Improving Adjunctive Pharmacotherapy for Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: Beyond the HORIZONS-AMI Trial

Dean J. Kereiakes, MD, FACC

The Christ Hospital Heart and Vascular Center/The Carl and Edyth Lindner Center for Research and Education, Cincinnati, OH

Patients who present with acute coronary syndromes, particularly ST-segment elevation myocardial infarction (STEMI), have abnormalities in platelet size and function that predispose to thrombotic events. Both preprocedural platelet reactivity and mean platelet volume are directly correlated with the occurrence of adverse ischemic events and impaired microvascular reperfusion following primary percutaneous coronary intervention (PCI) for STEMI. The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial demonstrated a similar ischemic event rate to 30 days with a significantly lower bleeding event rate (enhanced net clinical benefit) in favor of bivalirudin monotherapy (with provisional platelet glycoprotein [GP] IIb/IIIa receptor blockade) in comparison with unfractionated heparin plus GP IIb/IIIa blockade in patients undergoing primary PCI for STEMI. The bivalirudin monotherapy was associated with a highly significant greater incidence of acute stent thrombosis. This observation provides the opportunity for strategies that enhance periprocedural platelet inhibition to reduce stent thrombosis and to potentially improve the safety and efficacy of periprocedural adjunctive pharmacotherapy above that achieved by bivalirudin monotherapy alone.
[Rev Cardiovasc Med. *2009;10(2):72-82*]

Key words: Myocardial infarction • Primary percutaneous coronary intervention • Bivalirudin • Stent thrombosis

Following either spontaneous or iatrogenic (during percutaneous coronary intervention [PCI]) plaque rupture, the arterial endothelial barrier is disrupted and subendothelial matrix proteins (collagen, von Willebrand factor [VWF]) are exposed to blood. Platelets adhere to specific cell receptors for collagen (glycoprotein [GP] VI, GP Ia/IIa) as well as VWF (GP Ib-IX) and become

activated.[1,2] Activated platelets degranulate and secrete platelet agonists, chemotaxins, clotting factors, and vasoconstrictors that promote platelet aggregation, thrombus formation, and vasospasm.[3] Following platelet activation, GP IIb/IIIa receptors on the platelet surface undergo a rapid conformational change so that they can bind to soluble fibrinogen. Upon binding to GP IIb/IIIa, the bivalent fibrinogen (as well as other adhesive proteins, including fibronectin, vitronectin, and VWF) further mediates platelet aggregation by crosslinking the surfaces of activated platelets via GP IIb/IIIa. The acuity of the clinical syndrome depends, in part, upon the quantity of thrombus present and the consequent degree of coronary obstruction, which ranges from incomplete (unstable angina, non–ST-segment elevation myocardial infarction) to complete thrombotic occlusion (ST-segment elevation myocardial infarction [STEMI]). This article will examine the potential use of periprocedural GP IIb/IIIa receptor blockade with abciximab intracoronary bolus, the novel platelet $P2Y_{12}$, and thrombin receptor antagonists.

Platelet Reactivity

The platelet plays a central role in both the pathogenesis of atherothrombosis and the development of acute coronary syndromes (ACS) and, thus, is a logical target of therapy for these disease processes.[2-4] Patients who present with ACS demonstrate abnormalities in platelet size and function. An increase in platelet surface expression of P-selectin (CD62), GP IIb/IIIa, and CD40L accompanies the heightened state of platelet activation in ACS.[5,6] The platelets of patients with ACS demonstrate exaggerated responsiveness to low levels of exogenous agonist (ex vivo), as well as a differential response to standard doses of antiplatelet therapies.[7] Following administration of the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial loading dose of tirofiban (10 μg/kg), patients with ACS manifest a lower level of measured platelet inhibition than do their stable angina counterparts.[8] A similar observation has been made following the administration of clopidogrel 300-mg oral load and 75 mg/d to patients who have undergone coronary stent deployment. A differential (reduced) magnitude of clopidogrel-mediated platelet inhibition of aggregation and activation was observed in patients with unstable compared with stable angina symptoms (Pierre Théroux, MD, personal communication). The heightened state of platelet reactivity in ACS is protracted. One month following presentation for ACS in the Thrombolysis In Myocardial Infarction 12 (TIMI 12) study, a significant increase in platelet surface expression of CD62 was observed, signifying persistent platelet activation despite pharmacologic therapy.[9] Increased platelet reactivity in ACS is accompanied by an increase in platelet volume. Mean platelet volume is increased in approximate proportion to the acuity of the clinical syndrome and increased further following PCI.[10] A direct correlation between a larger mean platelet volume and platelet surface expression for both CD62 and GP IIb/IIIa has been made.[11]

In summary, patients who present with ACS have large, hyperactive, hyper-responsive platelets as well as a differential response to standard dose regimens of antiplatelet therapies. The importance of these observations is greatly enhanced by the fact that baseline platelet reactivity as measured either directly by agonist-stimulated aggregation or indirectly as indicated by platelet volume has been correlated with the occurrence of adverse clinical events following both elective PCI[12,13] as well as primary PCI for STEMI.[14,15] Those patients with the highest level of preprocedural platelet reactivity demonstrate the highest incidence of periprocedural ischemic events, including myocardial infarction, urgent repeat revascularization, and stent thrombosis. Preprocedural platelet reactivity has also been correlated with late adverse clinical outcomes, including both angiographic and clinical restenosis following elective PCI.[16] In addition, impaired microvascular reperfusion as reflected by TIMI myocardial blush grade 0/1 or electrocardiographic ST-segment resolution at or below 50% has been correlated with baseline preprocedural platelet reactivity prior to primary PCI for STEMI.[15]

Multi-Receptor Blockade

Because platelet activation is a complex process involving multiple redundant pathways, therapeutic strategies, which include simultaneous blockade of multiple receptors (cyclooxygenase [COX-1] by aspirin, $P2Y_{12}$ by a thienopyridine, and GP IIb/IIIa by a GP IIb/IIIa inhibitor), are intuitively attractive and have been demonstrated to achieve incremental inhibition of platelet activation and aggregation[17,18] (Figure 1). The combination of a thienopyridine and a GP IIb/IIIa inhibitor provides incremental platelet inhibition (compared with either agent alone),[19] which has been translated into enhanced clinical benefit as reflected by a greater reduction in adverse ischemic events.[20,21] In the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS)[22] and the CLEAR PLATELETS 1b[23] trials, a higher level of platelet inhibition was achieved during PCI in patients treated with a combination of clopidogrel and eptifibatide compared

