Use of Antiplatelet Inhibitors in Peripheral Vascular Interventions

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ABSTRACT

In the past decade, a tremendous amount of information has been gathered about platelet function and its impact on percutaneous vascular interventions. Strategies for prevention of platelet aggregation have moved beyond aspirin administration. Powerful oral antiplatelet agents such as ticlopidine (Ticlid) and clopidogrel (Plavix) have been developed to prevent platelet aggregation and thrombosis. The discovery of the glycoprotein IIb/IIIa receptor, which is responsible for platelet aggregation, has led to the development of receptor antagonists. These drugs include abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat). Several large studies have demonstrated that these drugs can improve outcomes in coronary interventions. Because most of the data regarding antiplatelet agents in percutaneous interventions comes from studies of coronary interventions, knowledge of these studies is necessary before using the antiplatelet drugs in peripheral vascular interventions. This article reviews the use of these agents in percutaneous coronary artery interventions and discusses their potential use in peripheral interventions.

KEYWORDS: Blood, platelets, arteries, transluminal angioplasty, thrombosis, drugs

Objectives: Upon completion of this article, the reader will understand the use of antiplatelet agents in percutaneous coronary artery interventions and be able to discuss their potential use in peripheral interventions.

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Over the past decade, our understanding of the role of the platelet in acute vascular events including those associated with percutaneous interventions has increased dramatically. Although aspirin was introduced in the late 1890s, its antiplatelet effect was not discovered until the 1960s.[1,2] Aspirin primarily affects the biosynthesis of cyclic prostanoids such as thromboxane A_2 (TXA_2) by irreversibly inhibiting both the function of cyclooxygenase (COX-1) in platelets and the vascular synthesis of prostacyclin.[3,4] Although the efficacy of aspirin in preventing thrombotic complications during percutaneous coronary interventions (PCIs) is well established,[5–8] aspirin is a relatively weak platelet antagonist and some patients may be resistant to its effects. Other non–TXA_2-dependent activators of platelet aggregation such as thrombin, adenosine diphosphate (ADP), and collagen[3,4] are not affected by aspirin. The current general recommendation for

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aspirin use during PCI is an empirical dose of aspirin, 80 to 325 mg, given at least 2 hours prior to an intervention.[9]

Pharmacologic therapy during peripheral vascular interventions (PVIs) is often focused on preventing thrombus formation through the use of oral warfarin and intravenous heparin. These anticoagulants work by blocking thrombin production and the subsequent conversion of fibrinogen to fibrin, respectively. The main elements of thrombus include fibrin, thrombin, and platelets, and until recently little consideration has been given to the effect of platelet aggregation, which also contributes to local thrombus formation and distal platelet microembolization.[10]

A new class of parenteral drugs is available that blocks the final common pathway for platelet aggregation, the glycoprotein (GP) IIb/IIIa platelet receptor, a class of cell surface receptors known as integrins. Because there is little published experience with these drugs in PVIs,[11,12] it is important to examine experience in coronary interventions to determine the possible applications of these parenteral IIb/IIIa inhibitors for noncoronary vascular procedures.

In addition to these intravenous agents, the oral thienopyridines such as ticlopidine (Ticlid, Roche Laboratories, Nutley, NJ) and clopidogrel (Plavix, Sanofi Pharmaceuticals, New York, NY) have been used in combination with aspirin during PCI to block platelet aggregation and prevent subacute thrombosis.[13] As with the intravenous agents, there is little available literature on the use of these agents during peripheral arterial interventions. This article deals with all currently available GP IIb/IIIa platelet receptor inhibitors in addition to the oral agents to allow one to incorporate their use into the current practice of noncoronary percutaneous vascular interventions.

PLATELET FUNCTION

To understand the antiplatelet drugs, one must understand how platelet activation and aggregation is initiated. Damage to a blood vessel, including that experienced during angioplasty, exposes adhesive glycoproteins such as von Willebrand factor and collagen. Platelets have receptors for these glycoproteins that are usually covered by the normal endothelial lining. The glycoprotein receptors are activated and bind immediately to the glycoproteins to cover the injured area. This initial process, called adhesion, results in the adherence of platelets to the damaged subendothelial surface and is performed by other receptors such as the GP Ib/IX complex.[14] After binding to the subendothelial layer, platelets undergo a conformational change at the GP IIb/IIIa site that allows them to bind to fibrinogen and von Willebrand factor. Because both fibrinogen and von Willebrand factor have multiple binding sites, they can bind to multiple platelets, causing cross-linking and platelet aggregation.

