Platelet Activation and Progression to Complications

Dean J. Kereiakes, MD, FACC,* Alan D. Michelson, MD†

*The Heart Center of Greater Cincinnati and The Lindner Center at The Christ Hospital, Cincinnati, OH; †Center for Platelet Function Studies, Departments of Pediatrics, Medicine and Pathology, University of Massachusetts Medical School, Worcester, MA

Platelets localize, amplify, and sustain the coagulant response at an injury site and release procoagulant platelet-derived microparticles. Abnormalities in platelet size and function may be present in acute coronary syndromes and following percutaneous coronary intervention (PCI). Platelet functional assessment prior to PCI is a predictor for the subsequent occurrence of adverse clinical events. Trials of glycoprotein IIb-IIIa inhibitors as adjunctive pharmacotherapy for PCI show that the magnitude of platelet inhibition achieved by therapy correlates with the degree of clinical benefit observed. In general, optimal periprocedural outcomes require high levels of platelet inhibition. Combined administration of antiplatelet therapies may produce additive or synergistic inhibition of platelet-mediated thrombosis.

[Rev Cardiovasc Med. *2006;7(2):75-81*]

Key words: Platelet activation • Glycoprotein IIb-IIIa inhibitors • Acute coronary syndromes • Percutaneous coronary intervention • Platelet inhibitor therapy

Release date: June 2006
Expiration date: June 30, 2007
Estimated time to complete activity: 1.0 hours

PIM Postgraduate Institute for Medicine

Sponsored by Postgraduate Institute for Medicine.

Daiichi-Sankyo

Lilly

This activity is supported by an educational grant from Daiichi-Sankyo/Eli Lilly.

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and MedReviews, LLC. PIM is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation
Postgraduate Institute for Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Formation of the hemostatic plug at sites of vascular injury begins with the arrest of circulating platelets on exposed collagen and continues with the recruitment of additional platelets into a growing platelet mass that will eventually be stabilized with cross-linked fibrin.[1] Formation of a platelet plug can be thought of as occurring in 3 phases: initiation, extension, and perpetuation (Figure 1). Initiation occurs when circulating platelets arrest and are activated by exposed collagen and von Willebrand factor (VWF), allowing the