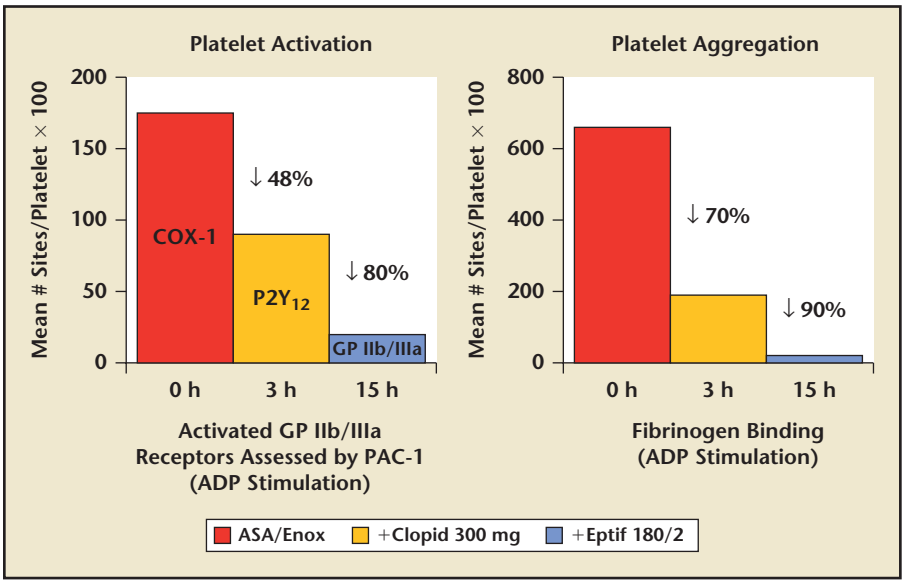


Figure 1. *Incremental inhibition of platelet activation and aggregation follows the sequential addition of different platelet receptor blocking agents to patients with acute coronary syndrome in the PEACE trial. Patients were initially treated with aspirin (COX-1 receptor inhibition) and enoxaparin followed by the addition of a clopidogrel 300-mg oral load ($P2Y_{12}$ receptor inhibition) and eptifibatide 180 μg/kg bolus, 2 μg/kg/min infusion (GP IIb/IIIa receptor inhibition) in sequence. PEACE, Platelet Activity Extinction in Non-Q-Wave Myocardial Infarction with Aspirin, Clopidogrel, and Eptifibatide; GP, glycoprotein; ADP, adenosine diphosphate; ASA, aspirin; Enox, enoxaparin; Clopid, clopidogrel; Eptif, eptifibatide. Reprinted from* Journal of the American College of Cardiology, *Volume 46, Giugliano RP, Braunwald E. The year in non-ST-segment elevation acute coronary syndromes. Pages 906-919.*[17] *Copyright © 2005, with permission from the American College of Cardiology.* www.medreviews.com

with clopidogrel treatment alone and was associated with a greater reduction in markers of both inflammation (high-sensitivity C-reactive protein, tumor necrosis factor-α) as well as periprocedural myocardial necrosis (creatinine kinase-MB, troponin, myoglobin). In the Troponin in Planned PTCA/Stent Implantation with or without Administration of the Glycoprotein IIb/IIIa Receptor Antagonist Tirofiban (TOPSTAR) trial, the addition of tirofiban to patients treated with aspirin and clopidogrel prior to PCI reduced periprocedural myocardial necrosis as reflected by troponin T elevation.[24] Finally, in the Intracoronary Stenting Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT) II trial, patients with high-risk ACS were pretreated with aspirin and clopidogrel (600 mg) after coronary angiography but at least 2 hours prior to PCI.[25] At the time of PCI, patients were randomly assigned to treatment with either intravenous (IV) abciximab or placebo, and all patients received concomitant weight-adjusted unfractionated heparin (UFH) intravenously. Patients who received periprocedural abciximab enjoyed a 25% relative reduction in ischemic events (death, myocardial infarction, urgent repeat revascularization) through 30 days. Abciximab clinical benefit was greatest in those patients who had an elevated preprocedural serum troponin level.[25] These data support the concepts that high levels of periprocedural platelet inhibition should be targeted, particularly in high-risk patients, and that higher levels of inhibition are associated with better clinical outcomes. In addition, incremental levels of platelet inhibition can be achieved by combining agents that block various pathways (COX-1, $P2Y_{12}$, GP IIb/IIIa) of platelet activation and aggregation.

Dethrombosis and Platelet Receptor Blockade

Platelet GP IIb/IIIa inhibitors are associated with dose-dependent disaggregation of platelet-rich thrombus.[26] The mechanism responsible for platelet disaggregation ("dethrombosis") is the high affinity of the GP IIb/IIIa inhibitor agent for the GP IIb/IIIa receptor, which displaces fibrinogen, the primary ligand bridging activated GP IIb/IIIa receptors in the process of platelet aggregation.[27] However, marked differences exist in the pharmacokinetics, pharmacodynamics, and specific-receptor affinity for the available GP IIb/IIIa inhibitor agents. Separate and distinct binding sites on the GP IIb/IIIa receptor complex have been identified for abciximab and for the "small molecule" GP IIb/IIIa inhibitors (eptifibatide, tirofiban) by means of differential displacement of site-specific monoclonal antibodies: Mab1 (LYP18), a complex-specific, ligand recognition site (bound by abciximab), and Mab2 (4F8), a β3 subunit specific site (bound by the small molecule GP IIb/IIIa inhibitors).[28] In addition to binding a separate site on the GP IIb/IIIa receptor, abciximab has a unique pharmacokinetic and pharmacodynamic profile. Abciximab demonstrates high affinity (low Kd) and the small molecule inhibitors demonstrate low affinity (high Kd) for binding to the GP IIb/IIIa receptor[29] (Figure 2). This difference is reflected in the ratio of platelet-bound to free (in serum) drug.[30] Whereas the vast majority of abciximab molecules are platelet-bound (with a bound to free ratio of ~4:1), the converse is true for the small molecule inhibitors (with a bound to free ratio of ~1:250-500). The differential high affinity/low Kd of abciximab may explain the observations of van Werkum and colleagues[31] in a randomized comparative trial of abciximab versus high-dose tirofiban (25 μg/kg

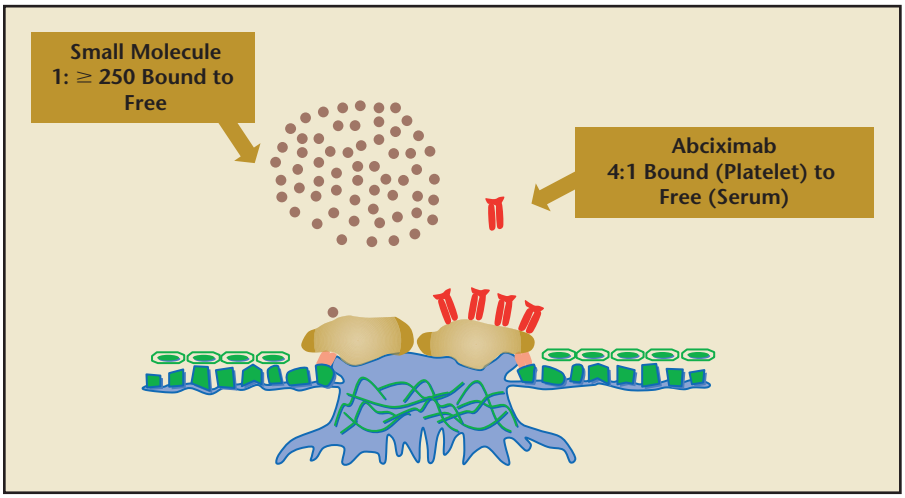
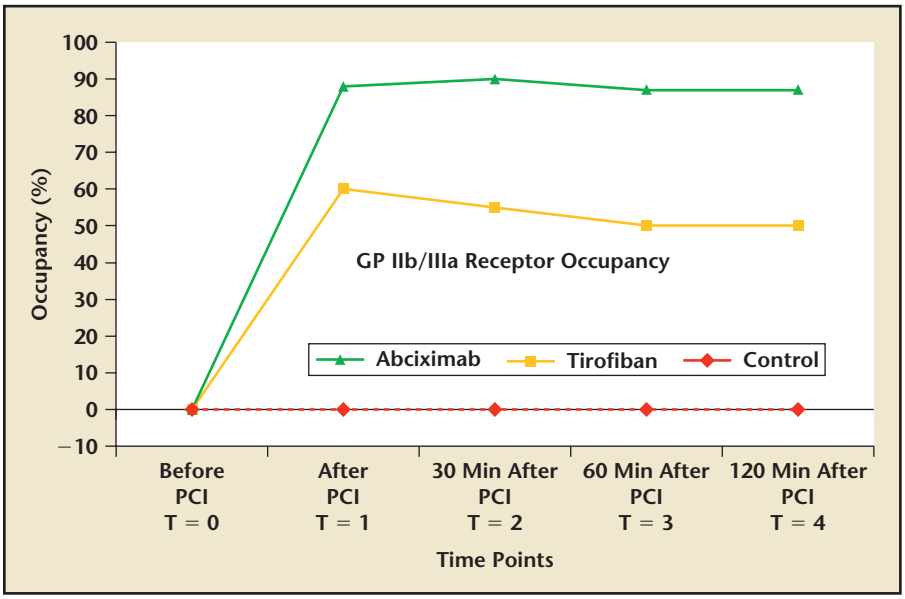


