Future Perspectives on Antithrombin and Antiplatelet Therapies: Novel Antiplatelet and Antithrombin Therapies

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The recognition that thrombosis is fundamental to acute coronary syndromes (ACS) has inspired the development of novel therapies to inhibit platelet aggregation and thrombus formation. Several recent advances have been made in the management of patients undergoing percutaneous coronary revascularization and those with acute coronary syndromes to improve early and late clinical outcomes. The research efforts leading to these improvements in care have focused on antiplatelet and anticoagulant therapies coupled with early invasive treatment options. In particular, ongoing clinical trials seek to refine treatment strategies for patients relative to individual risk presentation and to determine the appropriate timing of the administration of antithrombotic therapies and revascularization. Simultaneous with attention toward improving efficacy with novel antithrombotic therapies, however, is an ongoing need to minimize bleeding risk. The purpose of this review is to provide a pathophysiologic rationale for the development of novel antiplatelet and antithrombin therapies in ACS and percutaneous coronary intervention, to examine the results of recent trials, and to present future directions for clinical investigation.

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The routine care of patients with cardiovascular disease has rapidly evolved into a new treatment paradigm characterized by dramatic advances in the understanding of disease biology through the identification of receptors, agonists, and antagonists that enable the development of therapies targeted against specific biologic processes. While ongoing translational research seeks to establish the genotypic and phenotypic bases for ischemic heart disease susceptibility and drug response, recent discoveries have provided insight into the influence of individual variation on the development of atherosclerotic disease,

arterial thrombosis, and the development of effective anticoagulant therapies.

The continuing rigorous evaluation of the safety and efficacy of antithrombotic therapies in cardiovascular disease reflects this changing approach to the development of novel pharmacologic agents modeled after our evolving understanding of the pathophysiology, therapeutic applications, and clinical outcomes of patients with acute coronary syndromes (ACS) and those undergoing coronary revascularization. In particular, several recent therapeutic advances have been made in the management of patients with ACS and those undergoing percutaneous coronary intervention (PCI) to improve early and late clinical outcomes. The focus of these research efforts leading to improvements in care has been on the potential to inhibit platelet aggregation and thrombin formation coupled with early invasive treatment options. In parallel with the development of effective antiplatelet and anticoagulant therapies, however, is the need to maintain safety with specific attention toward minimizing bleeding risk. The purpose of this review therefore is to provide a pathophysiologic rationale for antithrombotic therapies in both ACS and PCI, examine the results of recent trials, and present future directions for clinical investigation.

Several recent therapeutic advances have been made in the management of patients with acute coronary syndromes and those undergoing percutaneous coronary intervention to improve early and late clinical outcomes.

Oral Antiplatelet Agents: Aspirin and Thienopyridines

Despite improved outcomes in PCI patients and high-risk patients with ACS, current standard therapies have limitations. For example, reports persist of high clinical event rates among non-ST-elevation (NSTE) ACS patients following treatment,[1,2] motivating the need for improved antiplatelet and anticoagulant therapy. Although aspirin remains a relatively weak antiplatelet agent, in a systematic overview of 60,000 high-risk patients with prior cardiovascular disease, aspirin therapy resulted in an approximate 25% relative reduction ($P < .00001$) in subsequent vascular events, although the total event rate remained high despite aspirin therapy, with a 15% incidence of recurrent myocardial infarction (MI), stroke, or vascular death.[3]