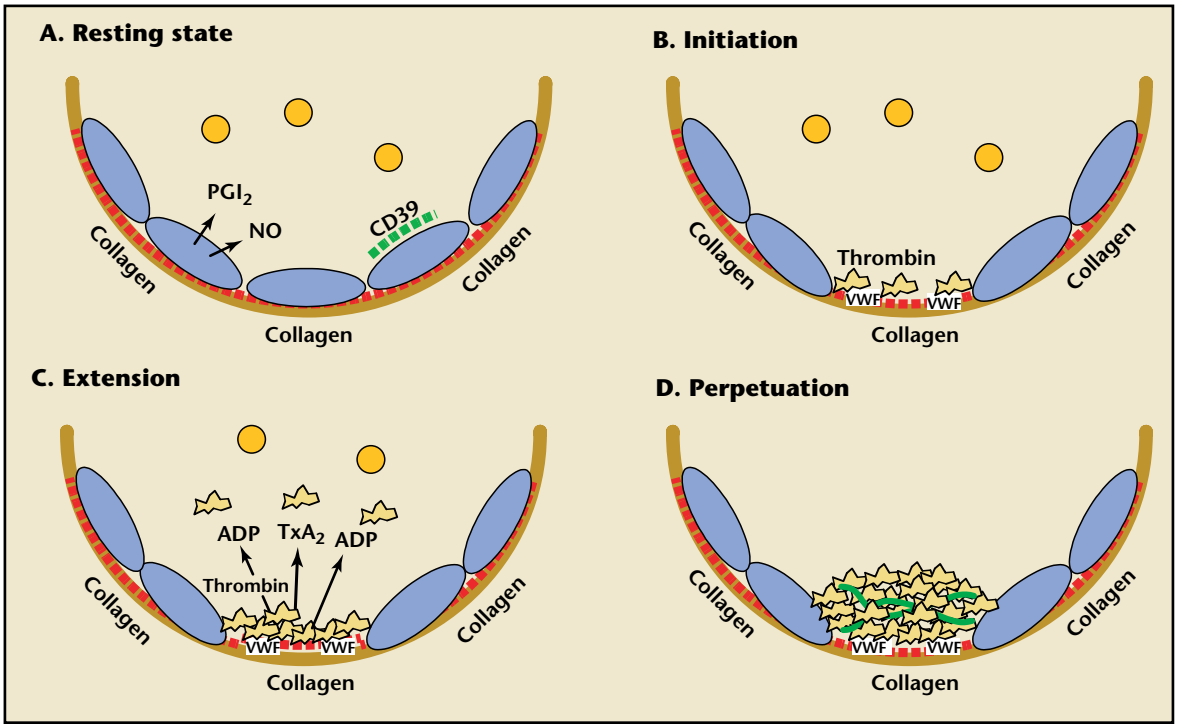

Figure 1. *Steps in platelet plug formation.* **(A)** *Prior to vascular injury, platelets are maintained in the resting state by a combination of inhibitory factors that place a "threshold" that must be surmounted in order for platelets to be activated. These factors include prostaglandin (PG) I_2 and nitric oxide (NO) released from endothelial cells, and CD39, an ADPase on the surface of endothelial cells that hydrolyzes any small amounts of adenosine diphosphate (ADP) that might otherwise cause inappropriate platelet activation.* **(B)** *The development of the platelet plug is initiated by the exposure of collagen and the local generation of thrombin. This causes platelets to adhere via collagen and von Willebrand (VWF) factor and spread on the connective matrix, forming a monolayer.* **(C)** *The platelet plug is extended as additional platelets are activated via the release or secretion of thromboxane (Tx) A_2, ADP, and other platelet agonists, most of which are ligands for G protein–coupled receptors on the platelet surface.* **(D)** *Finally, close contacts between platelets in the growing hemostatic plug, along with a fibrin meshwork, help to perpetuate and stabilize the platelet aggregate. Reproduced with permission from Woulfe D, et al.*[1] www.medreviews.com

accumulation of a platelet monolayer that supports thrombin generation and the formation of platelet aggregates. Key to this phase of platelet activation is the presence of receptors on the platelet surface that can bind to collagen (integrin α2β1 and glycoprotein [GP] VI) and VWF (GPIb-IX-V and GPIIb-IIIa [integrin αIIbβ3]), initiating intracellular signaling.[1] Extension occurs when additional platelets accumulate on the initial monolayer, a process for which GPIIb-IIIa activation is certainly essential, but not necessarily sufficient. Key to this phase is the presence of receptors on the platelet surface that can respond rapidly to locally generated thrombin, secreted adenosine diphosphate (ADP), and released thromboxane A_2 to activate phospholipase C, increase the cytosolic Ca^{++} concentration, and suppress synthesis of cyclic adenosine monophosphate.[1] Perpetuation refers to the late events of platelet plug formation that stabilize the platelet plug and prevent premature disaggregation (Figure 1). Perpetuation is less well understood than initiation and extension, but recent studies point to a central role for outside-in signaling through cell-surface integrins and to the signals generated by receptor tyrosine kinases, including members of the Eph and Axl families.[1] Platelets localize, amplify, and sustain the coagulant response at the injury site and release procoagulant platelet-derived microparticles. Platelets contain a variety of inflammatory modulators (such as CD40 ligand [CD40L][2]), which are released upon platelet activation.

Platelet Size and Function

Abnormalities in platelet size and function may be present in acute coronary syndromes (ACSs) and following percutaneous coronary intervention (PCI). Both of these clinical scenarios are accompanied by plaque rupture (either spontaneous or iatrogenic), with denudation of the endothelium and exposure of subendothelial thrombogenic matrix proteins (VWF and collagen; see