Figure 2. *Marked differences in the relative affinity for the platelet GP IIb/IIIa receptor and in the ratio of platelet-bound to free (in serum) drug between abciximab and small molecule GP IIb/IIIa inhibitors. For abciximab, 4 monoclonal antibodies are bound to platelet receptors for every 1 monoclonal antibody that is free in serum. Conversely, for small molecule GP IIb/IIIa inhibitors, only 1 molecule is bound to the platelet receptor for every 250 to 500 molecules free in serum. GP, glycoprotein. Reprinted with permission from Kereiakes DJ.*[30] www.medreviews.com

bolus, 0.15 μg/kg/min infusion) administered to patients undergoing primary PCI for STEMI. Using a dual monoclonal antibody technique to measure specific platelet receptor occupancy, abciximab was demonstrated to provide a greater degree of receptor blockade (occupancy), which remained at or greater than 80% during the periprocedural timeframe (Figure 3). In addition, the lesser affinity of the small molecule inhibitors for the GP IIb/IIIa receptor is reflected by the observation that competitive receptor binding by high levels of serum fibrinogen is associated with a reduced level of measured platelet inhibition by eptifibatide.[32] Higher levels (≥ 80%) of platelet GP IIb/IIIa receptor occupancy during GP IIb/IIIa inhibitor therapy have been correlated to a greater extent of successful myocardial reperfusion during the treatment of STEMI.[33] Indeed, "complete" reperfusion (as reflected by the concomitant presence of TIMI flow grade 3, TIMI myocardial perfusion grade 3, and electrocardiographic ST-segment resolution ≥ 70%) was more prevalent in patients who achieved at least 80% GP IIb/IIIa receptor occupancy than in those who did not.

The differential pharmacokinetic off rates (Kd) of currently available GP IIb/IIIa inhibitors affect recovery of platelet aggregability following discontinuation of therapy. Recovery of platelet aggregability is much more rapid (4-8 hours) following discontinuation of the small molecule GP IIb/IIIa inhibitors than following abciximab.[4] Recovery of aggregability after discontinuation of abciximab is at or less than 50% complete at 24 hours. The gradual "redistribution" of abciximab across GP IIb/IIIa receptors reflects high-affinity, reversible binding of this agent, with receptor occupancy rates of 30% at 8 days and 10% at 15 days following a single abciximab IV bolus.[34] These specific pharmacokinetic and pharmacodynamic properties of abciximab are likely responsible for the observation of Dangas and colleagues[35] from the Controlled Abciximab and Device Investigation

Figure 3. *Platelet GP IIb/IIIa receptor occupancy measured by a dual-monoclonal antibody technique in a randomized comparative trial of abciximab versus high-dose (25 μg/kg bolus, 0.15 μg/kg/min infusion) tirofiban during primary percutaneous coronary intervention for STEMI. The higher level of platelet receptor occupancy demonstrated for abciximab likely reflects a greater affinity for the GP IIb/IIIa receptor as well as a lower coefficient for dissociation (Kd). GP, glycoprotein; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention. Reprinted from* Journal of the American College of Cardiology, *Volume 43, van Werkum JW et al. Investigating platelet activation with abciximab and high-dose tirofiban in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. Page 99A.*[31] *Copyright © 2004, with permission from the American College of Cardiology.* www.medreviews.com



to Lower Late Angioplasty Complications (CADILLAC) trial. In CADILLAC, all patients who received coronary stent deployment during primary PCI for STEMI were administered an oral clopidogrel loading dose (300 mg) by protocol and were randomly assigned to receive either IV abciximab or placebo. Only those stented patients who received abciximab therapy (by both intention-to-treat as well as treatment-received analyses) demonstrated absence of early stent thrombosis.[34]

HORIZONS-AMI

The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial randomly assigned 3602 patients who presented with STEMI to receive either bivalirudin therapy with provisional GP IIb/IIIa administered only for prespecified "bailout" scenarios or UFH plus GP IIb/IIIa receptor blockade prior to primary PCI.[36] All patients received concomitant therapy with aspirin (300-325 mg/d in hospital; 75-81 mg post discharge) and clopidogrel (300-600 mg load; 75 mg/d). The trial primary endpoint of major adverse cardiovascular events ([MACE]; composite occurrence of all-cause death, reinfarction, ischemic target vessel revascularization, or stroke) was assessed at 30 days following treatment. Although the occurrence of MACE was similar between treatments, major bleeding events (TIMI criteria) were observed less frequently following bivalirudin therapy (4.9% vs 8.3%; $P \leq .0001$ with UFH/GP IIb/IIIa), which resulted in greater net clinical benefit for bivalirudin-treated patients.

However, careful analysis of the Kaplan-Meier event curves demonstrates early "hazard" in bivalirudin-treated patients for both MACE and

