Anticoagulant Therapy for Percutaneous Coronary Intervention

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Percutaneous coronary intervention (PCI) is the most commonly performed invasive therapeutic cardiac procedure and plays an important role in the treatment of ischemic heart disease. Since the first description of coronary angioplasty in a human by Gruntzig,1 the technique, equipment, and associated pharmacotherapy have undergone substantial evolution, leading to significant improvements in periprocedural complications.2 In particular, procedural anticoagulant therapy has been the focus of numerous clinical trials, and several options are now available and supported by practice guidelines; each agent has both advantages and disadvantages, and procedural pharmacotherapy continues to be a focus of drug development. The purpose of this review is to summarize the goals of anticoagulant therapy during PCI, the pharmacokinetics and pharmacodynamics of available agents, and the clinical data surrounding each agent and to identify new agents in development.

Goals of Anticoagulant Therapy and the Role of Thrombin

The goals of pharmacotherapy during PCI are 2-fold: (1) to mitigate the sequelae of iatrogenic plaque rupture from balloon angioplasty or stenting and (2) to reduce the risk of thrombus formation on intravascular PCI equipment. Central to these thrombotic events is thrombin (factor IIa). Iatrogenic damage to the endothelium during PCI leads to increased expression of tissue factor, activation of the coagulation cascade, and formation of activated factor Xa. This ultimately leads to the generation of thrombin, conversion of fibrinogen to fibrin, and thrombus formation.3 In addition to its effects on fibrin, thrombin also directly activates platelets, enhances platelet aggregation, and is proinflammatory.4 Because of its multiple actions in promoting thrombosis, the focus of most anticoagulant agents is thrombin inhibition. Available agents for use include unfractionated heparin (UFH), low-molecular-weight heparins (LMWH, of which enoxaparin has the largest body of clinical data), the synthetic pentasaccharides (of which fondaparinux has the largest body of clinical data), and the direct thrombin inhibitors (DTIs, of which bivalirudin has the largest body of clinical data) (Table).

Some studies have called into question whether antithrombin therapy is necessary for low-risk elective PCI when aggressive upstream antiplatelet therapy is implemented; however, for most patients undergoing PCI, especially those with high-risk angiographic or clinical features (complex plaques and acute coronary syndromes [ACS]), procedural antithrombin therapy is recommended.5 Importantly, the use of anticoagulation must balance reduction in thrombotic complications (periprocedural myocardial infarction [MI] and catheter thrombus) with the risk of periprocedural bleeding. Hemorrhagic complications in patients with ischemic heart disease are associated with death, recurrent MI, stent thrombosis, and stroke.7 Many patient characteristics associated with increased risk for bleeding are also independent predictors of ischemic outcomes,8 underscoring the importance of appropriate dosing of antithrombotic therapy to minimize both ischemic and hemorrhagic complications after PCI.

Currently Available Anticoagulants

Unfractionated Heparin

Historically, the most commonly used antithrombin agent for PCI is UFH, which is a heterogeneous mixture of glycosaminoglycans of varying weights. Each molecule of UFH has a binding site for factor Xa, thrombin (factor IIa), or both. The antithrombin activity of UFH depends on the activation of antithrombin, which inactivates thrombin; therefore, UFH and all drugs derived from it are indirect antithrombin agents. Advantages and disadvantages of UFH are listed in Table 1.

The dosing of UFH has undergone significant evolution during the history of PCI. Initial regimens involved high doses of UFH. For example, in the Bivalirudin Angioplasty Trial comparing bivalirudin and UFH, the dose of UFH given was a 175 U/kg bolus followed by an infusion of 15 U · kg⁻¹ · h⁻¹.9 Furthermore, if the activated clotting time (ACT, a measure of antithrombin activity) was <350 seconds, an additional 60 U/kg bolus was administered. This protocol was based on observational analyses in the era of balloon angioplasty, indicating that greater anticoagulant effect (measured with the ACT) was associated with lower complication rates, such as abrupt closure.10 A randomized trial of 400 patients undergoing balloon angioplasty with or without stenting compared a fixed dose of 15 000 U of UFH with a weight-adjusted dose of 100 IU/kg and found no significant difference in efficacy between the 2 regimens; the weight-adjusted dose strategy was associated with shorter sheath dwell times.11 A more recent analysis from the