Figure 1B), cholesterol clefts, etc. Similarly, both scenarios are associated with tissue factor production and thrombin generation (Figure 1), which provide additional potent stimuli for platelet activation and aggregation. Patients with ACS have increased platelet activation, as determined by increased platelet surface P-selectin (CD62P), platelet surface–activated GPIIb-IIIa, monocyte-platelet aggregates, and soluble CD40L.[3-7] The platelets of patients with ACS demonstrate an exaggerated response to low levels of agonist (eg, ADP, collagen)[3] and, therefore, a diminished response to standard doses of platelet-inhibitor therapies, such as clopidogrel and tirofiban.[8] These observations are consistent with an intrinsic state of platelet hyperactivation and aggregability. Platelet activation in ACS is protracted. For example, patients with ACS in the Thrombolysis in Myocardial Infarction (TIMI)-12 study demonstrated increased levels of platelet activation at 1-month follow-up.[9]

The platelets of patients with ACS demonstrate an exaggerated response to low levels of agonist (eg, ADP, collagen) and, therefore, a diminished response to standard doses of platelet-inhibitor therapies, such as clopidogrel and tirofiban.

Platelet functional assessment prior to PCI is a predictor for the subsequent occurrence of adverse clinical events.[10] For example, both platelet hyperactivity and platelet surface–activated GPIIb-IIIa are associated with stent thrombosis and/or post-PCI coronary occlusion.[11-13] Preprocedural platelet function has also been directly correlated with late angiographic restenosis and the requirement for target vessel revascularization (TVR).[14,15]

Mean platelet volume (MPV) correlates with the degree of platelet activation and is increased in proportion to the severity/acuity of the clinical syndrome.[16] MPV is greatest in the presence of unstable angina or ST-segment elevation myocardial infarction (STEMI), particularly following PCI with stent deployment.[16,17] In fact, MPV assessed prior to primary PCI for STEMI is directly correlated with the occurrence of post-procedural angiographic no-reflow and diminished epicardial coronary blood flow (ie, corrected TIMI frame count $\geq$ 40), as well as mortality in follow-up to 6 months.[17]

PCI is inherently thrombogenic and provokes both thrombin generation and platelet activation, despite the periprocedural administration of unfractionated heparin (UFH) and aspirin.[4,18] In fact, UFH directly activates platelets in a dose-dependent fashion and augments platelet responsiveness to low levels of agonists.[19] Furthermore, UFH is incapable of binding to either clot-bound thrombin (factor IIa) or factor Xa that has been incorporated into the platelet prothrombinase complex. These "bound" sources of further thrombin generation, in combination with UFH-mediated relative depletion in the anticoagulant cofactor antithrombin III, result in the occurrence of thrombin rebound and a hypercoagulable state following UFH administration.[20] The platelet activation that follows UFH administration can be eliminated by the concomitant administration of a GPIIb-IIIa inhibitor.[21]

Unfractionated heparin directly activates platelets in a dose-dependent fashion and augments platelet responsiveness to low levels of agonists.

Platelet Inhibitor Therapies

After more than a decade of experience with platelet inhibitor therapies for both ACS and PCI, several basic tenets have emerged. First, across multiple placebo-controlled, randomized clinical trials of GPIIb-IIIa inhibitors as adjunctive pharmacotherapy for PCI, the magnitude of platelet inhibition achieved by therapy correlates with the degree of clinical benefit observed (Figure 2). In general, the magnitude of reduction in the composite clinical endpoint of death and periprocedural myocardial infarction is inversely proportional to the degree of platelet inhibition achieved by the specific dose of the antiplatelet agent administered. This relationship is tempered by the frequency of major hemorrhagic events, which can negate the net clinical benefit of platelet inhibitor therapy. Therefore, in the absence of significant bleeding events, the relationship between platelet inhibition and clinical outcomes has been a basic therapeutic tenet that has contributed to the development of targeted levels for therapeutic platelet inhibition. For example, the increase in eptifibatide dose that was adopted for the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial,[22] when compared with the dose of eptifibatide used in the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT) trial,[23] was associated with a significantly greater magnitude and consistency (less interindividual variability) in platelet inhibition as well as further improvement in clinical outcomes. The reduction with