Agonists exist that activate platelets to bind fibrinogen at sites of vascular injury. The membrane signals induced by these agonists are transduced by several mechanisms including arachidonic acid metabolism and protein kinase C activation. Aspirin blocks only arachidonic acid metabolism and is therefore only a partial inhibitor of platelet aggregation.[3,4,15] Thienopyridines such as the oral medications ticlopidine and clopidogrel interfere with platelet membrane function by irreversibly inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. Regardless of what agonists activate the platelet, the final common pathway to platelet aggregation is the GP IIb/IIIa receptor.

The advantage of blocking the IIb/IIIa receptor is that platelet-to-platelet binding through fibrinogen or von Willebrand factor is prevented while platelet binding to the subendothelial elements (i.e., the surface of the damaged vessel) remains intact. A platelet monolayer or "bandage" is formed in an injured blood vessel to obtain hemostasis, but aggregation that can lead to local thrombosis or can break off and be carried downstream to embolize the distal microcirculation does not occur. Thus, these drugs prevent local thrombosis related to platelet aggregation that is not inhibited by standard anticoagulation and prevent platelet embolization to the distal vessels.[16]

PLATELET GP IIB/IIIA INHIBITORS

There are two general classes of drugs, differentiated by their molecular size.[17] Most of the large clinical trials with the IIb/IIIa antagonists have studied either their use in the treatment of acute coronary syndromes (ACSs) such as unstable angina and non–Q wave myocardial infarction (MI) or their use in PCI such as angioplasty, atherectomy, and coronary stenting. Three parenteral GP IIb/IIIa inhibitors currently have Food and Drug Administration (FDA) approval for these indications. Large prospective randomized clinical investigations have been performed comparing the use of these powerful antiplatelet drugs with the conventional therapy of heparin and aspirin during coronary interventions. The results have demonstrated significant clinical benefits of using the IIb/IIIa antagonists compared with the use of heparin and aspirin alone in decreasing the usual end points of coronary trials including MI, death, and need for target vessel revascularization, for example, coronary artery bypass graft (CABG) surgery.

Abciximab

The c7E3 antibody, a large molecule IIb/IIIa antagonist, was the first to be clinically studied and was licensed

in 1986 as abciximab (ReoPro) by Centocor (Malvern, PA) and jointly marketed with Eli Lilly (Indianapolis, IN). It is a monoclonal antibody that consists of the F(ab) portion of a murine-human chimeric immunoglobulin G. Abciximab binds noncompetitively to the GP IIb/IIIa receptor site with high affinity with a binding half-life of 2 hours. This results in the drug having a short plasma half-life but a prolonged receptor blockade.[18,19]

Abciximab is eliminated slowly from the body.[20] Although some receptor blockade can be detected as long as 2 weeks after an administration, profound inhibition (and enhanced bleeding time) persists only for 6–12 hours after drug infusion is discontinued.

The Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial, which began in 1991, was the first large-scale clinical evaluation of abciximab.[21] The trial involved 2099 high-risk patients with unstable angina, evolving acute MI, or unfavorable coronary artery morphologic characteristics undergoing percutaneous transluminal coronary angioplasty (PTCA) or atherectomy. They were randomly divided into three groups to undergo intervention with heparin (10,000 to 12,000 units) and aspirin alone or with the addition of abciximab given as a single bolus or a bolus with 12-hour infusion. At 30 days, there was a 35% reduction in composite end points of death, MI, and need for urgent revascularization compared with placebo (8.3% versus 12.8%, $p = 0.008$). This benefit was maintained at 6 months and at 3 years.[22,23]

The EPIC trial supported the hypothesis that the blockade of the GP IIb/IIIa receptor site on platelets during PTCA improved short- and long-term clinical outcomes significantly in patients at high risk for ischemic complications. A 12-hour infusion of abciximab was required for significant efficacy because a brief GP IIb/IIIa blockade with a bolus alone had limited clinical effect. In addition, because of an increase in bleeding complications with abciximab, there was a need for better arterial puncture management and refinement in the anticoagulation protocol.