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80
STEEPLE (Safety and Efficacy of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention: An Interna-
tional Randomized Evaluation) trial comparing intravenous
enoxaparin with intravenous UFH demonstrated that bleeding
increased significantly with ACT values $>325$ seconds,
whereas ischemic events increased when ACT values were
$<325$ seconds$^{12}$ (Figure 1). Taken together, these data sug-
gest that the therapeutic window for UFH is relatively narrow
and that a general relationship exists between UFH dosing
and outcomes such that lower doses of UFH are as effective
as higher doses and potentially safer.

Anticoagulation with UFH alone does not seem to be
sufficient for protection from ischemic sequelae, such as
periprocedural MI. One cause of these events is embolization
of platelet aggregates that form as a result of platelet
activation induced by UFH.$^{13}$ Therefore, aggressive antiplate-
let therapy is necessary to mitigate these adverse events.
Either the use of high-dose clopidogrel or glycoprotein
IIb/IIIa inhibitors (GPI) in elective PCI$^{14,15}$ or use of both in
patients with ACS undergoing PCI$^{16}$ reduces periprocedural
ischemic complications if UFH or a derivative of UFH is used
as the antithrombin agent. If a GPI is used, lower doses of
UFH with a target ACT of 200 to 250 seconds are associated
with a reduction in bleeding complications without an appreci-
able increase in ischemic events.$^{17}$

Another limitation of UFH is the potential risk of developing
heparin-induced thrombocytopenia with or without thrombosis
syndrome [HIT(TS)].$^{18}$ The development of HIT(TS) is more
commonly associated with prolonged use of UFH, such as in the
treatment of venous thromboembolic disease and ACS. It is
relatively rare in the setting of PCI but can be seen with repeated
exposures to UFH.$^{19}$ The development of thrombocytopenia in
patients undergoing PCI is an ominous sign and is associated
with increased mortality.$^{20}$

| Table. Advantages and Disadvantages of Existing Antithrombin Therapies |
|------------------|-------------------------------|-----------------------|
| **Agent** | **Advantages** | **Disadvantages** |
| UFH | Easily monitored at bedside | Little activity against clot-bound thrombin |
| | Reversible | Platelet activation |
| | Familiarity | Risk for heparin-induced thrombocytopenia |
| | Available both subcutaneously and intravenously | |
| Enoxaparin | More reliable antithrombin effect than UFH | No ability to monitor effect at the bedside |
| | Available both subcutaneously and intravenously | Subcutaneous dosing not more efficacious than UFH |
| | Intravenous dosing associated with less bleeding than UFH | Platelet activation |
| | Partially reversible | Risk for heparin-induced thrombocytopenia |
| Fondaparinux | Associated with less bleeding than enoxaparin | No ability to monitor effect at the bedside |
| | Associated with improved survival in non-ST-segment elevation ACS | Not reversible |
| | | Not enough activity against thrombin to prevent catheter thrombosis |
| | | Risk for heparin-induced thrombocytopenia (rare) |
| Bivalirudin | No platelet activation | Efficacy may depend on pretreatment with clopidogrel |
| | Associated with less bleeding than UFH and enoxaparin with or without GPI | |
| | Associated with lower mortality in primary PCI | Associated with increased risk of acute stent thrombosis in primary PCI |

Figure 1. Relationship between activated clotting time and 48-hour noncoronary artery bypass grafting-related major bleeding and 30-day mortality, myocardial infarction, or urgent target vessel revascularization (Reprinted with permission, Figures 3A and 3C, from Montalescot et al$^{12}$).
Low-Molecular Weight Heparin