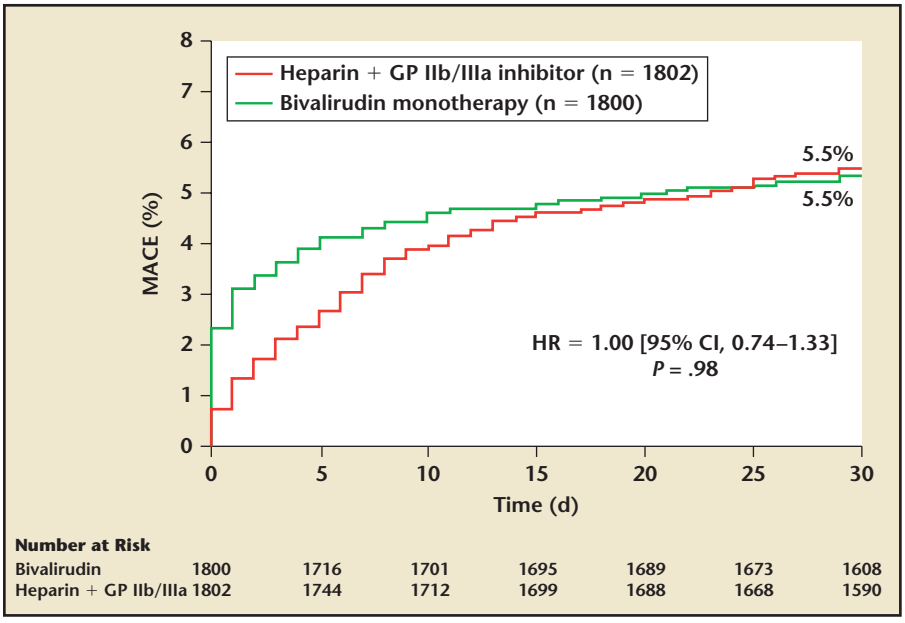
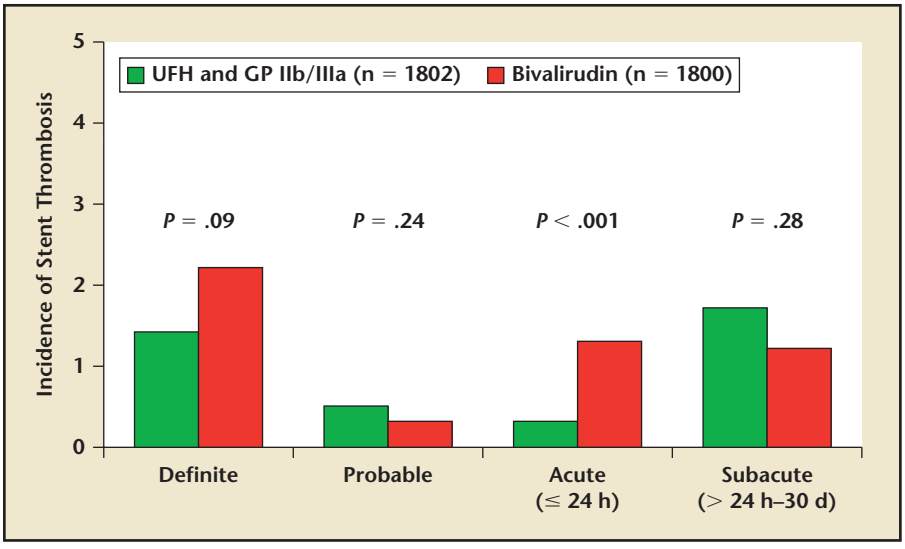


Figure 4. *MACE over time stratified by randomly assigned pharmacologic treatment regimens in the HORIZONS-AMI trial. Although the MACE event rate at 30 days was similar between treatments, early hazard for MACE is observed in the patients treated with bivalirudin monotherapy. MACE, major adverse cardiovascular events; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; GP, glycoprotein; HR, hazard ratio; CI, confidence interval. Adapted with permission from Stone GW et al. Bivalirudin during primary PCI in acute myocardial infarction.* N Engl J Med. *2008;358:2218-2230.*[36] *Copyright © 2008 Massachusetts Medical Society. All rights reserved.* www.medreviews.com

mortality (Figure 4). The early hazard following bivalirudin monotherapy is largely explained by a highly significant, more than 4-fold increase in the incidence of acute (≤ 24 hours) stent thrombosis using the Academic Research Consortium (ARC) definition (Figure 5). A similar

Figure 5. *The incidence of stent thrombosis to 30 days (Academic Research Consortium definitions) stratified by randomly assigned pharmacologic treatment as well as the time course for occurrence. A more than 4-fold increase in the incidence of acute (≤ 24 hours) stent thrombosis is observed in patients treated with bivalirudin monotherapy. UFH, unfractionated heparin; GP, glycoprotein. Data from Stone GW et al.*[36] www.medreviews.com



hazard for early stent thrombosis following bivalirudin monotherapy (in conjunction with aspirin and clopidogrel) has been reported from a "real world" registry of primary PCI for STEMI.[37] Early stent thrombosis following bivalirudin therapy occurs despite its putative effects on platelet function (inhibition of thrombin-induced platelet activation) and may in part be explained by wide interindividual variability in platelet inhibitory response to clopidogrel therapy.[38] Indeed, hyporesponsiveness or "resistance" to clopidogrel has been observed in approximately 1 in 4 individuals (range, 5% to 44%) undergoing elective PCI.[38,39] The time course and magnitude of platelet inhibition as well as the prevalence of resistance are altered by an increase in the oral clopidogrel loading dose from 300 mg to 600 mg.[40,41] A higher level of platelet inhibition is achieved more rapidly and resistance is less frequent (~8% vs ~28%, respectively) following the 600-mg loading dose compared with the 300-mg loading dose. Nevertheless, even following the 600-mg oral loading dose, more than 4 hours is required to achieve maximum platelet inhibitory effect, and the degree of interindividual variability remains wide (20%-80% residual platelet aggregation in response to 5 μM adenosine diphosphate).[42]

Strategies to Enhance Periprocedural Platelet Inhibition

Enhanced periprocedural platelet inhibition in bivalirudin-treated patients undergoing PCI may be achieved by concomitant GP IIb/IIIa receptor blockade, more effective $P2Y_{12}$ receptor inhibition, and/or the addition of a novel thrombin receptor antagonist. Safety in regard to minimization of bleeding events will be central to achieving net clinical benefit from any strategy aimed toward enhanced platelet inhibition and stent thrombosis reduction. The specific pharmacokinetic and pharmacodynamic properties of abciximab make it uniquely suited among available GP IIb/IIIa blocking agents for bolus-only administration. Furthermore, the route of abciximab bolus administration appears to influence the magnitude of relative benefit achieved. In a randomized, controlled clinical trial, a standard weight-adjusted bolus (0.25 mg/kg) of abciximab was administered either via an intracoronary (IC) dose over 1 to 2 minutes or via an IV dose to patients undergoing primary PCI for STEMI and was followed by the standard 12-hour infusion (0.125 μg/kg/min).[43] All patients received concomitant periprocedural UFH. Targeted intracoronary administration of the abciximab bolus dose was associated with a reduction in both infarct size and the occurrence of adverse clinical events.[43] Prior studies have suggested that the relative benefit of IC versus IV abciximab bolus administration is greatest in those patients with diminished TIMI flow grades 0 to 1 on baseline pre-PCI angiography or in patients with cardiogenic shock and poor coronary perfusion.[44] The hypothesized mechanistic basis for IC administration of GP IIb/IIIa inhibitors is that high local concentrations of drug are associated with increased levels of targeted platelet receptor occupancy (fewer receptors are available for crosslinking with fibrinogen) and more effective platelet thrombus dissaggregation.[45] Greater GP IIb/IIIa receptor blockade would, in turn, reduce the incidence of microcirculatory thrombus, enhance myocardial perfusion, and, ultimately, improve clinical outcomes. Furthermore, the durability of abciximab receptor occupancy as reflected by the gradual recovery of platelet aggregability provides a smooth transition for oral clopidogrel-mediated platelet inhibition to become effective.