Because of the success of EPIC, two additional trials were started. The Evaluation in PTCA to Improve Long-term Outcome with c7E3 GP IIb/IIIa blockade (EPILOG) trial demonstrated improvement in outcomes using a lower (70 U/kg) weight-adjusted heparin dose in patients undergoing low-risk PTCA with abciximab.[24] The other large trial, called CAPTURE (c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina),[25] investigated the use of abciximab to treat patients with ACS prior to PTCA. CAPTURE also demonstrated a significant reduction in clinical end points using the reduced heparin dose regimen.

The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial compared coronary artery stenting with the standard heparin dose (100 U/kg) with PTCA or stenting with abciximab and low-dose heparin (70 U/kg). With abciximab, there was a 54% reduction in the primary end points of death and MI with comparable bleeding complications in all groups.[26]

Eptifibatide

Eptifibatide (Integrilin), developed by Cor Therapeutics (South San Francisco CA) and Schering-Plough Corporation (Kenilworth, NJ), is one of the two low-molecular-weight drugs that competes with the IIb/IIIa receptor by competitive inhibition. Because of this, there is a much shorter receptor blockade and a longer plasma half-life.[18,19] This drug does not carry an antibody response and has a plasma elimination half-life of $\sim$2.5 hours. Primary excretion of eptifibatide is by the kidneys, and the dose of this drug must be adjusted in patients with renal insufficiency.

Several large-scale clinical trials with eptifibatide have been done to obtain FDA approval for treatment in both ACS and elective PCI. Because of dosing issues raised in the review of the in vitro studies, successive clinical trials witnessed an increase in the dose of the drug. The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT) II trial was a randomized placebo-controlled study evaluating the use of eptifibatide in patients undergoing PCI with heparin alone versus one of two doses of eptifibatide.[27] This study showed a statistically significant 25% reduction in the end points of the higher dose group at 24 hours.

IMPACT II investigators realized that the study dose of eptifibatide was lower than optimal, achieving only 30–50% receptor blockade rather than the 80% expected. Given the success of IMPACT II despite the lower than optimal dose, the dose was raised in the subsequent Platelet IIb/IIIa Underpinning the Receptor for Suppression of Unstable Ischemia Trial (PURSUIT), which studies patients with ACS.[28] There was a statistically significant reduction in primary end points at 30 days. The FDA approved two different doses of eptifibatide based on the results of these two trials, one for elective PCI and another for ACS.

Further dosing studies and pharmacodynamic modeling resulted in increasing the eptifibatide dose to a double-bolus strategy with an infusion lasting 18 to 24 hours for the most recent investigation of eptifibatide with coronary stenting. This trial was called the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial and evaluated the use of eptifibatide as an adjunct to nonemergent PTCA and stenting.[29] The trial was ended early because of a substantial benefit at 48 hours with the composite end points of 6.6% versus 10.5% and at 30 days with 6.8% versus 10.8% for eptifibatide and placebo, respectively. The beneficial results persisted despite excluding the high-risk patients and despite utilizing the

contemporary protocol of stenting (treating patients with clopidogrel or ticlopidine, using high-pressure inflation and low-dose heparin).[30] The 6-month data from ESPRIT demonstrated a significant reduction in overall end point between the eptifibatide group (14.2%) and the placebo group (18.3%) ($p = 0.008$).

Tirofiban

Tirofiban hydrochloride (Aggrastat) (Merck, Whitehouse Station, NJ) is the other low-molecular-weight GP IIb/IIIa inhibitor. It specifically competes for the receptors by mimicking the GP IIb-IIIa binding sequences of the natural ligand. Plasma clearance is linear with a half-life of 1.6 hours. Tirofiban is excreted by both renal and nonrenal mechanisms and does not produce an antibody response.[31]

The first large ACS trials involving tirofiban are called Platelet Receptor inhibition for Ischemic Syndrome Management (PRISM) and Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS).[32,33] PRISM-PLUS involved patients with unstable angina or a non–Q-wave MI and the primary end points were reduced by 32% ($p = 0.004$) with the use of tirofiban.[33]

The use of tirofiban with high-risk PTCA and atherectomy was evaluated in the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis trial (RESTORE).[34] Although there was a statically significant reduction in composite end points at 48 hours, this effect was not significant at 30 days. Tirofiban did not receive FDA approval for use with elective PCI. The incidence of intracranial and retroperitoneal bleeding was similar among the groups.