Because of the limitations of heparin (Table), several other alternatives have been studied in the setting of PCI. The LMWH are derived from UFH and range in molecular weight from 3000 to 5000 Da. These agents have greater activity against factor Xa than against thrombin and, therefore, have the potential for greater thrombin inhibition because factor Xa catalyzes the formation of thrombin. The most studied of the LMWH is enoxaparin, which has an ex vivo anti-Xa:anti-IIa ratio of 4:1 and an in vivo ratio of up to 12:1. Potential advantages of enoxaparin over UFH are listed in Table 1.13

Disadvantages include some degree of platelet activation and risk for HIT(TS), although the risk for the latter is less than that with UFH. Enoxaparin is partially reversible with the administration of protamine sulfate, which should be dosed at 1 mg for every 1 mg of enoxaparin. Because of its greater anti-Xa activity, enoxaparin cannot readily be monitored with a point-of-care ACT; therefore, direct measurement of anti-Xa levels is used to assess its antithrombotic effect. An observational study of 803 patients with ACS treated with 1 mg/kg twice daily of subcutaneous enoxaparin demonstrated that 30-day mortality was strongly linked to anti-Xa levels <0.5 IU/mL.21 On the basis of this study, anti-Xa levels of >0.5 IU/mL are considered to be therapeutic for enoxaparin and are the basis of dosing for studies involving PCI.22

An important aspect of enoxaparin therapy is that the drug is bioavailable with either parenteral or subcutaneous administration. The subcutaneous route is used in the setting of ACS,23 and the parenteral route (either alone or in addition to the subcutaneous dosing) is used for PCI.22,24 The usual subcutaneous dose for ACS treatment is 1 mg/kg twice daily in patients with normal renal function and 1 mg/kg once daily in patients with severe renal dysfunction (creatinine clearance <30 mL/min). Because of its half-life, the anti-Xa effect of subcutaneous enoxaparin wanes over 8 hours, and additional dosing is necessary to maintain therapeutic anticoagulation during PCI. The Pharmacokinetics of Enoxaparin in PCI investigators found that a booster dose of intravenous 0.3 mg/kg enoxaparin given 8 to 12 hours after a subcutaneous 1 mg/kg dose resulted in anti-Xa levels well above 0.5 IU/mL.25

This supplemental dosing strategy was used in the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial that randomized 10,027 high-risk patients with ACS to either subcutaneous enoxaparin or intravenous UFH.24 Although a proportion of patients assigned to one strategy crossed over to the other agent, enoxaparin was statistically noninferior to UFH with respect to the primary end point of death or MI at 30 days; among patients undergoing PCI, there was no significant difference in the rate of unsuccessful PCI, abrupt closure, or emergency coronary artery bypass grafting between the study arms. The bleeding results from the SYNERGY trial were complex due to different bleeding definitions used—a significantly higher rate of thrombolysis in MI (TIMI) major bleeding among patients assigned to enoxaparin, but no significant difference in the rate of Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe bleeding, TIMI minor bleeding, or blood transfusions between the enoxaparin and UFH arms. The role of enoxaparin for elective PCI in patients with ST-segment elevation MI (STEMI) who have received fibrinolysis was examined in an analysis from the ExTRACT-TIMI-25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment, Thrombolysis in MI-Study 25) study.26 In ExTRACT, 4670 patients underwent PCI at a median of 109 to 122 hours after fibrinolysis. The 2272 patients randomized to enoxaparin had a significant reduction in 30-day death or MI (10.7% versus 13.8%, P=0.001) without an increase in TIMI major bleeding. Because of its double-blind design (unlike SYNERGY), the ExTRACT data provide the best evidence that enoxaparin is superior to UFH in reducing ischemic complications when it is used consistently (ie, no addition of UFH) in the setting of elective PCI after fibrinolysis. When used consistently in the setting of non-ST-segment elevation ACS, it also may be superior to UFH but may be associated with increased bleeding risk.27