Novel $P2Y_{12}$ receptor antagonists promise to provide more rapid, more intense, and more uniform platelet inhibition than is observed following clopidogrel therapy. Prasugrel, a novel "third-generation" orally administered thienopyridine, exhibits more rapid metabolic conversion to active metabolite as well as more rapid and intense platelet inhibition when compared with clopidogrel administered as either a 300-mg or 600-mg loading dose.[46,47] In addition, patients who are "resistant" to clopidogrel are almost invariably responsive to prasugrel.[48,49] In the pivotal Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38 (TRITON- TIMI 38) trial, 13,608 patients with ACS in whom PCI was planned were randomly assigned to therapy with either clopidogrel (300-mg load, 75 mg/d) or prasugrel (60-mg load, 10 mg/d).[50] Prasugrel therapy was associated with a significant reduction in the primary efficacy endpoint of the trial (composite occurrence of cardiovascular death, nonfatal myocardial infarction, or stroke) compared with clopidogrel (9.9% vs 12.1%, respectively; $P < .001$). Furthermore, a 52% reduction in ARC-defined definite/probable stent thrombosis was observed in favor of prasugrel for the trial as a whole. Subgroup analysis of the 3532 patients who presented with STEMI and subsequently underwent either primary (n = 2438, 69%) or secondary (n = 1094, 31%) PCI demonstrated a 51% relative risk reduction in early (30-day) ARC definite/probable stent thrombosis in favor of prasugrel (Figure 6A). No difference in TIMI major or minor noncoronary bypass graft surgery–related

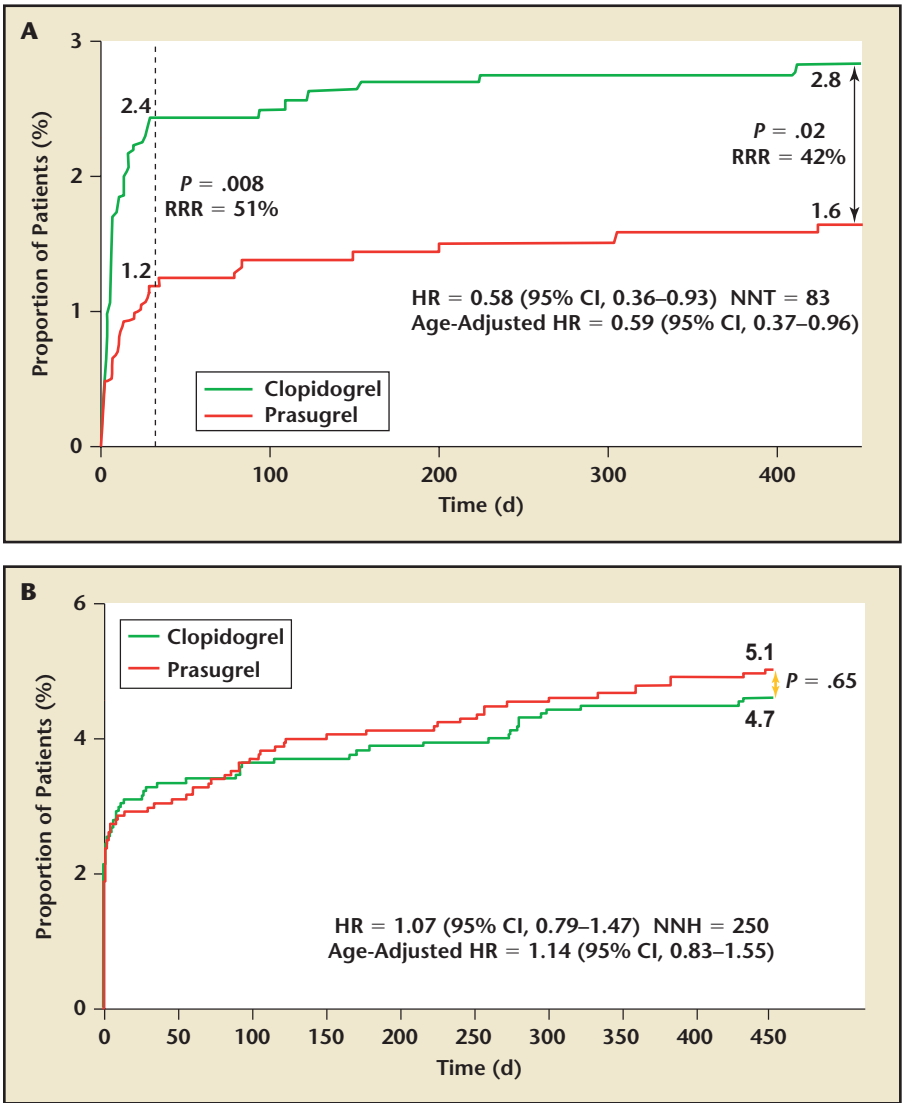


Figure 6. (A) *Incidence of stent thrombosis (Academic Research Consortium definite or probable definitions) through 1 year by randomly assigned pharmacologic treatment regimen in patients who had primary or secondary PCI for STEMI in the TRITON-TIMI 38 trial. Oral prasugrel therapy was associated with a highly significant 51% reduction in early stent thrombosis when compared with clopidogrel.* **(B)** *The incidence of TIMI major or minor noncoronary bypass-related bleeding events through 1 year by randomly assigned pharmacologic treatment regimen in patients who had primary or secondary PCI for STEMI in TRITON-TIMI 38. No difference is observed in bleeding event rates between treatments despite the demonstrated reduction in stent thrombosis in favor of prasugrel. PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TRITON-TIMI, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction; RRR, relative risk reduction; HR, hazard ratio; CI, confidence interval; NNT, number needed to treat; NNH, number needed to harm. Reprinted from* The Lancet, *Volume 373, Montalescot G et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomized controlled trial. Pages 723-731.*[51] *Copyright © 2009, with permission from Elsevier.* www.medreviews.com

bleeding was observed between treatment regimens[51] (Figure 6B). Thus, prasugrel appears to represent an especially attractive alternative to clopidogrel for PCI in STEMI.

Cangrelor (The Medicines Company®, Parsippany, NJ) is a novel, parenterally administered adenosine 5'-triphosphate derivative (nonthienopyridine) that provides reversible blockade of the $P2Y_{12}$ receptor.[52,53] Following IV infusion, rapid, steady-state pharmacokinetics are achieved and are associated with a high level (≥ 90%) of $P2Y_{12}$ receptor inhibition and little interindividual variability. One challenge to the administration of Cangrelor for primary PCI in STEMI will be the ability to safely and effectively transition this agent with an oral $P2Y_{12}$ receptor inhibitor. Preliminary data demonstrate a competitive effect by Cangrelor on platelet inhibition by both clopidogrel and prasugrel.[54,55] The presence of Cangrelor on the $P2Y_{12}$ receptor precludes access by clopidogrel and prasugrel active metabolites, which are only transiently available following metabolic aversion. Thus, Cangrelor presence may effectively block the platelet inhibitory effect of a clopidogrel oral loading dose (Figure 7).