Summary of the IIB/IIIA Agents

One problem in reviewing the data from these investigations is the difficulty in comparing the different drugs. The studies have each employed slightly different methodologies, including variations in end points and the adjunctive use of oral antiplatelet drugs. In addition, over the course of these studies, the technology of PCI has changed.[31] For example, when the early abciximab studies were performed, few stents were used. These patients were more likely to undergo emergent bypass surgery, a study end point. The more recent trials were handicapped by the current greater use of stenting causing a decrease in the need for emergent bypass. This results in a lower number of end points being reached in the control groups, thus reducing the impact of the study drug. The only direct comparison between two different IIb/IIIa inhibitors occurred when tirofiban was evaluated against abciximab in a trial entitled Do Tirofiban and ReoPro Give Similar Efficacy Trial (TARGET).[35] A modified version of the RESTORE trial was used to determine whether tirofiban and abciximab would have comparable efficacy in reducing the incidence of adverse cardiac ischemic events during the first 30 days after intracoronary stent placement. The tirofiban group had a significantly inferior result compared with abciximab: 7.55% versus 6.01%, odds ratio 1.26, $p = 0.037$. The differences between these two drugs could be related to dosing issues with tirofiban or to the non-IIb/IIIa effects of abciximab.

The relative contraindications to using GP IIb/IIIa inhibitors are similar to those for thrombolysis, although the rate of intracranial hemorrhage in studies with these agents has been generally not significantly greater than the rate of the heparin control groups.[36,37] Previous warfarin therapy should be discontinued and the international normalized ratio (INR) should be < 1.5. When using GP IIb/IIIa inhibitors, heparin should be titrated to a target ACT in the range 200–300 seconds usually with a bolus of 50–70 U/kg.[9] Intraprocedurally, additional doses of heparin 20 U/kg may be administered to maintain an ACT of 200 seconds. Heparin is generally not used after the procedure.

Single-wall arterial entry is recommended. The vascular access sheath can be removed, despite an ongoing infusion of a GP IIb/IIIa inhibitor, when the ACT normalizes (ACT $<$ 150–180 seconds). Closure devices may be used with success.[38–41] During infusion, patients are monitored in the intensive care unit with platelet counts obtained prior to the procedure and then 4 and 24 hours after termination of the infusion. If platelets decrease acutely (e.g., a platelet decrease to less than 100,000 cells/mL and a decrease of at least 25% from pretreatment value), additional platelet counts should be obtained to exclude a pseudothrombocytopenia. There is a significantly increased incidence of abciximab causing mild thrombocytopenia ($<$ 90,000 to 100,000/μL) and severe thrombocytopenia ($<$ 50,000/μL) compared with placebo (4.2% versus 2.0% and 1.0% versus 0.4%, respectively).[42] The low-molecular-weight GP IIb/IIIa inhibitors did not significantly cause thrombocytopenia when compared with the placebo.

Abciximab is given as an intravenous bolus of 0.25 mg/kg administered several minutes prior to an intervention. A weight-adjusted continuous infusion of 0.125 μg/kg/min to a maximum of 10 μg/min is administered over 12 hours after the bolus. On average, there is a 35-second increase in the activated clotting time with abciximab.[43] Over $\sim$2 weeks, the receptor blockade slowly drops, although the bleeding time becomes normal in $\sim$12 hours after termination of the infusion. Concerns regarding a possible immune response following readministration of abciximab have been raised. Although antibodies to abciximab have been detected,

however, readministration of the drug appears to be safe.[44,45] No dose adjustment for patients with renal failure is necessary.

The most current dosing for eptifibatide is a 180 μg/kg bolus followed by a 2 μg/kg/min infusion for 18–24 hours and an additional 180 μg/kg bolus after 10 minutes from the first bolus based on the ESPRIT trial. From the TARGET trial, the most current dosing for tirofiban is a bolus of 10 μg/kg over 3 minutes followed by an infusion of 0.15 μg/kg/min for 18–24 hours. For both of these low-molecular-weight GP IIb/IIIa receptor blockers, the bleeding time normalizes 3–4 hours after discontinuation of the drug. There are no issues with readministration of the drugs. Both drugs require dose adjustments in patients with renal failure.

If emergent surgery is needed, there is a risk of bleeding in patients who have been treated with these agents. Dyke showed an increased bleeding risk in patients treated with abciximab who underwent emergent CABG.[46] He suggested that eptifibatide or tirofiban, with their rapidly reversible antiplatelet effect, may represent a safer alternative. In the PURSUIT trial with eptifibatide, the major bleeding complication rate after emergent CABG was the same among the groups and the perioperative MI rate was significantly reduced in patients who received eptifibatide.[46,47] If possible, when using abciximab, surgery should be postponed for at least 12 hours or a platelet transfusion should be given. For eptifibatide or tirofiban, there seems to be no need to delay surgery.