Enoxaparin also can be administered intravenously. The STEEPEL trial23 randomly assigned 3528 patients to 1 of 3 arms: 0.5 mg/kg intravenous enoxaparin, 0.75 mg/kg intravenous enoxaparin, or weight-adjusted UFH (target ACT of 200 to 300 seconds if a GPI was used or 300 to 350 seconds if no GPI was used). The lowest rate of non–coronary artery bypass grafting–related major bleeding at 48 hours was seen in the 0.5-mg/kg enoxaparin arm (Figure 2). A total of 78.8% of patients assigned to the 0.5-mg/kg arm achieved therapeutic levels of anticoagulation compared with 91.8% of patients in the 0.75-mg/kg arm and 19.7% of patients in the UFH arm (P<0.001 for comparison of either enoxaparin arm to the UFH arm). Enrollment into the 0.5-mg/kg arm was stopped early by the data safety monitoring board because of an early signal of increased mortality (although not statistically significant) against the control arm. However, by the end of the study, there was no significant difference in mortality across the 3 arms. Moreover, the 1-year results demonstrated a nonsignificant trend toward improved survival among patients assigned to the 0.5-mg/kg dose. A subsequent meta-analysis of 13 trials comparing intravenous LMWH with intravenous UFH found that a strategy of intravenous LMWH was associated with a significant reduction in major bleeding (adjusted odds ratio, 0.57; 95% CI, 0.40 to 0.82) with no significant difference in death, MI, or target vessel revascularization.28 These data demonstrate that the use of intravenous enoxaparin as anticoagulation during elective PCI is associated with a better safety profile than weight-adjusted UFH, with no compromise in protection from ischemic events. But is limited by our inability to measure levels of anticoagulation.

Synthetic Pentasaccharides

Fondaparinux is an indirect inhibitor of factor Xa that has no effect on thrombin. Structurally, it is a synthetic pentasaccharide that works through antithrombin. It has a half-life of 17 to 21 hours and is not reversible. Although it is extremely rare, heparin-induced thrombocytopenia has been described with fondaparinux therapy.29 Its activity upstream from thrombin makes it an attractive anticoagulant for both ACS and PCI. The initial phase 2 experience with fondaparinux during PCI was in the Arixa Study in Percutaneous Coronary Intervention: A Randomized Evaluation trial that randomized 350 patients undergoing elective or urgent PCI to 2 different doses of intravenous fondaparinux (2.5 and 5.0 mg).
or weight-adjusted UFH. The study showed statistical noninferiority of both fondaparinux doses and UFH with respect to total (major and minor) bleeding (7.7% UFH versus 6.4% fondaparinux, \( P = 0.61 \)) and the composite of death, MI, urgent target vessel revascularization (uTVR), or use of bailout GPI (6.0% UFH versus 6.0% fondaparinux, \( P = 0.97 \)).30 The OASIS (Organization to Assess Strategies in Acute Ischemic Syndromes) 5 trial studied fondaparinux for the management of non-ST-segment elevation ACS and was statistically noninferior to enoxaparin with respect to the 9-day composite of death, MI, and refractory ischemia and superior with respect to 30-day major bleeding (2.2% versus 4.1%, \( P < 0.001 \)).31 Moreover, 30- and 180-day mortality were significantly lower among patients assigned to fondaparinux (30-day mortality, 3.5% versus 2.9%, \( P = 0.02 \); 180-day mortality, 6.5% versus 5.8%, \( P = 0.05 \)), making fondaparinux the only antithrombin agent to improve survival in patients with non–ST-segment elevation ACS. It is possible that its effect on bleeding complications partly explains its effect on mortality.

Among the 6238 patients who underwent PCI, there was a significant reduction in bleeding at 9 days among patients assigned to fondaparinux (2.4% versus 5.1%, \( P < 0.00001 \)). However, there was a significantly higher rate of catheter-related thrombosis in the fondaparinux arm in patients who underwent catheterization with or without PCI (1.3% versus 0.5%, \( P = 0.001 \)), prompting a protocol change to mandate the use of UFH at the time of PCI in patients assigned to fondaparinux. The mean dose of UFH used during PCI was 47 IU/kg.32 The OASIS 6 trial in patients with STEMI corroborated the PCI-related risks of using fondaparinux alone during primary PCI.33 Patients undergoing primary PCI in the fondaparinux arm had a significantly higher rate of 30-day death or reinfarction than patients in the UFH arm. On the basis of these data, current guidelines recommend the addition of agents with activity against factor IIa during PCI in patients treated with fondaparinux.6