Accordingly, more recent evaluations have been made of orally administered antiplatelet agents not active through the cyclooxygenase pathway to prevent ischemic complications as alternatives to or in combination with aspirin. Clopidogrel is a thienopyridine derivative that decreases adenosine diphosphate (ADP)-induced platelet aggregation. Formulated as an inactive prodrug, clopidogrel requires in vivo conversion by hepatic cytochrome P450 3A4 to an active metabolite that results in noncompetitive inhibition of the platelet ADP receptor subtype $P2Y_{12}$. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, clopidogrel significantly reduced the incidence of MI, stroke, or vascular death compared with aspirin (5.3% vs 5.8%, $P = .043$).[4] In addition, ACS patients treated with combined aspirin and clopidogrel in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial experienced significantly fewer ischemic events after a mean follow-up period of 9 months compared with patients assigned to aspirin therapy alone (9.3% with clopidogrel and aspirin vs 11.5% with aspirin alone, $P = .00005$ for the primary composite endpoint of cardiovascular death, stroke, and MI).[5] Although the occurrence of major bleeding was significantly greater with combined therapy (3.6% with aspirin and clopidogrel vs 2.7% with aspirin alone, $P = .0003$), there was no excess in major bleeding in the clopidogrel group after the initial 30 days, suggesting that most of the risk may have occurred in the setting of revascularization procedures. As a result, contemporary guidelines for the treatment of NSTE ACS emphasize prompt administration of aspirin and clopidogrel for patients in whom a noninvasive strategy is planned and for patients scheduled to undergo PCI.[6] However, consideration of potential bleeding risks among patients whose treatment outcomes are initially unknown but who may undergo surgical revascularization has raised uncertainty regarding the role of combination therapy as initial therapy in the routine management of NSTE ACS. In an observational study of 224 patients undergoing non-urgent bypass surgery and with background aspirin use, treatment with clopidogrel within 7 days of surgery was associated with significantly higher postoperative bleeding and a 10-fold greater likelihood of undergoing repeat operation for bleeding complications (6.8% vs 0.6%, $P = .018$).[7]

Unlike surgical revascularization, however, treatment with clopidogrel in the periprocedural setting of catheter-based revascularization has been associated with significant early

and long-term benefit. In a nonrandomized substudy of the CURE trial (PCI-CURE), compared with aspirin pretreatment alone, patients receiving dual antiplatelet therapy for a median of 10 days prior to PCI experienced a significant reduction in the 30-day occurrence of death, MI, and urgent target vessel revascularization (4.5% vs 6.4%, $P = .03$).[8] The Clopidogrel for the Reduction of Events During Observation (CREDO) study randomized 2116 patients intended to undergo PCI to either pretreatment with 300 mg clopidogrel within 24 hours prior to PCI or alternatively 75 mg at the time of revascularization.[9] Patients randomized to the pretreatment arm also received combined aspirin and clopidogrel for 1 year following revascularization. Although a trend toward reduced 28-day ischemic adverse events favored pretreatment with clopidogrel (6.8% vs 8.3%, $P = .23$), long-term clopidogrel therapy was associated with a significant reduction in the 1-year occurrence of death, MI, and stroke compared with aspirin alone (8.5% vs 11.5%, $P = .02$).[9]

More recently, the potential efficacy of a higher loading dose of clopidogrel has been examined in patients undergoing PCI. Because administration of large loading doses of clopidogrel more rapidly achieve inhibition of ADP-induced platelet aggregation,[10] the benefit of additional glycoprotein (GP) IIb/IIIa inhibition to a clopidogrel pretreatment strategy has been recently debated. The Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) trial randomized 2159 patients scheduled for elective PCI to treatment with either abciximab or placebo.[11] All patients received a 600-mg dose of clopidogrel at least 2 hours prior to the procedure. At 30 days, the incidence of death, MI, and urgent target vessel revascularization (TVR) did not significantly differ between treatment groups (4.0% vs 4.0%, $P = .82$). Although the occurrence of major bleeding also did not differ, the development of profound thrombocytopenia was significantly more common with abciximab (1.0% vs 0, $P = .002$).

Importantly, none of the patients enrolled in ISAR-REACT presented with high-risk ACS characteristics, and all patients underwent PCI. Thus, while outcomes remain uncertain for NSTE ACS patients with high-risk features (eg, recent MI or electrocardiographic ST-segment deviation > 0.1 mV) who do not undergo PCI, the recent ISAR-REACT 2 trial has provided some insight for those ACS patients who are treated with oral antiplatelet therapy alone.[12] In this study, 2022 patients with NSTE ACS undergoing PCI were treated with 600 mg of clopidogrel and aspirin followed by randomization to treatment with either abciximab or placebo. The primary endpoint was a composite of death, myocardial infarction, and ischemia-driven TVR at 30 days postprocedure. Treatment with abciximab was associated with a significant reduction in both the primary endpoint (11.9% vs 8.9%, $P = .03$) in addition to a reduction in 30-day death or myocardial infarction (11.5% vs 8.6%, $P < .05$). This clinical benefit associated with abciximab was particularly apparent among patients with elevated troponin levels (N = 1049; 8.3% placebo vs 13.1% abciximab, $P = .02$ for death, MI, ischemic-driven urgent revascularization) compared with troponin-negative patients (N = 973; 4.6% vs 4.6%, $P = .98$). The occurrences of major and minor bleeding did not statistically vary between treatment groups. Thus, among the higher risk NSTE ACS patients undergoing PCI who are treated with aspirin, clopidogrel (600 mg) and unfractionated heparin, the adjunctive use of abciximab is associated with a significant improvement in early clinical outcome.