PLATELET GP IIB/IIIA INHIBITORS IN PERIPHERAL VASCULAR INTERVENTIONS

The use of heparin during PVIs focuses on the effects of thrombin. However, platelet aggregation causing thrombosis also plays a role in all percutaneous arterial interventions. Little attention has been given to the role of antiplatelet medications for improving outcomes during PVI. Although several abstracts exist for the use of GP IIb/IIIa inhibitors in PVI, there are no published large prospective randomized trials.[12] Stavropoulos et al reported the safe use of abciximab during a small number of complex infrainguinal interventions.[11] In addition, there have been published investigations dealing with IIb/IIIa inhibitors as adjuncts to carotid interventions with abciximab[48–50] and eptifibatide.[51] In a prospective registry, Cecena et al[52] reported no neurological complications in 49 carotid interventions in high-grade stenoses performed in 45 high-risk patients with the use of concurrent abciximab. Thromboembolic complications were entirely prevented in the periprocedural period with the use of a GP IIb/IIIa receptor antagonist. However, Wholey et al reported a higher incidence of neurologic complications when GP IIb/IIIa inhibitors were used during carotid stenting compared with control subjects who did not receive the GP IIb/IIIa inhibitors in a retrospective study of 550 patients.[53]

Based on the literature from the coronary artery interventions, the main reason to consider using IIb/IIIa antiplatelet agents during peripheral interventions is that they aid in preventing acute and subacute thromboses better than heparin. In addition, they serve to prevent distal embolization of platelet aggregates into the microcirculation. However, because of their high cost and lack of proven benefit in PVI in the literature, the use of the IIb/IIIa antagonists should be limited to procedures that carry a high risk to the patient in the event of an arterial thrombosis. This includes infrapopliteal angioplasty, particularly with a single runoff vessel or long-segment superficial femoral artery stenoses or occlusions.

For peripheral interventions, one advantage of abciximab in that the infusion lasts only 12 hours. This may allow patients to be discharged from the intensive care unit and hospital in the morning following the intervention. This decrease in hospitalization may offset some of the difference in price between the three agents, with abciximab costing two to three times as much as the others. An advantage of eptifibatide and tirofiban is that they are less expensive than abciximab. In addition, if there is a need for urgent surgery, their antiplatelet effect wears off within a few hours of discontinuation of the drug, whereas abciximab requires 12 hours or a transfusion of platelets to normalize the bleeding time.

ORAL ANTIPLATELET AGENTS

Thienopyridines are a class of oral antiplatelet drugs that includes ticlopidine and clopidogrel. These drugs work synergistically with aspirin to reduce platelet aggregation and prevent subacute thrombosis associated with coronary stenting.[9,54–56] These medications seem to be underutilized by the interventional radiology community. This underutilization is partly due to the FDA labeling, which does not approve of their use with vascular interventions. Clopidogrel does, however, have the FDA indication to prevent recurrent ischemic events in patients with peripheral vascular disease. Although conventional short-term anticoagulation with heparin for PVIs may be sufficient, the use of these oral agents may prove advantageous given their ease of administration and the literature demonstrating their benefit during coronary interventions. In addition, cardiologists have been using these oral antiplatelet medications instead of warfarin to prevent subacute thrombosis after coronary artery stenting.

Ticlopidine is a thienopyridine that interferes with platelet membrane function by irreversibly inhibiting ADP-induced platelet-fibrinogen binding. Several prospective randomized trials, such as the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial[57] and the Stent Anticoagulation Restenosis Study (STARS), supported the conclusion that aspirin and

ticlopidine represented a better postcoronary stenting regimen than the use of warfarin (Coumadin).[28] However, patients receiving ticlopidine need to be monitored for neutropenia, which it causes in 2.4% of patients.[58] Severe neutropenia occurs in 0.8% of patients taking ticlopidine.[58] Because of this complication, most physicians now use clopidogrel, a thienopyridine that is associated with a much lower incidence of neutropenia and thrombotic thrombocytopenic purpura than ticlopidine.[59,60]

Clopidogrel was substituted for ticlopidine because of the evidence from the randomized, "blinded" Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial. The CAPRIE trial evaluated 19,185 patients with a previous history of stroke, MI, and vascular disease for the ability of clopidogrel versus aspirin to reduce the risk of a repeated vascular event. The trial demonstrated an overall risk reduction of 8.7% ($p = 0.043$) in favor of clopidogrel compared with aspirin.[61] In addition, three prospective randomized studies, the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS),[62] Ticlid or Plavix Post-Stents (TOPPS),[63] and the Muller et al[64] study, have demonstrated that clopidogrel is better tolerated and safer than ticlopidine and is not significantly different in its ability to prevent subacute stent thrombosis.