### Direct Thrombin Inhibitors

The DTIs do not depend on antithrombin for their anticoagulant effect and, therefore, are active directly against thrombin. They carry no risk of HIT(TS) (Table). The DTI that has been the most studied in PCI is bivalirudin, which is an irreversible inhibitor of thrombin with a half-life of \( \approx 25 \) minutes. The early experience with bivalirudin during PCI was the Bivalirudin Angioplasty Trial,9 which included 4098 patients with unstable angina or postinfarction angina undergoing balloon angioplasty. In the overall trial population, bivalirudin did not significantly reduce the incidence of the primary composite end point of in-hospital death, MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin (11.4% bivalirudin versus 12.2% UFH) but did reduce the risk of bleeding (3.8% bivalirudin versus 9.8% UFH, \( P < 0.001 \)). In a prespecified subgroup of 704 patients with postinfarction angina, bivalirudin was superior to UFH with respect to both primary efficacy end point (9.1% versus 14.2%, \( P = 0.04 \)) and bleeding (3.0% versus 11.1%, \( P < 0.001 \)).

Since the publication of the Bivalirudin Angioplasty Trial, >25 000 patients have been randomized in comparative trials examining bivalirudin against UFH or enoxaparin with or without GPI across the spectrum of risk from elective PCI to primary PCI for STEMI. Its role against UFH+GPI in the setting of coronary stenting in a lower risk elective population was evaluated in 2 trials: REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) trial34 and ISAR-REACT 3 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 3).35 REPLACE-2 randomized 6010 patients undergoing urgent or elective PCI in a double-blind, double-dummy fashion either to UFH+planned GPI or to bivalirudin with provisional use of GPI given only for procedural complications. The trial was statistically powered to show noninferiority of the bivalirudin strategy to the UFH+GPI strategy with respect to the primary quadruple composite end point.

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**Figure 2.** Rates of the major end points in the STEEPLE trial. Major non-CABG bleeding, \( P = 0.01 \) for comparison between UFH and 0.5 mg/kg enoxaparin and \( P = 0.051 \) for comparison between enoxaparin 0.5 mg/kg and enoxaparin 0.75 mg/kg; target anticoagulation reached, \( P < 0.001 \) for comparison between UFH and enoxaparin 0.5 mg/kg and \( P = 0.001 \) for comparison between UFH and enoxaparin 0.5 mg/kg and \( P = 0.30 \) for comparison between enoxaparin 0.5 mg/kg and enoxaparin 0.75 mg/kg. uTVR indicates urgent target vessel revascularization.
point of 30-day death, MI, urgent target vessel revascularization, or major bleeding (the so-called “net adverse clinical events” [NACE]). The bivalirudin strategy (7.2% of patients in the bivalirudin arm received bailout GPI) was noninferior to UFH+GPI with respect to the primary end point (9.2% bivalirudin versus 10.0% UFH+GPI, \(P=0.32\)). Analysis of the individual 30-day end points demonstrated that there were no significant differences between bivalirudin and UFH+GPI in death, MI, or urgent target vessel revascularization; the difference in NACE was driven by a significant reduction in major bleeding (2.4% versus 4.1%, \(P<0.001\)). The 1-year mortality rates were statistically similar in both arms but trended lower in all prespecified subgroups (Figure 3A), especially those at high risk for post-PCI mortality, including patients aged >75 years, women, and those with diabetes mellitus.\(^{36}\) The ISAR-REACT 3 trial compared bivalirudin with
UFH alone in 4570 patients undergoing elective PCI. All patients were treated with 600 mg of clopidogrel at least 2 hours before the procedure. The trial was powered to examine whether bivalirudin was superior to UFH with respect to 30-day NACE. There was no significant difference between bivalirudin and UFH with respect to the primary end point (8.3% versus 8.7%, \( P=0.57 \)); however, major bleeding was significantly lower in patients assigned to bivalirudin (3.1% versus 4.6%, \( P=0.008 \)). Of note, relatively higher doses of UFH were used in this trial (140 IU/kg), which may have increased the bleeding rate in the UFH arm and magnified the differences in bleeding between UFH and bivalirudin. However, taken together, the REPLACE-2 and ISAR-REACT 3 trials indicate that bivalirudin is a reasonable alternative to UFH alone or with GPI in patients undergoing elective PCI. Although bivalirudin does not seem more efficacious than either UFH strategy in this setting, it is significantly safer.