Despite the benefit of long-term dual antiplatelet therapy with aspirin and clopidogrel among patients with ACS and those undergoing PCI, several uncertainties regarding clopidogrel treatment remain. Although the relationship between clopidogrel dose, timing of pretreatment, and clinical benefit has been recently clarified in broad patient populations undergoing PCI, individual patient variability in responsiveness to clopidogrel treatment measured by platelet aggregation studies may be common and associated with an increased likelihood of ischemic events following revascularization.[13-15] In addition, long-term treatment with clopidogrel and aspirin in patients with stable vascular disease or for primary prevention may not provide clinical benefit and instead may be associated with increased risk of adverse events. In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) trial, 15,603 patients with either clinically relevant cardiovascular disease or multiple risk factors were randomized to clopidogrel 75 mg/day plus low-dose aspirin (75-162 mg/day) or placebo plus low-dose aspirin.[16] The primary endpoint was a composite outcome of myocardial infarction, stroke, or death from cardiovascular causes, and the median follow-up period was 28 months. Overall, the occurrence of the primary endpoint did not statistically differ between treatment groups (6.8% clopidogrel/aspirin vs 7.3% aspirin/placebo, $P = .22$). However, combination antiplatelet therapy was associated with a trend toward higher severe bleeding rates (1.7% vs 1.3%, $P = .09$),

and among patients in the primary prevention group, the endpoint of cardiovascular death was significantly more common with aspirin and clopidogrel (3.9% vs 2.2%, $P = .01$). Although performed as a subgroup analysis, these findings imply the need for thoughtful consideration regarding which patients should be treated with long-term dual antiplatelet therapy.

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Development of Novel Thienopyridines and Other Platelet Purinergic Receptor Antagonists

Uncertainty regarding variable responsiveness, or "resistance," to clopidogrel has motivated the development of alternative inhibitors of platelet purinergic receptors (eg, $P2Y_{12}$, $P2Y_1$, $P2X_1$). Prasugrel is a third-generation thienopyridine that undergoes pre-hepatic conversion by circulating esterases and is therefore not dependent upon cytochrome 3A4 metabolism (Table 1).[17] Compared with clopidogrel, prasugrel has much less interindividual variability, more rapid onset of platelet aggregation, and significantly greater potency.[18,19] Specifically, resistance to thienopyridine therapy may be less frequent and platelet inhibition greater with a 60 mg dose of prasugrel compared with 300 mg of clopidogrel.[18] In the phase 2, dose-ranging Joint Utilization of Medications to Block Platelets Optimally-Thrombolysis in Myocardial Infarction 26 (JUMBO-TIMI 26) trial, 904 patients undergoing PCI were randomized to standard dosing of clopidogrel (600 mg loading dose followed by 75 mg daily) or 1 of 3 prasugrel regimens.[20] There were no significant differences in the primary endpoint of noncoronary artery bypass-related bleeding events (TIMI major and minor) between prasugrel- and clopidogrel-treated patients. Although directionally lower in the prasugrel group, 30-day major adverse cardiac events were also lower, yet these differences were not significantly different (7.2% vs 9.4%; hazard ratio 0.76, 95% CI 0.46 to 1.24). The ongoing phase 3 Trial to Assess Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel

Table 1
Selected New Generation Antiplatelet and Antithrombin Therapies

Agent	Mechanism of Action	Route of Administration	Clearance	Contemporary ACS/PCI Trials
Antithrombin Agents				
Enoxaparin	Indirect, semi-selective Xa inhibition	Intravenous, subcutaneous	Renal	A to Z, ACUITY, EARLY ACS, ESSENCE, OASIS 5, PROTECT-TIMI 20, SYNERGY, TIMI 11B
Fondaparinux	Indirect Xa, selective Xa antagonism	Subcutaneous	Renal	OASIS 5, OASIS 6
Bivalirudin	Direct thrombin inhibition	Intravenous	Renal	ACUITY, HORIZONS, REPLACE-2, PROTECT-TIMI 30
Antiplatelet Agents				
Cangrelor	Direct $P2Y_{12}$ platelet receptor inhibition	Intravenous	Endothelial-derived endonucleotidases	CHAMPION-PCI
Prasugrel	Indirect $P2Y_{12}$ platelet receptor inhibition	Oral	Pre-hepatic metabolism to active metabolite by circulating esterases	JUMBO-TIMI 26, TRITON-TIMI 38

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; A to Z, Aggrastat to Zocar; ACUITY, Acute Catheterization and Urgent Intervention Thrombotic Strategy; EARLY ACS, Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events; OASIS, Organization to Assess Strategies in Acute Ischemic Syndromes-5; PROTECT-TIMI, Randomized Trial to Evaluate the Relative Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Anti-platelet and Anti-thrombotic Agents-Thrombolysis In Myocardial Infarction; SYNERGY, Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; TIMI, Thrombolysis In Myocardial Infarction; HORIZONS, Harmonizing Outcomes with Revascularization and Stents; REPLACE, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; CHAMPION-PCI, Cangrelor: A Clinical Trial Comparing Cangrelor to Clopidogrel in Subjects Who Require Percutaneous Coronary Intervention; JUMBO-TIMI, Joint Utilization of Medications to Block Platelets Optimally-Thrombolysis In Myocardial Infarction; TRITON-TIMI, Trial to Assess Therapeutic Outcomes by Optimizing Platelet Inhibition-Thrombosis in Myocardial Infarction-Thrombolysis In Myocardial Infarction.

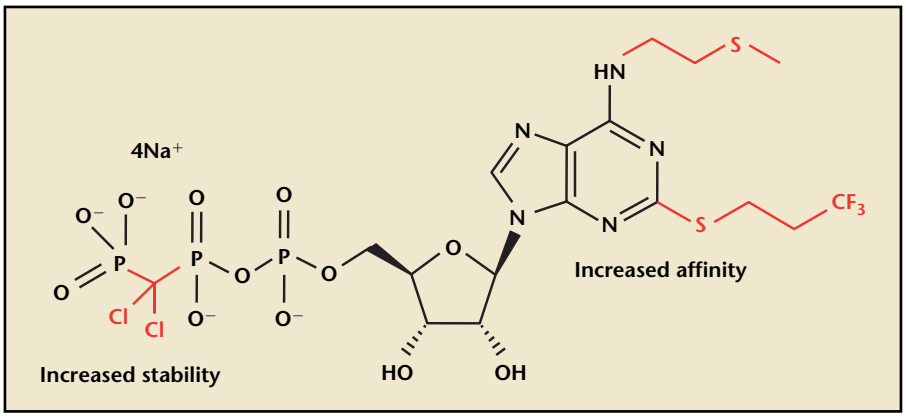

Figure 1. *Chemical structure of cangrelor. The triphosphate chain increases stability of the drug, and the sulfide chain promotes increased affinity for the P2Y$_{12}$ receptor.*

(TRITON-TIMI 38) will clarify the safety and efficacy of prasugrel compared with clopidogrel in approximately 13,000 patients undergoing PCI.

In addition to prasugrel, alternative purinergic receptor inhibitors have been developed. Specifically, the P2Y$_{12}$ platelet receptor is one of at least 3 purinoreceptors bound by adenosine.[21] Upon adenosine-induced activation, the P2Y$_{12}$ receptor promotes platelet activation by decreasing levels of cyclic adenosine monophosphate. Cangrelor is an intravenous selective P2Y$_{12}$ receptor inhibitor (Figure 1 and Table 1). As an adenosine triphosphate analogue, cangrelor is a direct inhibitor of the P2Y$_{12}$ receptor and therefore does not require metabolic conversion to an active metabolite.[22,23] Although highly resistant to ectonucleotidase degradation, cangrelor has a brief half life in vivo (3-5 minutes), and its metabolism is not dependent upon hepatic or renal function and occurs through sequential dephosphorylation to a nucleoside metabolite that is 10,000-fold less active than the parent compound.