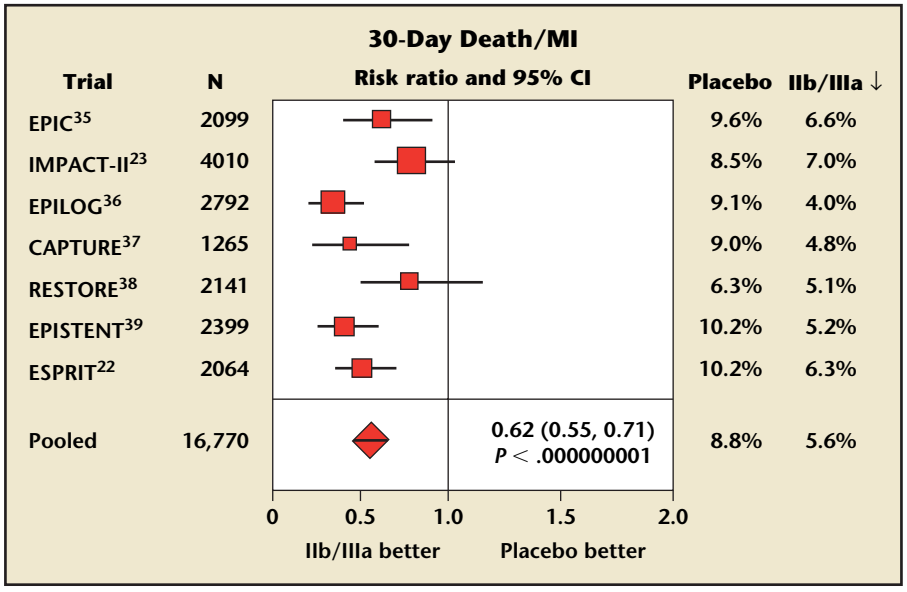

Figure 2. *Incidence of the composite clinical endpoint of death or myocardial infarction (MI) to 30 days in placebo-controlled randomized trials of glycoprotein (GP) IIb-IIIa inhibitor therapy during percutaneous coronary intervention. The Evaluation of 7E3 for the Prevention of Ischaemic Complications (EPIC), Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIa Receptor Blockade (EPILOG), Chimeric 7E3 Antiplatelet Therapy in Unstable Angina REfractory to Standard Treatment (CAPTURE), and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trials administered abciximab, the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) and Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trials administered eptifibatide, and the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial administered tirofiban. In general, the incidence of death or MI was inversely proportional to the magnitude of platelet inhibition achieved. Platelet inhibition was least in the IMPACT-II and RESTORE trials, which demonstrated the least relative benefit of GPIIb-IIIa inhibition versus placebo. Similarly, the increased dose of eptifibatide administered in the ESPRIT trial (compared with the IMPACT-II trial) was associated with greater platelet inhibition as well as greater clinical benefit.* www.medreviews.com

eptifibatide compared with placebo in the composite occurrence of death, myocardial infarction, and urgent TVR to 30 days post-PCI was 35.3% in ESPRIT versus 16.7% in IMPACT (combined dosing regimens).[22,23] In addition, in the AU-Assessing Ultegra (GOLD) trial, periprocedural platelet inhibition was measured and correlated with clinical outcomes following GPIIb-IIIa inhibitor therapy.[24] The 2 time points and measured levels of platelet inhibition that best correlated with a lower incidence of major adverse cardiovascular events were at 10 minutes ($\geq$ 95% vs $<$ 95% inhibition) and at 8 hours ($>$ 70% versus $<$ 70% inhibition) following initiation of GPIIb-IIIa inhibitor therapy.[24] Finally, in a randomized controlled trial of periprocedural abciximab versus tirofiban following elective coronary stent deployment (Do Tirofiban And ReoPro Give Similar Efficacy Trial [TARGET]), tirofiban was demonstrated to be inferior to abciximab for preventing the composite occurrence of death, myocardial infarction, or urgent TVR to 30 days.[25] The relative ineffectiveness of the tirofiban dose administered in TARGET (10 μg/kg bolus; 0.15 μg/kg/min per minute infusion) for reducing adverse clinical events has been explained by a lesser relative magnitude of platelet inhibition achieved (when compared with the standard bolus and 12-hour infusion of abciximab).[26]