The role of bivalirudin in a higher risk non–ST-segment elevation ACS population was studied in the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. This open-label trial randomized 13 819 patients to 1 of 3 strategies: UFH or enoxaparin+GPI, bivalirudin+GPI, or bivalirudin with provisional GPI (administered for severe refractory ischemia or procedural complications). The primary end point was the 30-day incidence of NACE. ACUITY was statistically powered for separate comparisons between the UFH+GPI arm and the bivalirudin+GPI and bivalirudin monotherapy arms, and sequential hierarchical testing for both noninferiority and superiority was used. Two aspects of the ACUITY trial design deserve mention: (1) the noninferiority margin was 25%, which is considerably wider than previous ACS trials, and (2) the median time from randomization to catheterization was approximately 4 hours; therefore, ACUITY is predominantly a trial of a pharmacoinvasive strategy. The UFH+GPI and bivalirudin+GPI arms had similar rates of 30-day NACE (11.8% bivalirudin+GPI versus 11.7% UFH or enoxaparin+GPI) and major bleeding (5.3% versus 5.7%). The bivalirudin monotherapy strategy was superior to either GPI arm with respect to the primary end point (10.1% bivalirudin alone versus 11.7% UFH or enoxaparin+GPI, \( P=0.02 \)), which was driven by a significant reduction in major bleeding (3.0% UFH+GPI versus 5.7% bivalirudin, \( P<0.001 \)). On the basis of the noninferiority boundary defined in the trial, bivalirudin monotherapy was statistically noninferior to either GPI arm with respect to the 30-day mortality, MI, or urgent target vessel revascularization. The outcomes among the subset of patients undergoing PCI were similar to the overall trial findings with no difference in ischemic events, but lower rates of bleeding were found among patients randomized to bivalirudin alone. The mortality rates were also similar (Figure 3B). The fact that the combination of bivalirudin and GPI did not seem to reduce bleeding risk suggests that the addition of GPI to any antithrombin agent increases bleeding risk. There seems to be no safety advantage of bivalirudin in the presence of concomitant GPI.

Interestingly, there was a significant interaction between preangiography exposure to clopidogrel and bivalirudin such that there was a higher risk of 30-day NACE among patients who were randomized to bivalirudin and did not receive early clopidogrel. A post hoc analysis of patients undergoing PCI suggested that to preserve the beneficial effect of bivalirudin on NACE, clopidogrel could be administered up to 30 minutes after PCI and that mortality was numerically lower but not statistically significant. Another post hoc analysis of the timing and predictors of stent thrombosis from the ACUITY trial found that stent thrombosis occurring within 30 days of PCI occurred just as frequently in the UFH+GPI arm as in either bivalirudin arms. After adjustment, failure to administer preprocedure thienopyridine was a significant predictor of stent thrombosis. Despite the limitations of the ACUITY trial design (eg, wide noninferiority margin) and the potential interaction with clopidogrel pretreatment, it seems that bivalirudin monotherapy is a safer strategy than UFH, enoxaparin, or bivalirudin+GPI. Whether it is more efficacious in non–ST-segment elevation ACS is controversial.