In 2 separate phase 2 dose-ranging trials involving patients with NSTE ACS, treatment with cangrelor, aspirin, and heparin was determined safe and well tolerated up to a dose of 4 μg/kg per minute while achieving > 95% inhibition of platelet aggregation.[24,25] Recently, treatment with cangrelor was examined in patients undergoing PCI.[26] In a 2-part study, patients (N = 200) were initially randomized to an infusion of either placebo or varying doses of cangrelor (up to 4 μg/kg per minute) in addition to aspirin and unfractionated heparin (UFH), In the second part, 199 patients were randomized to therapy with cangrelor (4 μg/kg per minute) or abciximab prior to PCI. Combined major and minor bleeding did not statistically differ between patients treated with cangrelor or placebo in the first part of the study (13% cangrelor vs 8% placebo, *P* = NS) or among patients receiving cangrelor or abciximab in the second part (7% cangrelor vs 10% abciximab, *P* = NS). At 30 days, among patients undergoing PCI in the second part of the study, major adverse events were also similar (7.6% vs 5.3%, *P* = NS). Platelet inhibition with cangrelor was maximal by 15 minutes following drug infusion, and except for the 4 μg/kg dose, platelet function returned to baseline within 15 minutes of drug discontinuation. Mean inhibition of platelet aggregation was 100% for both cangrelor (4 μg/kg per minute dose) and abciximab. However, recovery of platelet function following termination of drug infusion was more rapid with cangrelor compared with abciximab. In summary, treatment with cangrelor is associated with rapid, reversible inhibition of platelet aggregation with favorable safety and efficacy compared with contemporary therapies. These findings serve as the foundation for the forthcoming Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI trial, in which approximately 9,000 patients undergoing PCI will be randomized to treatment with either cangrelor or placebo to evaluate the primary endpoint of death, myocardial infarction, or urgent revascularization at 48 hours following the index procedure.

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Antithrombin Therapies

A mainstay of conventional therapy in patients with ACS and those undergoing PCI has been adjunctive antithrombin treatment. In clinical trials involving patients with ACS, however, the addition of heparin or early direct thrombin inhibitors has conferred only a modest benefit with regard to clinical outcomes. In a

systematic overview of 6 trials of aspirin versus aspirin and UFH, no individual trial reached statistical significance and the combined risk of MI or death was reduced by a relative 33% ($P = .06$) in patients given aspirin and heparin.[27] In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-IIb investigation, treatment with the direct thrombin inhibitor hirudin resulted in a nonsignificant ($P = .06$) 10% relative reduction in the 30-day composite endpoint of death or infarction among patients with NSTE ACS.[2]

Although UFH appears to provide a benefit in patients with ACS and during revascularization, its use is associated with a number of challenges. In particular, it is difficult to titrate heparin dosing within a therapeutic range. Both insufficient and excessive doses are associated with worse clinical outcomes, and event rates increase when it is discontinued, although GP IIb/IIIa inhibition may attenuate this rebound effect.[28] Heparin is also associated with thrombocytopenia and the potential to cause malignant thrombosis.