Additional investigations are evaluating the long-term benefit of the combination of clopidogrel and aspirin. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial was designed to evaluate the acute and long-term benefit of aspirin and clopidogrel in patients with ACS.[65] The hypothesis that the acute and long-term (up to 1 year) combination of clopidogrel with aspirin was better than aspirin alone in preventing major ischemic events following PCI was examined in a CURE subgroup analysis, the PCI-CURE trial.[65,66] The combination yielded a significantly lower rate of cardiovascular death, MI, or any revascularization ($p = 0.03$). There was no significant increase in major bleeding complications between the groups.

For patients undergoing coronary artery stenting, the recommended dose of clopidogrel is a loading dose of 300 mg given before or at the time of the intervention followed by 75-mg daily dose for 4–6 weeks along with aspirin.[9] The thienopyridines can be administered after the use of the parenteral IIb/IIIa inhibitors to provide consistent platelet blockade over several weeks.[66,67]

The findings from the cardiology literature suggest that these drugs could be useful following renal, visceral, superficial femoral artery, and other small vessel interventions. Patients are often anticoagulated with heparin for a short time after infrainguinal angioplasty as well as renal and visceral artery stenting, and further investigation into potentially substituting clopidogrel would seem justified. In addition, the greatest benefit from the CAPRIE trial was in patients with PVD. In these patients, the relative risk reduction was 23.8% for clopidogrel over aspirin.[61] This finding, along with the benefit demonstrated in the PCI-CURE study, suggests that the use of clopidogrel and aspirin after many PVIs could be advantageous. Further study in this area must weigh the potential benefits of clopidogrel against the possibilities of side effects and additional cost of using this drug over aspirin alone.

CONCLUSIONS

Although knowledge gained during the use of antiplatelet medications in coronary artery interventions may answer some questions regarding the use of these drugs during peripheral interventions, many questions remain unanswered related to differences in vessel size, blood flow, and the nature of the distal arterial bed. Only randomized prospective trials using these drugs during PVIs will fully answer these questions. Until these trials are completed, we can only attempt to apply the lessons learned during PCI to peripheral arterial interventions. The use of GP IIb/IIIa receptor antagonists may be useful in complex infrainguinal and infrageniculate interventions, particularly when there are limited runoff vessels that have a high risk of thrombosis. These agents could also be considered during interventions in which distal platelet embolization would involve significant morbidity, such as in the renal or mesenteric arteries. Finally, clopidogrel and aspirin could be considered instead of postprocedure heparin during procedures that involve an increased risk for subacute thrombosis.

REFERENCES

1. Weiss H. Impaired platelet-connective-tissue reaction in man after aspirin ingestion. Lancet 1967;2:495–497
2. Dresser H. Pharmakologisches über Aspirin (acetylsalicyl Säure). Pflugers Arch 1899;76:306–318
3. Breddin HK. Antiplatelet agents in cardiovascular and cerebrovascular diseases. Clin Appl Thromb Hemost 1998; 4:87–95
4. Awtry E, Loscalzo J. Aspirin. Circulation 2000;101:1206–1218
5. Popma JJ, Ohman EM, Weitz J, Lincoff AM, Harrington RA, Berger P. Antiplatelet therapy in patients undergoing percutaneous coronary intervention. Chest 2001;119:321S–336S
6. Barnathan ES, Schwartz J, Taylor L, et al. Aspirin and dipyridamole in prevention of acute coronary thrombosis complicating coronary angioplasty. Circulation 1987;76:125–134
7. Schwartz L, Bourassa MG, Lesperance J, et al. Aspirin and dipyridamole in prevention of restenosis after percutaneous transluminal coronary angioplasty. N Engl J Med 1988;318: 1714–1719
8. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged

antiplatelet therapy in various categories of patients. BMJ 1994;308:81–106
9. Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines): executive summary. Circulation 2001;103:3019–3041
10. Moliterno DJ, Topol EJ. Conjunctive use of platelet glycoprotein IIb/IIIa antagonists and thrombolytic therapy for acute myocardial infarction. Thromb Haemost 1997;78: 214–219
11. Stavropoulos SW, Solomon JA, Soulen MC, Clark TW, Shlansky-Goldberg RD. Use of abciximab during infrainguinal peripheral vascular interventions: initial experience. Radiology 2003;227:657–661
12. Benenati J, Shlansky-Goldberg R, Meglin A, et al. Thrombolytic and antiplatelet therapy in peripheral vascular disease with use of reteplase and/or abciximab. The SCVIR Consultants' Conference; May 22, 2000; Orlando, FL. Society for Cardiovascular and Interventional Radiology. J Vasc Interv Radiol 2001;12:795–805
13. Kereiakes DJ. Oral blockade of the platelet glycoprotein IIb/IIIa receptor: fact or fancy? Am Heart J 1999;138:S39–S46
14. Becker RC. Thrombosis and the role of the platelet. Am J Cardiol 1999;83:3E–6E
15. Roth GJ, Calverley DC. Aspirin, platelets and thrombosis: theory and practice. Blood 1994;83:885–898
16. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. Circulation 2000;101:570–580
17. Sabatine MS, Jang IK. The use of glycoprotein IIb/IIIa inhibitors in patients with coronary artery disease. Am J Med 2000;109:224–237
18. Scarborough RM, Kleiman NS, Phillips DR. Platelet glycoprotein IIb/IIIa antagonists. What are the relevant issues concerning their pharmacology and clinical use? Circulation 1999;100:437–444
19. Kereiakes DJ, Runyon JP, Broderick TM, Shimshak TM. IIb's are not IIb's. Am J Cardiol 2000;85:23C–31C
20. Mascelli MA, Lance ET, Damaraju L, Wagner CL, Weisman HF, Jordan RE. Pharmacodynamic profile of short-term abciximab treatment demonstrates prolonged platelet inhibition with gradual recovery from GP IIb/IIIa receptor blockade. Circulation 1998;97:1680–1688
21. The EPIC Investigators. 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
22. Topol EJ, Ferguson JJ, Weisman HF, et al. Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication. JAMA 1997;278:479–484
23. Topol E, Califf R, Wiesman HF, et al. Randomised trial of coronary interventions with antibody against IIb/IIIa integrin for reduction of clinical restenosis. Lancet 1994;343:881–886
24. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336:1689–1696
25. The ERASER Investigators. Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). Circulation 1999;100:799–806
26. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998;352:87–92
27. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II. Lancet 1997;349:1422–1428
28. Leon MB, Baim DS, Donald S, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med 1998;339:1665–1671
29. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000;356:2037–2044
30. Ferguson JJ. What have we learned from ESPRIT? What will we learn from TARGET? J Invasive Cardiol 2000;12:317–319
31. Herrmann HC. Tirofiban: an overview of the phase III trials. J Invasive Cardiol 1999;11:7c–13c
32. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. N Engl J Med 1998;338:1498–1505
33. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. N Engl J Med 1998;338:1488–1497
34. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. Circulation 1997;96:1445–1453
35. 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
36. Memon MA, Blankenship JC, Wood GC, Frey CM, Menapace FJ. Incidence of intracranial hemorrhage complicating treatment with glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis of major clinical trials. Am J Med 2000;109:213–217
37. Tcheng JE. Clinical challenges of platelet glycoprotein IIb/IIIa receptor inhibitor therapy: bleeding, reversal, thrombocytopenia, and retreatment. Am Heart J 2000;139:S38–S45
38. Chamberlin JR, Lardi AB, McKeever LS, et al. Use of vascular sealing devices (VasoSeal and Perclose) versus assisted manual compression (Femostop) in transcatheter coronary interventions requiring abciximab (ReoPro). Catheter Cardiovasc Interv 1999;47:143–147; discussion 148
39. Lunney L, Karim K, Little T. Vasoseal hemostasis following coronary interventions with Abciximab. Cathet Cardiovasc Diagn 1998;44:405–406
40. Sesana M, Vaghetti M, Albiero R, et al. Effectiveness and complications of vascular access closure devices after interventional procedures. J Invasive Cardiol 2000;12:395–399
41. Warren BS, Warren SG, Miller SD. Predictors of complications and learning curve using the Angio-Seal closure device