The most recent phase 3 trial of bivalirudin is the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial that randomized 3602 patients with STEMI undergoing primary PCI to either UFH+GPI or bivalirudin. Both 30-day major bleeding and 30-day NACE served as the primary end points. There was a significantly lower rate of both the primary bleeding end point (4.9% bivalirudin versus 8.3% UFH+GPI, \( P=0.001 \)) and the primary NACE end point (9.2% versus 12.1%, \( P=0.005 \)) among patients assigned to bivalirudin. The 30-day ischemic end points of death, MI, urgent target vessel revascularization, or stroke were nearly identical between the 2 arms (5.4% versus 5.5%, \( P=0.95 \)). Two interesting divergent outcomes also were seen in the HORIZONS AMI trial: a significant increase in 24-hour (ie, acute) stent thrombosis in the bivalirudin arm (1.3% versus 0.3%, \( P<0.001 \)) but a significant reduction in 30-day mortality in the bivalirudin arm (2.1% versus 3.1%, \( P=0.047 \)). This reduction in mortality was present at 1 year as well (3.4% versus 4.8%, \( P=0.029 \); Figure 3C). Similar to what was seen with fondaparinux in the OASIS 5 trial, one potential explanation for the mortality findings in HORIZONS AMI is the significant reduction in bleeding complications seen with bivalirudin, although this is speculative. Whether the increase in acute stent thrombosis is a reflection of the clopidogrel interaction seen in the ACUITY is not clear. A post hoc analysis of the HORIZONS AMI trial examined the effect of preprocedure dose of clopidogrel (300 mg versus 600 mg) and found that a 600-mg loading dose was associated with lower rates of 30-day mortality, reinfarction, and subacute stent thrombosis than with a 300-mg loading dose, but other factors, such as short procedure times or discontinuation of the bivalirudin infusion immediately after PCI (effectively creating a window of time post-PCI where there was no antithrombin activity and clopidogrel had not yet taken effect), also may have contributed to this finding. Of note, the use of UFH before randomization was associated with a lower risk for acute stent thrombosis (see below).

### Switching Between Antithrombins

Patients undergoing PCI often arrive in the cardiac catheterization laboratory on anticoagulant therapy that was initiated...
either in the emergency department or in other healthcare settings. Given the array of antithrombin choices available for PCI, patients in the catheterization laboratory often receive therapy that is either added to existing antithrombin therapy (ie, "stacked" therapy) or different from previously used antithrombin therapy that has been discontinued (eg, "switched" antithrombin therapy). Although the data are limited, some stacked or switched strategies seem safe, and other combinations are associated with worse outcomes.

Analysis from the SYNERGY trial showed an association between the addition of UFH to enoxaparin and an increased risk for 30-day mortality or MI as well as an increased risk for transfusion compared with patients who maintained consistent therapy throughout hospitalization. A post hoc analysis examining the effect of prerandomization therapy on outcomes showed an association between consistent therapy with enoxaparin and a lower risk for 30-day mortality or MI, with a trend toward increased bleeding compared with consistent UFH therapy. The STACKENOX (STACK-on to ENOXaparin) study demonstrated that the addition of UFH to enoxaparin resulted in high levels of anti-Xa activity, which may partly explain these results as well as the increased bleeding seen in the enoxaparin arm of the OASIS 5 trial that mandated the addition of UFH to enoxaparin if the last enoxaparin dose was > 6 hours before PCI. On the basis of these data, current guidelines recommend maintaining enoxaparin therapy through PCI using the dosing algorithm reviewed previously.