Although low-molecular-weight heparins (LMWHs) may provide several conceptual advantages over UFH, the absolute benefit compared with UFH is less defined. First, through preferential inhibition of factor Xa over thrombin, LMWHs produce more effective anticoagulation earlier in the coagulation cascade and may therefore be a more efficient antithrombin agent. They also are less likely to cause heparin-induced thrombocytopenia, and current formulations do not require therapeutic monitoring. In several preliminary, direct, comparative trials among patients with NSTE ACS, the LMWHs have been at least as effective, if not superior to, UFH.[29-31] However, among 10,027 ACS patients randomized to treatment with either UFH or enoxaparin in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, treatment with enoxaparin was statistically noninferior to, but not superior to, therapy with UFH.[32] Further, major and minor bleeding complications tended to be higher among patients assigned to treatment with enoxaparin, particularly when crossing over between the 2 antithrombin therapies occurred. Overall, in systematic overview of trials comparing UFH and enoxaparin among individuals with NSTE ACS (N = 21,946), there were no significant differences between the 2 treatments with regard to blood product transfusions or TIMI major bleeding.[33] However, the 30-day endpoint of death or myocardial infarction was significantly lower among patients receiving enoxaparin (10.1% vs 11.0%, odds ratio 0.91, 95% confidence interval, 0.83 to 0.99), a benefit that was particularly evident among patients not receiving any antithrombin therapy prior to randomization (8.0% vs 9.4%, odds ratio 0.81, 95% CI, 0.70 to 0.94).

Compared with patients with non-ST-elevation ACS, however, therapy with enoxaparin in combination with fibrinolytic therapy for ST-elevation MI may be superior to adjunctive use of unfractionated heparin.

Compared with patients with NSTE ACS, however, therapy with enoxaparin in combination with fibrinolytic therapy for ST-elevation MI may be superior to adjunctive use of UFH. In the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT TIMI 25) trial, 20,506 patients with ST-elevation MI treated with fibrinolytic therapy were randomized to treatment with either UFH or enoxaparin.[34] At 30 days, treatment with enoxaparin was associated with a significant reduction in the composite endpoint of death or MI (12.0% vs 9.9%, $P < .0001$). Although rates of intracranial hemorrhage did not differ between treatment groups, the occurrence of nonfatal major bleeding was significantly more common with enoxaparin (2.1% vs 1.4%, $P < .0001$).

In contrast to UFH and LMWHs, direct antithrombins have a number of advantages including (1) highly specific and potent thrombin inhibition; (2) lack of dependence on antithrombin III for anticoagulant effect; (3) inactivation of both clot-bound and free thrombin; and (4) lack of aggregatory effects on platelets. In a systematic overview of 11 randomized trials involving nearly 36,000 patients, direct thrombin inhibitors were associated with a lower risk of death or MI at 30 days compared with UFH (7.4% vs 8.2%, $P = .02$).[35] Subgroup analyses indicated a benefit with direct thrombin inhibitors in both ACS and PCI. Notably, there was an apparent reduction in ischemic events with bivalirudin and hirudin, but not with univalent agents.

More recent evaluation of bivalirudin in PCI has suggested the potential for equivalent outcomes without the use of GP IIb/IIIa inhibitors in selected patients (Table 1). Results from the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial, comparing UFH plus mandatory GP IIb/IIIa inhibition with

bivalirudin plus provisional GP IIb/IIIa inhibitors in PCI, indicate that the latter treatment strategy may have similar efficacy yet result in less bleeding complications.[36] At 30 days, the occurrence of the composite endpoint did not differ between groups, but use of bivalirudin resulted in significantly less bleeding (4.2% vs 2.4%, $P < .001$). Similarly, among 857 high-risk NSTE ACS patients undergoing PCI in the Randomized Trial to Evaluate the Relative Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Anti-platelet and Anti-thrombotic Agents (PROTECT TIMI 30), the primary endpoint of coronary flow reserve (as a measure of myocardial perfusion) did not statistically differ between patients randomized to treatment with either eptifibatide (and either UFH or enoxaparin) or bivalirudin.[37] Major bleeding also did not statistically vary between groups, yet both post-PCI ischemia by Holter monitoring and the post-PCI achievement of grade 3 myocardial blush were significantly improved among patients receiving heparin and GP IIb/IIIa inhibition.