As previously noted, platelet activation is markedly increased in patients with STEMI, and a direct relationship between the degree of platelet activation and the subsequent extent of myocardial necrosis has been observed.[27] A relationship also exists between the magnitude of pharmacologic platelet inhibition and the adequacy of coronary/myocardial reperfusion in STEMI. The patients with the greatest platelet inhibition following adjunctive pharmacotherapy for primary PCI of STEMI have improved parameters of both epicardial blood flow (higher TIMI flow grades) and myocardial perfusion (higher TIMI myocardial blush grades; $>$ 50% to 70% ST-segment resolution) postprocedure.[28,29]

Combined Therapies

Additive or synergistic inhibition of platelet aggregation may accompany combined administration of antiplatelet therapies.[29-32] In the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets Study (CLEAR-PLATELETS), a combination of eptifibatide and clopidogrel administered prior to PCI exerted a greater magnitude of platelet inhibition than did clopidogrel alone, an effect that was associated with lower periprocedural occurrence of elevated myocardial necrosis markers (eg, troponin, myoglobin).[31] A similar observation was made in the Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment (ISAR-REACT) 2 trial.[33] In the ISAR-REACT 2 trial, 2022 high-risk ACS patients received treatment with clopidogrel 600 mg oral loading dose prior to undergoing coronary angiography with the intent of PCI. Following angiography, patients were randomly assigned to receive either abciximab (0.25 mg/kg bolus,

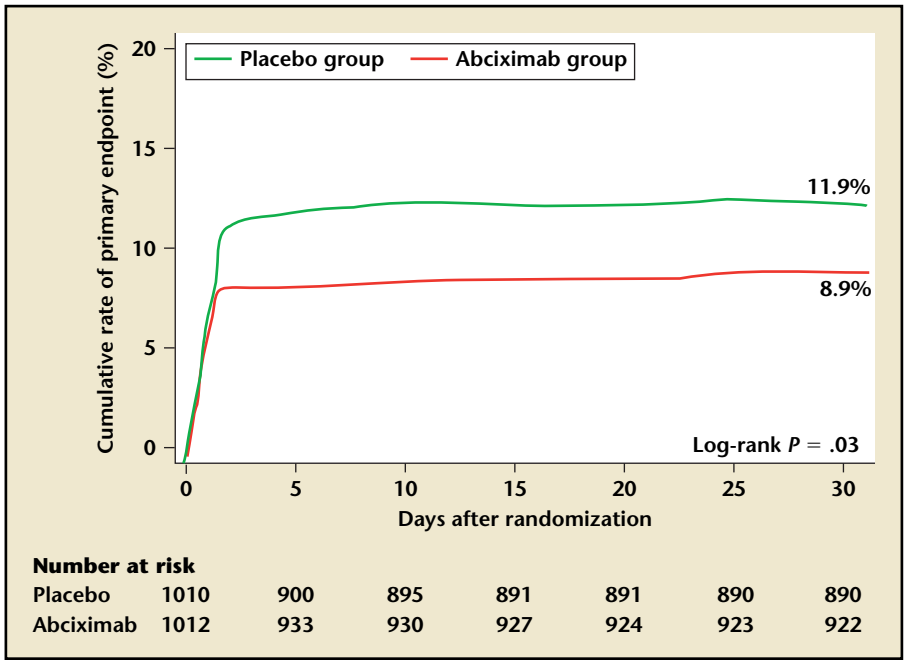

Figure 3. *Cumulative incidence of the composite primary endpoint (death, myocardial infarction, or urgent target vessel revascularization) to 30 days in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR REACT 2) trial. All patients received a clopidogrel 600 mg oral loading dose at least 2 hours prior to percutaneous coronary intervention and were randomly assigned to receive either abciximab or placebo following coronary angiography. Abciximab therapy was associated with a 25% reduction in the primary endpoint. Thus, abciximab provides clinical benefit in excess of that provided by the combination of aspirin and clopidogrel. Reproduced with permission from Kastrati A, et al.*[33] www.medreviews.com