Finally, platelet thrombin receptor antagonists, such as SCH 530348, are currently in clinical development for administration during PCI and ACS. To date, this agent has been administered concomitantly with aspirin and clopidogrel and compared with aspirin and clopidogrel alone.[56,57]

Summary

The HORIZONS-AMI trial has provided a valuable step forward in the evolution of adjunctive pharmacotherapy for primary PCI in STEMI. In HORIZONS, the administration of bivalirudin monotherapy was associated with a marked reduction in the incidence of major bleeding, enhanced net clinical benefit, and a survival advantage to both 30 days and at 1 year follow-up.[36,58] Nevertheless, an early hazard for stent thrombosis was evident following bivalirudin monotherapy, which presents an opportunity for further

pharmacotherapeutic iteration to provide even greater clinical benefit. In this regard, it is likely that enhanced periprocedural and postprocedural platelet inhibition with IC abciximab bolus only and/or orally administered prasugrel will reduce the incidence of stent thrombosis associated with bivalirudin and clopidogrel (300-mg to 600-mg load) therapy as administered in the HORIZONS trial. Furthermore, the relative inadequacy of the bivalirudin antiplatelet effect in the context of clopidogrel response variability and limited potency is underscored by an analysis of stent thrombosis stratified by a nonrandomly assigned (investigator discretion) clopidogrel loading dose (Gregg W. Stone, MD, personal communication).

Stent thrombosis was observed less frequently in those patients who received the 600-mg oral loading dose of clopidogrel (~63% of study population) as compared with the 300-mg oral loading dose of clopidogrel (~35% of study population) in the HORIZONS trial. This nonrandomized observation argues in favor of the higher loading dose of clopidogrel when administered in conjunction with bivalirudin for primary PCI. The adjunctive pharmacotherapeutic strategy utilizing currently available agents that my colleagues and I have adopted includes IV bivalirudin bolus and infusion, IC abciximab weight-adjusted bolus only administered immediately following coronary guidewire recanalization of the infarct-related artery, oral aspirin (nonenteric) at a dose of 325 mg chewed on initial presentation, and clopidogrel at a dose of 600 mg administered orally at the time of PCI. Bivalirudin IV infusion is discontinued at the end of the PCI procedure, and vascular access sheaths are removed 2 hours later. The goal

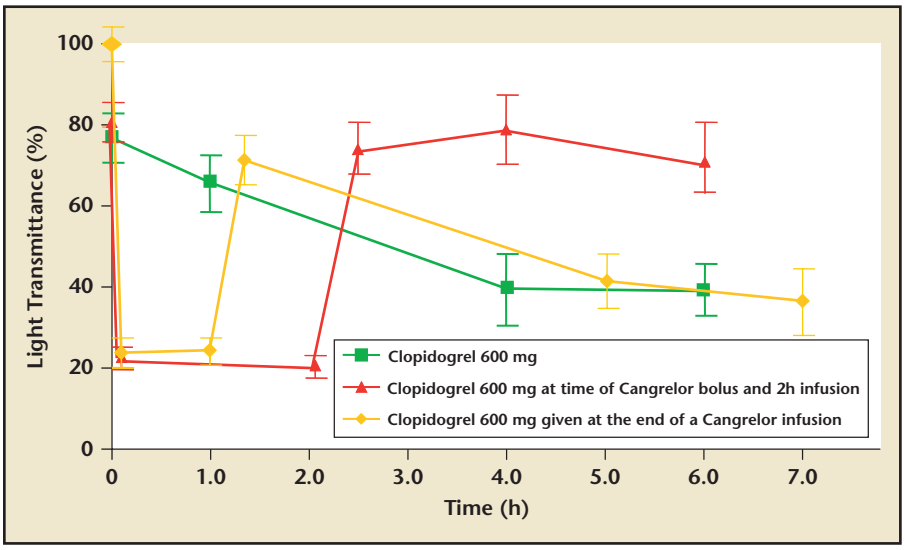
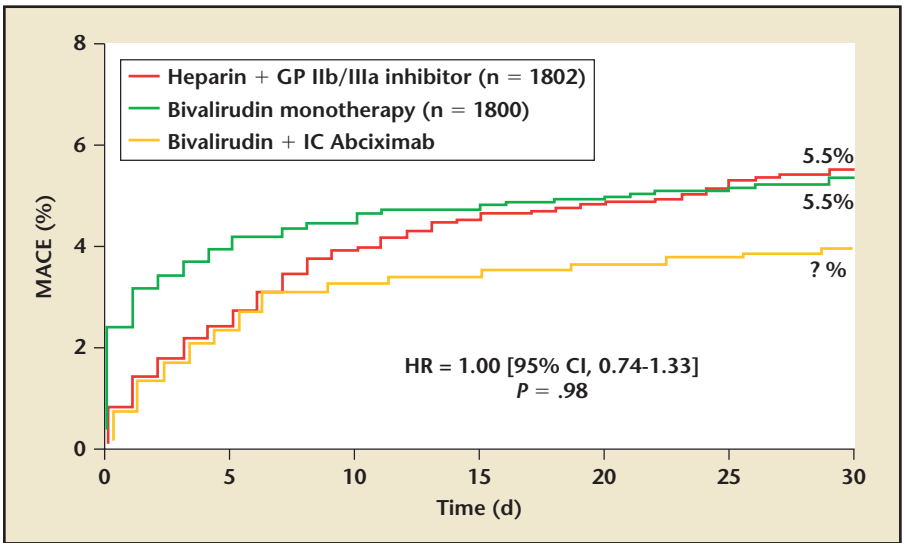


Figure 7. *Platelet aggregation over time following an oral 600-mg loading dose of clopidogrel administered alone or in varying time sequence to an intravenous bolus and infusion of Cangrelor. The platelet inhibitory effect of the clopidogrel active metabolite is either not apparent (when administered at the time of the Cangrelor bolus and 2-hour infusion) or is delayed (when administered at the end of the Cangrelor infusion). The presence of Cangrelor on the platelet $P2Y_{12}$ receptor precludes access for the transiently available clopidogrel active metabolite following metabolic conversion of the clopidogrel prodrug. Reprinted from* Thrombosis Research, *Volume 121, Steinhubl SR et al. Transitioning patients from cangrelor to clopidogrel: pharmacodynamic evidence of a competitive effect. Pages 527-534.*[54] *Copyright © 2008, with permission from Elsevier.* www.medreviews.com

Figure 8. *A hypothetical MACE rate over time for bivalirudin and abciximab intracoronary bolus pharmacologic regimen during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction is superimposed on the event rates observed following either unfractionated heparin and GP IIb/IIIa inhibitor or bivalirudin monotherapy in the HORIZONS-AMI trial. The combination of bivalirudin plus abciximab intracoronary bolus provides the potential to reduce the acute stent thrombosis observed in the bivalirudin monotherapy cohort as well as subacute stent thrombosis, which may have been associated with shorter duration (12-18 hours) eptifibatide infusion administered in the unfractionated heparin and GP IIb/IIIa cohort. MACE, major adverse cardiovascular event; GP, glycoprotein; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; CV, cardiovascular; IC, intracoronary; HR, hazard ratio; CI, confidence interval. Adapted with permission from Stone GW et al. Bivalirudin during primary PCI in acute myocardial infarction.* N Engl J Med. *2008;358:2218-2230.*[36] *Copyright © 2008 Massachusetts Medical Society. All rights reserved.* www.medreviews.com



of this strategy is to reduce the incidence of acute stent thrombosis associated with bivalirudin monotherapy (Figure 8). In addition, this strategy could reduce the incidence of subacute stent thrombosis that may have accompanied the use of shorter duration (12-18 hours by protocol) eptifibatide infusions, which comprised 44.4% of the UFH plus GP IIb/IIIa treatment arm of the HORIZONS trial. Indeed, a prior analysis of the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial demonstrated that eptifibatide infusion durations of less than 16 hours conferred little, if any, clinical benefit in a stable, elective PCI population.[59] Future clinical trials that incorporate abciximab IC bolus only and/or prasugrel in conjunction with IV bivalirudin are required to establish the safety, efficacy, and, it is hoped, incremental net clinical benefit of these strategies when compared with the bivalirudin monotherapy treatment algorithm used in the HORIZONS AMI trial. ■