Other switch or stacked strategies are associated with either improved outcomes or reduced bleeding. For example, as reviewed previously, the addition of UFH during PCI to background fondaparinux therapy is not only safe, but also necessary to reduce catheter-related thrombosis. Similarly, 3 analyses have examined the effect of adding bivalirudin during PCI to background UFH or enoxaparin. Post hoc analyses of the REPLACE-2 and the ACUITY trials showed that switching to bivalirudin during PCI from either UFH or enoxaparin (used with or without GPI) is associated with statistically similar rates of ischemic events and statistically significant lower rates of bleeding. The SWITCH (Switching from Enoxaparin to Bivalirudin in Patients with Acute Coronary Syndromes without ST-segment Elevation Undergoing Percutaneous Coronary Intervention) trial randomized 91 patients with ACS treated with enoxaparin and undergoing PCI to receive bivalirudin within 4 hours, 8 hours, or 12 hours of the last enoxaparin dose. With the primary end point being major bleeding, no significant increase in major bleeding was found, regardless of when bivalirudin was administered. Finally, a specific aspect of the HORIZONS AMI trial should be noted. Approximately 65% of the patients randomized to the bivalirudin arm had received UFH before randomization and, therefore, were switched to bivalirudin during primary PCI. This did not significantly affect the overall impact of bivalirudin on major adverse cardiac events or major bleeding, but as mentioned previously, the use of UFH before randomization was associated with a significant reduction in acute stent thrombosis among patients assigned to bivalirudin, suggesting that an early use of antithrombin therapy in patients with STEMI is necessary to optimize outcomes.

Agents in Development

Although both ischemic and bleeding complications after PCI have improved greatly over time, existing antithrombin strategies all have limitations (Table 1). Therefore, this continues to be an active area of investigation. Several agents directed at various targets in the coagulation cascade are in development for the management of ACS and for use during PCI. They can be grouped broadly into novel heparin agents, RNA aptamers, oral factor Xa inhibitors, and oral DTIs.

M118 is an engineered LMWH compound that provides a constant ratio of factor Xa:factor IIa inhibition (unlike enoxaparin), shows dose-dependent increases in ACT, and is reversible with protamine sulfate. It is currently being studied in the phase 2 Evaluation of M118 IN Percutaneous Coronary Intervention trial. RNA aptamers are single-stranded oligonucleotides that fold into 3D conformations, allowing them to bind with target proteins with high specificity, and are reversible with an antidote. The Reg-1 drug-antidote pair directed against factor IX has been studied in a phase 2 elective PCI trial. The phase 1a and 1b trials (in healthy individuals and in patients with coronary artery disease treated with aspirin and clopidogrel, respectively) demonstrated that the drug and antidote are well tolerated and result in dose-dependent increases in the activated partial thromboplastin time and reversal of the pharmacologic effect within minutes of administering the antidote. The oral DTI dabigatran is currently being studied in the setting of ACS and in the setting of elective PCI. Omatixaban is an intravenous factor Xa inhibitor that has been studied in the setting of elective PCI in the phase 2 SEPIA-PCI trial. Compared with UFH, omatixaban at a dose of 0.140 mg/kg followed by 0.200 mg · kg⁻¹ · h⁻¹ was significantly better at suppressing markers of thrombin generation with no increase in TIMI major bleeding. A range of doses also has been studied in a large phase 2 ACS trial that showed lower rates of death, MI, urgent target vessel revascularization, or bailout GPI at doses 0.105 to 0.140 mg · kg⁻¹ · h⁻¹ than with UFH but numerically higher rates of non–coronary artery bypass grafting-related TIMI major or minor bleeding.

Conclusions

PCI results in iatrogenic plaque rupture that increases the risk for thrombosis and ischemic complications. The central role of thrombin in this process makes it an essential target for pharmacotherapy. Currently available agents—UFH, enoxaparin, fondaparinux, and bivalirudin—all act against thrombin either directly or indirectly through antithrombin. Given the advantages and disadvantages of existing therapies, there should be continued focus on developing new anticoagulants that provide adequate anticoagulation to reduce ischemic complications while simultaneously minimizing bleeding risk. The next phase in the development of antithrombin therapies for PCI should focus on how to better select the most appropriate therapy for the individual patient undergoing PCI, considering not only the clinical setting, such as primary PCI for STEMI or elective PCI for stable angina, but also the angiographic and baseline clinical characteristics of the patients, such as age and renal function. This needs to focus on how to best define the trade-off between reducing...
the risk for bleeding events and reducing the risk for ischemic events. To achieve this, robust models will be needed that can accurately predict these events to optimize therapies. Such a line of investigation will need to be evaluated in prospective clinical trials to help the intervention community have the best antithrombin therapy for the individual patient.

**Disclosures**

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**References**