following interventional and diagnostic catheterization. Catheter Cardiovasc Interv 1999;48:162–166
42. Dasgupta H, Blankenship JC, Wood GC, Frey CM, Demko SL, Menapace FJ. Thrombocytopenia complicating treatment with intravenous glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis. Am Heart J 2000;140:206–211
43. Moliterno DJ, Califf RM, Aguirre FV, et al. Effect of platelet glycoprotein IIb/IIIa integrin blockade on activated clotting time during percutaneous transluminal coronary angioplasty or directional atherectomy (the EPIC trial). Evaluation of c7E3 Fab in the Prevention of Ischemic Complications trial. Am J Cardiol 1995;75:559–562
44. Madan M, Kereiakes DJ, Hermiller JB, et al. Efficacy of abciximab readministration in coronary intervention. Am J Cardiol 2000;85:435–440
45. Tcheng JE, Kereiakes DJ, Braden GA, et al. Readministration of abciximab: interim report of the ReoPro readministration registry. Am Heart J 1999;138:S33–S38
46. Dyke CM. Safety of glycoprotein IIb-IIIa inhibitors: a heart surgeon's perspective. Am Heart J 1999;138:307–316
47. Dyke CM, Bhatia D, Lorenz TJ, et al. Immediate coronary artery bypass surgery after platelet inhibition with eptifibatide: results from PURSUIT. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy. Ann Thorac Surg 2000;70:866–871
48. Wallace RC, Furlan AJ, Moliterno DJ, Stevens GH, Masaryk TJ, Perl J II. Basilar artery rethrombosis: successful treatment with platelet glycoprotein IIB/IIIA receptor inhibitor. AJNR Am J Neuroradiol 1997;18:1257–1260
49. Qureshi AI, Suri MF, Khan J, Fessler RD, Guterman LR, Hopkins LN. Abciximab as an adjunct to high-risk carotid or vertebrobasilar angioplasty: preliminary experience. Neurosurgery 2000;46:1316–1324
50. Connors JJI, Wojak JC. Intracranial angioplasty. J Invasive Cardiol 1998;10:298–303
51. New G, Roubin GS, Iyer SS, Vitek JJ. Use of the glycoprotein IIb/IIIa inhibitor eptifibatide in a patient undergoing carotid artery stenting. J Invasive Cardiol 2000;12:23D–24D
52. Cenena FA, Hoelzinger DH, Miller JA, Abu-Shakra SA. The platelet IIb/IIIa inhibitor abciximab as adjunctive therapy in carotid stenting of potential thrombotic lesions. J Interv Cardiol 1999;12:355–361
53. Wholey MH, Wholey MH, Eles G, et al. Evaluation of glycoprotein IIb/IIIa inhibitors in carotid angioplasty and stenting. J Endovasc Ther 2003;10:33–41
54. Herbert J, Dol F, Bernat A, et al. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. Thromb Haemost 1998;80:512–518
55. Bossavy JP, Thalamas C, Sagnard L, et al. A double-blind randomized comparison of combined aspirin and ticlopidine therapy versus aspirin or ticlopidine alone on experimental arterial thrombogenesis in humans. Blood 1998;92:1518–1525
56. Moshfegh K, Redondo M, Julmy F, et al. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy. J Am Coll Cardiol 2000;36:699–705
57. Schomig A, Neumann FJ, Kastrati A, et al. A randomised comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084–1089
58. Moloney BA. An Analysis of the Side-Effects of Ticlopidine New York: Springer-Verlag; 1993
59. Bennett CL, Connors JM, Carwile JM. Thrombotic thrombocytopenic purpura associated with clopidogrel. N Engl J Med 2000;342:1773–1777
60. Hankey GJ. Clopidogrel and thrombotic thrombocytopenic purpura. Lancet 2000;356:269–270
61. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329–1339
62. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators FT. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;102:624–629
63. Berger PB. Clopidogrel instead of ticlopidine after coronary stent placement: is the switch justified. Am Heart J 2000;140:354–358
64. Muller C, Buttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. Circulation 2000;101:590–593
65. Mehta SR, Yusuf S, and the CURE Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J 2000;21:2033–2041
66. Mehta SR, Yusuf S, Peter RJG, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–533
67. 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