Acknowledgment: Dr. Kereiakes has received grant and/or research support from Abbott/Bioabsorbable Vascular Solutions, Amylin Pharmaceuticals, Biologics Delivery Systems Group, Cordis/Johnson & Johnson, Boston Scientific, Medtronic, and Daiichi Sankyo. Dr. Kereiakes has received consulting fees from Devax, Eli Lilly and Company, Boston Scientific, Abbott Vascular Solutions, Medpace, Cordis/Johnson & Johnson, and REVA Medical.

References

1. Wilentz JR, Sanborn TA, Haudenschild C, et al. Platelet accumulation in experimental angioplasty: time course in relation to vascular injury. *Circulation*. 1987;75:636-642.
2. Ruggeri ZM. Platelets in atherothrombosis. *Nat Med*. 2002;8:1227-1234.
3. Gurbel PA, Bliden KP, Hayes KM, Tantry U. Platelet activation in myocardial ischemic syndromes. *Expert Rev Cardiovasc Ther*. 2004;2:535-545.
4. Mousa SA, Bennett JS. Platelets in health and disease: platelet GP IIb/IIIa structure and function: recent advances in antiplatelet therapy. *Drugs Future*. 1996;21:1141-1154.
5. Chakhtoura EY, Shamoon FE, Haft JI, et al. Comparison of platelet activation in unstable and stable angina pectoris and correlation with coronary angiographic findings. *Am J Cardiol*. 2000;86:835-839.
6. Andre P, Nannizzi-Alaimo L, Prasad SK, Phillips DR. Platelet-derived CD40L: the switch-hitting player of cardiovascular disease. *Circulation*. 2002;106:896-899.
7. Williams MS, Bush DE. Platelet hyperreactivity is present in acute coronary syndromes despite treatment with aspirin [abstract]. *Circulation*. 2003;108:IV-378.
8. Soffer D, Moussa I, Karatepe M, et al. Suboptimal inhibition of platelet aggregation following tirofiban bolus in patients undergoing percutaneous coronary intervention for unstable angina pectoris. *Am J Cardiol*. 2003;91:872-875.
9. Ault KA, Cannon CP, Mitchell J, et al. Platelet activation in patients after an acute coronary syndrome: results from the TIMI-12 trial. Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol*. 1999;33:634-639.
10. Pizzulli L, Yang A, Martin JF, Luderitz B. Changes in platelet size and count in unstable angina compared to stable angina or noncardiac chest pain. *Eur Heart J*. 1998;19:80-84.
11. Guthikonda S, Alviar CL, Vaduganathan M, et al. Role of reticulated platelets and platelet size heterogeneity on platelet activity after dual antiplatelet therapy with aspirin and clopidogrel in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2008;52:743-749.
12. Kabbani SS, Watkins MW, Ashikaga T, et al. Usefulness of platelet reactivity before percutaneous coronary intervention in determining cardiac risk one year later. *Am J Cardiol*. 2003;91:876-878.
13. Goncalves SC, Labinaz M, LeMay M, et al. Impact of mean platelet volume on clinical outcomes after percutaneous coronary intervention [abstract]. *Am J Cardiol*. 2008;102:23i.
14. Campo G, Valgimigli M, Gemmati D, et al. Value of platelet reactivity in predicting response to treatment and clinical outcome in patients undergoing primary coronary intervention: insights into the STRATEGY study. *J Am Coll Cardiol*. 2006;48:2178-2185.
15. Huczek Z, Kochman J, Filipiak KJ, et al. Mean platelet volume on admission predicts impaired reperfusion and long-term mortality in acute myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol*. 2005;46:284-290.
16. Miyamoto S, Kawano H, Kudoh T, et al. Usefulness of preprocedural platelet aggregation to predict restenosis after percutaneous coronary intervention. *Am J Cardiol*. 2005;96:71-73.
17. Giugliano RP, Braunwald E. The year in non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:906-919.
18. Dalby M, Montalescot G, Bal dit Sollier C, et al. Eptifibatide provides additional platelet inhibition in non-ST-elevation myocardial infarction patients already treated with aspirin and

Main Points

- In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial of patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, the administration of bivalirudin monotherapy was associated with a marked reduction in the incidence of major bleeding, enhanced net clinical benefit, and a survival advantage to both 30 days and at 1-year follow-up.
- The HORIZONS-AMI trial showed an early hazard for stent thrombosis following bivalirudin monotherapy.
- Stent thrombosis was observed less frequently in those patients who received the 600-mg oral loading dose of clopidogrel (~63% of study population) as compared with the 300-mg oral loading dose of clopidogrel (~35% of study population).
- It is likely that enhanced periprocedural and postprocedural platelet inhibition with an intracoronary abciximab bolus only and/or orally administered prasugrel will reduce the incidence of stent thrombosis associated with bivalirudin and clopidogrel.
- Safety in regard to minimization of bleeding events will be central to achieving net clinical benefit from any strategy aimed toward enhanced platelet inhibition and stent thrombosis reduction.