followed by a 0.125 μg/kg/min infusion for 12 hours) in conjunction with heparin 70 U/kg bolus or placebo (bolus and 12-hour infusion) with heparin 140 U/kg bolus. Periprocedural abciximab administration was associated with a 25% reduction in the composite clinical endpoint of death, myocardial infarction, and urgent TVR (11.9% with placebo vs 8.9% with abciximab; $P = .03$; Figure 3). Those non–ST segment–elevation ACS patients at higher risk as reflected by an elevated preprocedural troponin level derived preferential benefit from procedural abciximab administration despite pretreatment with clopidogrel. All of these observations are consistent with the premise that "more is better" with respect to periprocedural platelet inhibition for improving procedural outcomes, as long as periprocedural bleeding events can be controlled or prevented.

Main Points

- Abnormalities in platelet size and function may be present in both acute coronary syndromes (ACS) and following percutaneous coronary intervention (PCI). Platelet activation in ACS is protracted and shows a diminished response to standard doses of platelet-inhibitor therapies such as clopidogrel and tirofiban. Platelet functional assessment prior to PCI is a predictor for the subsequent occurrence of adverse clinical events, including stent thrombosis and/or post-PCI coronary occlusion.
- Unfractionated heparin (UFH) directly activates platelets in a dose-dependent fashion and augments platelet responsiveness to low levels of agonists; furthermore, UFH is incapable of binding to either factor IIa or Xa. This, in combination with UFH-mediated relative depletion of antithrombin III, results in thrombin rebound and a hypercoagulable state following UFH administration. However, platelet activation associated with UFH administration can be eliminated by the concomitant administration of a glycoprotein IIb-IIIa inhibitor.
- The magnitude of platelet inhibition achieved by therapy correlates with the degree of clinical benefit, an observation that has led to the development of targeted levels for therapeutic platelet inhibition; however, this correlation is tempered by the frequency of occurrence of major hemorrhagic events, which can negate the net clinical benefit of platelet inhibitor therapy.
- Combined administration of antiplatelet therapies can lead to synergistic as well as additive inhibition of platelet aggregation. It thus appears that "more is better" with respect to periprocedural platelet inhibition for improving procedural outcomes, as long as bleeding events can be controlled or prevented.

Conclusion

Plaque disruption or other vascular injury results in platelet adhesion, activation, and aggregation. The level of preprocedural platelet reactivity is directly related to the occurrence of postprocedural adverse clinical outcomes. Specific patient subgroups (ACS, diabetes mellitus[34]) demonstrate abnormalities in baseline platelet size and function. Periprocedural platelet inhibitor therapies reduce the incidence of adverse clinical outcomes in direct proportion to the magnitude of platelet inhibition achieved. Optimal periprocedural outcomes require high levels of measured platelet inhibition. Additive or incremental platelet inhibition can be achieved by the concomitant administration of aspirin, a thienopyridine, and a GPIIb-IIIa inhibitor. These observations set the stage for the construct and development of novel and improved antiplatelet regimens for both ACS and PCI. ■

