PCI has become a complex task. Treatment guidelines are needed to help physicians incorporate cardiac risk, bleeding risk, and other key factors into their selection of the optimal antithrombotic regimen for an individual patient.

## Disclosures

The authors declare no conflicts of interest.

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