clopidogrel. Results of the platelet activity extinction in non-Q-wave myocardial infarction with aspirin, clopidogrel, and eptifibatide (PEACE) study. *J Am Coll Cardiol*. 2004;43: 162-168.
19. Kleiman NS, Grazeiadei N, Maresh K, et al. Abciximab, ticlopidine, and concomitant abciximab-ticlopidine therapy: ex vivo platelet aggregation inhibition profiles in patients undergoing percutaneous coronary interventions. *Am Heart J*. 2000;140:492-501.
20. Sabatine MS, Hamdalla HN, Mehta SR, et al. Efficacy and safety of clopidogrel pretreatment before percutaneous coronary intervention with and without glycoprotein IIb/IIIa inhibitor use. *Am Heart J*. 2008;155:910-917.
21. Chan AW, Moliterno DJ, Berger PB, et al. Triple antiplatelet therapy during percutaneous coronary intervention is associated with improved outcomes including one-year survival: results from the Do Tirofiban and ReoPro Give Similar Efficacy Outcome Trial (TARGET). *J Am Coll Cardiol*. 2003;42:1188-1195.
22. Gurbel PA, Bliden KP, Zaman KA, et al. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets: results of the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. *Circulation*. 2005;111:1153-1159.
23. Gurbel PA, Bliden KP, Tantry US. Effect of clopidogrel with and without eptifibatide on tumor necrosis factor-alpha and C-reactive protein release after elective stenting: results from the CLEAR PLATELETS 1b study. *J Am Coll Cardiol*. 2006;48:2186-2191.
24. Bonz AW, Lengenfelder B, Strotmann J, et al. Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary intervention after pretreatment with aspirin and clopidogrel (TOPSTAR trial). *J Am Coll Cardiol*. 2002;40: 662-668.
25. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA*. 2006; 295:1531-1538.
26. Marciniak SJ Jr, Mascelli MA, Furman MI, et al. An additional mechanism of action of abciximab: dispersal of newly formed platelet aggregates. *Thromb Haemost*. 2002;87:1020-1025.
27. Goto S, Tamura N, Ishida H. Ability of antiglycoprotein IIb/IIIa agents to dissolve platelet thrombi formed on a collagen surface under blood flow conditions. *J Am Coll Cardiol*. 2004; 44:316-323.
28. Quinn M, Deering A, Stewart M, et al. Quantifying GP IIb/IIIa receptor binding using 2 monoclonal antibodies. *Circulation*. 1999;99: 2231-2238.
29. Scarborough RM, Kleiman NS, Phillips DR. Platelet glycoproteins IIb/IIIa antagonists: what are the relevant issues concerning their pharmacology and clinical use? *Circulation*. 1999; 100:437-444.
30. Kereiakes DJ. Effects of GP IIb/IIIa inhibitors on vascular inflammation, coronary microcirculation, and platelet function. *Rev Cardiovasc Med*. 2006;7(suppl 4):S3-S11.
31. van Werkum JW, Gerritsen WBM, Felder HC, et al. Investigating platelet activation with abciximab and high-dose tirofiban in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention [abstract]. *J Am Coll Cardiol*. 2004;43:99A.
32. Mahmud E, Cavendish JJ, Tsmikas S, et al. Elevated plasma fibrinogen level predicts suboptimal response to therapy with both single- and double-bolus eptifibatide during percutaneous coronary intervention. *J Am Coll Cardiol*. 2007;49:2163-2171.
33. Gibson CM, Jennings LK, Murphy SA, et al. Association between platelet receptor occupancy after eptifibatide (integrilin) therapy and patency, myocardial perfusion, and ST-segment resolution among patients with ST-segment-elevation myocardial infarction: an INTEGRITI (Integrilin and Tenecteplase in Acute Myocardial Infarction) substudy. *Circulation*. 2004;110:679-684.
34. Mascelli MA, Lance ET, Damaraju L, et al. Pharmacodynamic profile of short-term abciximab treatment demonstrates prolonged platelet inhibition with gradual recovery from GB IIb/IIIa receptor blockade. *Circulation*. 1998;97: 1680-1688.
35. Dangas G, Aymong ED, Mehran R, et al. Predictors of and outcomes of early thrombosis following balloon angioplasty versus primary stenting in acute myocardial infarction and usefulness of abciximab (the CADILLAC trial). *Am J Cardiol*. 2004;94:983-988.
36. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358: 2218-2230.
37. Goswami N, Pfeiffer A, Moore A, Mishkel G. HORIZONS in the "real world": use of bivalirudin versus heparin + GP IIb/IIIa inhibitors in ST elevation myocardial infarction [abstract]. *Am J Cardiol*. 2008;102:49i.
38. Gurbel PA, Bliden KP, Hiatt BL, et al. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation*. 2003;107: 2908-2913.
39. Lau WC, Gurbel PA, Watkins PB, et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. *Circulation*. 2004;109:166-171.
40. Montalescot G, Sideris G, Meuleman C, et al. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol*. 2006;48:931-938.
41. Gurbel PA, Bliden KP, Hayes KM, et al. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. *J Am Coll Cardiol*. 2005;45: 1392-1396.
42. Hochholzer W, Trenk K, Frundi D, et al. Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation*. 2005;111: 2560-2564.
43. Thiele H, Schindler K, Friedenberger J, et al. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the randomized Leipzig immediate percutaneous coronary intervention abciximab IV versus IC in ST-elevation myocardial infarction trial. *Circulation*. 2008;118:49-57.
44. Wöhrle J, Grebe OC, Nusser T, et al. Reduction of major adverse cardiac events with intracoronary compared with intravenous bolus application of abciximab in patients with acute myocardial infarction or unstable angina undergoing coronary angioplasty. *Circulation*. 2003;107:1840-1843.
45. Gibson CM, Zorkun C, Kunadian V. Intracoronary administration of abciximab in ST-elevation myocardial infarction. *Circulation*. 2008;118:6-8.
46. Wallentin L, Varenhorst C, James S, et al. Prasugrel achieves greater and faster P2Y12 receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. *Eur Heart J*. 2008; 29:21-30.
47. Jakubowski JA, Matsushima N, Asai F, et al. A multiple dose study of prasugrel (CS-747), a novel thienopyridine P2Y12 inhibitor, compared with clopidogrel in healthy humans. *Br J Clin Pharmacol*. 2007;63:421-430.
48. Weerakkody GJ, Jakubowski JA, Brandt JT, et al. Greater inhibition of platelet aggregation and reduced response variability with prasugrel versus clopidogrel: an integrated analysis. *J Cardiovasc Pharmacol Ther*. 2007;12:205-212.
49. Brandt JT, Payne CD, Wiviott SD, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J*. 2007;153:e9-e16.
50. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007; 357:2001-2015.
51. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomized controlled trial. *Lancet*. 2009;373:723-731.
52. Storey RF, Wilcox RG, Heptinstall S. Comparison of the pharmacodynamic effects of the platelet ADP receptor antagonists clopidogrel and AR-C69931MX in patients with ischaemic heart disease. *Platelets*. 2002;13:407-413.
53. Greenbaum AB, Grines CL, Bittl JA, et al. Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: results from a 2-part, phase II, multicenter, randomized, placebo- and active-controlled trial. *Am Heart J*. 2006;151:689.e1-689.e10.
54. Steinhubl SR, Oh JJ, Oestreich JH, et al. Transitioning patients from cangrelor to clopidogrel: pharmacodynamic evidence of a competitive effect. *Thromb Res*. 2008;121:527-534.
55. Dovlatova NL, Jakubowski JA, Sugidachi A, Heptinstall S. The reversible P2Y antagonist

cangrelor influences the ability of the active metabolites of clopidogrel and prasugrel to produce irreversible inhibition of platelet function. *J Thromb Haemost*. 2008;6: 1153-1159.
56. Ahn HS, Chackalamannil S, Boykow G, et al. Development of proteinase-activated receptor 1 antagonists as therapeutic agents for thrombosis, restenosis, and inflammatory diseases. *Curr Pharm Des*. 2003;9:2349-2365.
57. Moliterno DJ, Jennings L, Becker RC, et al for the TRA*PCI Investigators. Results of a multinational randomized, double-blind, placebo-controlled study of a novel thrombin receptor antagonist SCH 530348 in percutaneous coronary intervention. Presented at: 56th Annual American College of Cardiology Scientific Sessions; March 24, 2007; New Orleans, LA.
58. Stone GW. Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. Paper presented at: 20th Annual Transcatheter Cardiovascular Therapeutics Symposium; October 15, 2008; Washington, DC.
59. Rebeiz AG, Pieper KS, O'Shea JC, et al. 16- to 18-hour infusions of eptifibatide seem optimal in reducing ischemic complications following percutaneous coronary intervention [abstract]. *Circulation*. 2001;104: II-386.