References

1. Woulfe D, Yang J, Prevost N, et al. Signal transduction during the initiation, extension, and perpetuation of platelet plug formation. In: Michelson AD, ed. *Platelets*. New York, NY: Academic Press/Elsevier Science; 2002:197-213.
2. Furman MI, Krueger LA, Linden MD, et al. Release of soluble CD40L from platelets is regulated by glycoprotein IIb-IIIa and actin polymerization. *J Am Coll Cardiol*. 2004;43:2319-2325.
3. Furman MI, Benoit SE, Barnard MR, et al. Increased platelet reactivity and circulating monocyte-platelet aggregates in patients with stable coronary artery disease. *J Am Coll Cardiol*. 1998;31:352-358.
4. Michelson AD, Barnard MR, Krueger LA, et al. Circulating monocyte-platelet aggregates are a more sensitive marker of in vivo platelet activation than platelet surface P-selectin: studies in baboons, human coronary intervention, and human acute myocardial infarction. *Circulation*. 2001;104:1533-1537.
5. Furman MI, Barnard MR, Krueger LA, et al. Circulating monocyte-platelet aggregates are an early marker of acute myocardial infarction. *J Am Coll Cardiol*. 2001;38:1002-1006.
6. Furman MI, Krueger LA, Linden MD, et al. GPIIb-IIIa antagonists reduce thromboinflammatory processes in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *J Thromb Haemostas*. 2005;3:312-320.
7. 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.
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. Michelson AD. Platelet function testing in cardiovascular diseases. *Circulation*. 2004;110:e489-e493.
11. 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.
12. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. *J Am Coll Cardiol*. 2005;46:1827-1832.
13. Neumann FJ, Gawaz M, Ott I, et al. Prospective evaluation of hemostatic predictors of subacute stent thrombosis after coronary Palmaz-Schatz stenting. *J Am Coll Cardiol*. 1996;27:15-21.
14. Steinhubl SR, Saucedo JF, Same DC, et al. Point-of-care measurement of platelet function before angioplasty strongly predicts future target vessel revascularization [abstract]. *J Am Coll Cardiol*. 2002;39:72A.
15. Miyamota 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.
16. 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.
17. 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.
18. Gregorini L, Marco J, Fajadet J, et al. Ticlopidine and aspirin pretreatment reduces coagulation and platelet activation during coronary dilation procedures. *J Am Coll Cardiol*. 1997;29:13-20.
19. Knight CJ, Panesar M, Wilson DJ, et al. Increased platelet responsiveness following coronary stenting. Heparin as a possible aetiological factor in stent thrombosis. *Eur Heart J*. 1998;19:1239-1248.
20. Matthai WH Jr, Kurnik PB, Groh WC, et al. Antithrombin activity during the period of percutaneous coronary revascularization: relation to heparin use, thrombotic complications and restenosis. *J Am Coll Cardiol*. 1999;33:1248-1256.
21. Furman MI, Kereiakes DJ, Krueger LA, et al. Leukocyte-platelet aggregation, platelet surface P-selectin, and platelet surface glycoprotein IIIa after percutaneous coronary intervention: effects of dalteparin or unfractionated heparin in combination with abciximab. *Am Heart J*. 2001;142:790-798.
22. The ESPRIT investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet*. 2000;356:2037-2044.
23. The IMPACT-II Investigators. Randomised placebo-controlled trial of eptifibatide on complications of percutaneous coronary intervention: IMPACT II. *Lancet*. 1997;349:1422-1428.
24. Steinhubl SR, Talley JD, Braden GA, et al. Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention: results of the GOLD (AU-Assessing Ultegra) multicenter study. *Circulation*. 2001;103:2572-2578.
25. Topol EJ, Moliterno DJ, Herrmann HC, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med*. 2001;344:1888-1894.
26. Herrmann HC, Swierkosz TA, Kapoor S, et al. Comparison of degree of platelet inhibition by abciximab versus tirofiban in patients with unstable angina pectoris and non-Q-wave myocardial infarction undergoing percutaneous coronary intervention. *Am J Cardiol*. 2002;89:1293-1297.
27. Frossard M, Fuchs I, Leitner JM, et al. Platelet function predicts myocardial damage in patients with acute myocardial infarction. *Circulation*. 2004;110:1392-1397.
28. de Prado AP, Fernandez-Vazquez F, Cuellas JC, et al. Association between level of platelet inhibition after early use of abciximab and myocardial reperfusion in ST-elevation acute myocardial infarction treated by primary percutaneous coronary intervention. *Am J Cardiol*. 2006;97:798-803.
29. 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.
30. 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
31. 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.
32. 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 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.
33. Kastrati A, Mehilli J, Neumann F, 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.

34. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes*. 2005;54:2430-2435.
35. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med*. 1994;330:956-961.
36. Lincoff AM, Tcheng JE, Califf RM, et al. Sustained suppression of ischemic complications of coronary intervention by platelet GP IIb/IIIa blockade with abciximab: one-year outcome in the EPILOG trial. Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade. *Circulation*. 1999;99:1951-1958.
37. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet*. 1997;349:1429-1435.
38. Gibson CM, Goel M, Cohen DJ, et al. Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. *J Am Coll Cardiol*. 1998;32:28-34.
39. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet*. 1998;352:87-92.