Aside from the setting of PCI, bivalirudin therapy has been recently examined as part of treatment for NSTE ACS. In the Acute Catheterization and Urgent Intervention Thrombotic Strategy (ACUITY) trial, 13,800 patients with moderate-high risk ACS were randomized to treatment with bivalirudin, bivalirudin and a GP IIb/IIIa inhibitor, or heparin (UFH or LMWH) and GP IIb/IIIa inhibition.[38] Patients assigned to treatment with a GP IIb/IIIa inhibitor (with bivalirudin or heparin) underwent a second randomization to receive the GP IIb/IIIa inhibitor either at randomization or instead during PCI. The primary endpoint was the 30-day composite of all-cause mortality, myocardial infarction, ischemia-driven revascularization, and major bleeding. Comparing patients treated with bivalirudin and GP IIb/IIIa blockade versus heparin and GP IIb/IIIa inhibition, there were no significant differences in either ischemic or bleeding events. Similarly, 30-day ischemic events did not differ among patients treated with bivalirudin versus those receiving heparin and a GP IIb/IIIa inhibitor (7.3% heparin and GP IIb/IIIa inhibition vs 7.8% bivalirudin and GP IIb/IIIa inhibition, $P = .011$ for noninferiority, $P = .32$ for superiority). However, major bleeding was significantly lower among patients treated with bivalirudin (5.7% vs 3.0%, $P < .0001$ for both noninferiority and superiority). In subgroup analysis, although there were no differences in net clinical outcome between bivalirudin and heparin-GP IIb/IIIa inhibition relative to troponin positivity, early treatment with a thienopyridine prior to PCI was associated with a significant reduction in the primary endpoint among patients receiving bivalirudin. Thus, in moderate to high risk NSTE ACS patients, treatment with bivalirudin is an acceptable substitute to heparin and GP IIb/IIIa inhibition with similar efficacy and a significant reduction in bleeding events. These results will require further consideration against the background of recent trials examining alternative antithrombin agents and early treatment with intravenous GP IIb/IIIa antagonists.

Thus, in moderate to high risk NSTE ACS patients, treatment with bivalirudin is an acceptable substitute to heparin and GP IIb/IIIa inhibition with similar efficacy and a significant reduction in bleeding events.

Future Directions: Development of Novel Antithrombotic Therapies and Indications

The recognition that thrombosis is fundamental to ACS and that its inhibition is essential in PCI has motivated the development of novel therapies targeting platelet aggregation and thrombus formation. In addition to bivalirudin, other novel anticoagulants are under investigation in the management of NSTE ACS. Fondaparinux is a synthetic pentasaccharide that indirectly inhibits factor Xa through highly selective binding to antithrombin III (Table 1). Against the background of numerous trials establishing its efficacy in the prevention of venous thromboembolism,[39,40] the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial was conducted to compare treatment with fondaparinux versus enoxaparin in 20,078 NSTE ACS patients to reduce early ischemic adverse events.[41] In this trial, the primary endpoint of death, MI, and refractory ischemia at 9 days was similar between treatment groups to fulfill noninferiority criteria (5.8% with fondaparinux vs 5.7% with enoxaparin, hazard ratio 1.01, 95% CI, 0.90 to 1.13). However, among patients treated with fondaparinux, major bleeding was significantly lower (2.2% vs 4.1%, $P < .001$). In addition, overall mortality was significantly lower in the fondaparinux group at 30 days and at 6 months (6.5% vs 5.8% at 6 months, $P = .05$). Despite the favorable reduction in mortality and adverse

bleeding events, the incidence of thrombotic events during PCI (eg, guiding catheter thrombus, angiographic thrombus with the vessel, no-reflow) was significantly more common among patients treated with fondaparinux (0.9% vs 0.4%, $P = .001$). Accordingly, the potential benefits of fondaparinux in reducing bleeding and ischemic events must be considered against the slight but increased likelihood of thrombotic complications among patients undergoing PCI.

Therapy with fondaparinux has also been evaluated in patients with acute ST-segment elevation MI. In the OASIS-6 trial, 12,092 patients with ST-segment elevation MI were randomized to treatment with either fondaparinux or either UFH or placebo depending upon whether heparin therapy was indicated.[42] Treatment with fondaparinux was associated with a significant reduction in the primary endpoint of death or recurrent MI at 30 days (11.2% vs 9.7%, $P = .008$). The individual endpoint of mortality was also significantly reduced with fondaparinux at both 9 and 30 days (8.9% vs 7.8%, $P = .03$). In addition, the occurrence of severe bleeding also tended to be lower with fondaparinux (1.3% vs 1.0%, $P = .13$). In subgroup analysis, significant benefit with fondaparinux was observed among patients receiving thrombolytic therapy and those not receiving any reperfusion therapy; however, no benefit was identified among patients undergoing primary PCI. Specifically, although the 30-day outcome of death or MI after primary PCI did not significantly differ between patients receiving UFH or fondaparinux, guiding catheter-related thrombotic complications (eg, abrupt closure, new angiographic thrombus, catheter thrombus, no reflow) were significantly more common in the fondaparinux group (22 events vs 0 events, $P < .001$). Considering the increased risk of catheter-related thrombotic events, the relatively brief required duration of anticoagulation for patients undergoing primary PCI and the long half-life of fondaparinux (potentially complicating vascular sheath removal), there is likely little advantage for treatment with fondaparinux as initial therapy for patients undergoing primary PCI.

Early clinical trials experience in both ACS and PCI with agents that directly inhibit factor Xa (eg, DX-9065a) also appear to be promising alternatives to unfractionated heparin.[43,44] In addition, the development of nucleic acid aptamers as novel anticoagulants may also be effective therapy in patients with ACS and PCI.[45] Specifically, aptamers are single-stranded, protein-binding oligonucleotides that can be specifically targeted to proteins of interest, for example, factor IX, factor X, or thrombin. In addition, a drug-antidote pair can be designed that may enable rapid neutralization of the anticoagulant effect. Early phase trials with a factor IX inhibitor and its antidote are ongoing.

Conclusions

Despite remarkable achievements in the care of patients with ACS and among those undergoing PCI, contemporary clinical trials are seeking to refine treatment strategies for patients relative to individual risk for both ischemic and bleeding events. Even with currently available therapies (eg, clopidogrel, bivalirudin), ongoing trials are designed to tailor antiplatelet and anticoagulant treatment in high-risk ACS patients and to define the interaction of these therapies with catheter-based revascularization. As in the example of thienopyridine pretreatment and bivalirudin in the ACUITY trial, such trials may clarify the complementary—rather than exclusionary—benefits of the presently available antiplatelet and antithrombin therapies to maintain efficacy (eg, reducing death and MI) while improving safety (eg, decreasing bleeding and thrombocytopenia). In addition, trials are ongoing to extend our understanding of anticoagulant therapies in more varied clinical settings. For example, the ongoing Harmonizing Outcomes with Revascularization and Stents (HORIZONS) trial is designed to compare treatment with bivalirudin or unfractionated heparin and GP IIb/IIIa inhibition in patients undergoing primary PCI. Other trials with direct and indirect inhibitors of the platelet $P2Y_{12}$ receptor may change antithrombotic management in patients who are undergoing percutaneous revascularization. These studies with currently available therapies, in addition to novel antiplatelet (eg, cangrelor, prasugrel) and antithrombin (eg, aptamers) therapies should only further improve clinical outcomes among patients at risk for cardiovascular thrombotic events. ■

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Main Points

- Despite improved outcomes in patients undergoing percutaneous coronary intervention (PCI) and high-risk patients with acute coronary syndrome (ACS), current standard therapies have limitations.
- Long-term treatment with clopidogrel and aspirin in patients with stable vascular disease or for primary prevention may not provide clinical benefit and instead may be associated with increased risk of adverse events.
- Uncertainty regarding variable responsiveness, or "resistance," to clopidogrel has motivated the development of alternative inhibitors of platelet purinergic receptors (eg, $P2Y_{12}$, $P2Y_1$, $P2X_1$).
- Treatment with cangrelor is associated with rapid, reversible inhibition of platelet aggregation with favorable safety and efficacy compared with contemporary therapies.
- The recognition that thrombosis is fundamental to ACS and that its inhibition is essential in PCI has motivated the development of novel therapies targeting platelet aggregation and thrombus formation. In addition to bivalirudin, other novel anticoagulants are under investigation in the management of non-ST-elevation ACS.
- Early clinical trials experience in both ACS and PCI with agents that directly inhibit factor Xa (eg, DX-9065a) also appear to be promising alternatives to unfractionated heparin.
- Other trials with direct and indirect inhibitors of the platelet $P2Y_{12}$ receptor may change antithrombotic management in patients undergoing percutaneous revascularization.

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