■ REVIEW ARTICLE

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Platelet Glycoprotein IIb/IIIa Antagonists

Pharmacology and Clinical Developments

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PLATELETS are critical for normal hemostasis and thrombus formation.[1] Thrombus formation initiated by platelets plays a central role in the pathogenesis of acute coronary syndromes (unstable angina and myocardial infarction). Platelets are involved in events causing angioplasty failure and stent thrombosis and may also play an important role in restenosis through the release of potent prothrombotic, vasoactive, mitogenic, and inflammatory factors.[2,3] The identification of the platelet glycoprotein IIb/IIIa receptor, a fibrinogen receptor important for platelet aggregation, has led to the development of receptor antagonists. Although aspirin lowers the risk of death and myocardial infarction (MI) in patients with acute coronary syndromes, intravenous glycoprotein IIb/IIIa antagonists further reduce the rates of ischemic events and coronary angioplasty complications and improve the results of coronary stenting.[2] Furthermore, uses of these drugs are extending to the treatment of cerebrovascular and peripheral vascular disease. This article provides an overview of the pharmacology of the glycoprotein IIa/IIIb antagonists and a commentary on the perioperative issues in patients receiving this class of drugs.

Platelet Physiology

Damaged endothelial surfaces associated with plaque rupture or fissure exposes highly thrombogenic components that induce platelet activation and initiate the coagulation cascade.[4] The glycoprotein IIb/IIIa receptor on the platelet surface is important for platelet aggregation. Platelet activation by exposure to vessel collagen and to thrombin generated by interaction of tissue factor

with plasma coagulation factors causes a conformational change in the glycoprotein IIb/IIIa receptor complex. Activated glycoprotein IIa/IIIb receptors become receptive to fibrinogen that, on binding to glycoprotein IIb/IIIa receptors located on two different platelets, builds the cross-link for platelet-to-platelet aggregation.[5] The initial thrombus contains a platelet-rich core (white thrombus) that may enlarge progressively from an increasingly large fibrin net that entraps erythrocytes and leukocytes to form the "red" thrombus. Blood flow declines as the thrombus develops, and interactions between additional platelet glycoprotein complexes (glycoprotein Ia/IIa with vessel wall collagen, glycoprotein Ic/IIa with fibronectin and laminin, and $\gamma\nu\beta3$ complex with vitronectin) enhance the adhesion of platelets to the vessel wall.

The changes in the plasma membrane of the adherent platelets activated by collagen and thrombin produce a negatively charged surface for factors IXa–VIIIa and Xa–Va complexes. This enhances the formation of the fibrin clot. Finally P-selectin and activated glycoprotein IIb/IIIa are exposed on the platelet surface, causing the platelet to bind to other platelets and leukocytes and recruit granulocytes and monocytes into the growing thrombus.

Structure and Function of the Glycoprotein IIb/IIIa Receptor

The platelet membrane glycoproteins are integrins (α and β subunits) that are found on virtually all cells.[6] The glycoprotein IIb/IIIa, an integrin (αIIb/β3 dimer) present on platelet surfaces, is a receptor for fibrinogen, fibronectin, vitronectin, von Willebrand factor, and thrombospondin. It mediates aggregation, adhesion, and spreading of platelets.[7,8] Platelet activation, associated with the release of agonists (epinephrine, serotonin, thromboxane A2) from the platelet-dense granules, leads to the recruitment of the internal pool of glycoprotein IIb/IIIa receptors, and this increases the number of surface receptors by 50%. The binding of prothrombin to glycoprotein IIb/IIIa enhances the conversion of prothrombin to thrombin.[9] Platelet activation increases the

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affinity for fibrinogen at the glycoprotein IIb/IIIa ligand-binding site by conformational changes and clustering of glycoprotein IIb/IIIa receptors on the platelet surface (known as "inside-out signaling"). This conformational change is mediated by chemical changes of the cytoplasmic domains of the α and β chains of the glycoprotein IIb/IIIa receptor.[7] The head domain of an intracellular protein, called talin, binds the intracellular part of integrin and regulates integrin function.[10] Agonist-stimulated increases in platelet cytosolic calcium concentration initiate actin filament turnover that removes cytoskeletal constraints on the glycoprotein IIb/IIIa receptor, leading to the binding for soluble fibrinogen and von Willebrand factor that mediate aggregation.[11,12] The bound ligand induces conformational changes in the receptor, exposing new binding sites, called ligand-induced binding sites. Although the exact role of the ligand-induced binding site has not been clearly defined, it is suggested the ligand-induced binding sites attract other glycoprotein IIb/IIIa receptors that merge on the platelet surface ("outside-in signaling"), resulting in clot retraction and the spread of platelets on an adhesive surface.[13]

Another integrin, the vitronectin receptor ($\alpha V/\beta 3$), shares the same β subunit with glycoprotein IIb/IIIa and cross-reacts with some glycoprotein IIb/IIIa antagonists and binds thrombospondin.[14] The vitronectin receptor is expressed in platelets as well as endothelial and smooth muscle cells.[15] Fibrinogen binds to the glycoprotein IIb/IIIa receptor, primarily through the terminal hexapeptide sequence chain [Lys-Gln-Ala-Gly-Asp-Val, (KQAGDV)] located at the carboxy terminus of the γ- of fibrinogen.[12] von Willebrand factor binds to platelets at the glycoprotein IIb/IIIa receptor *via* an arginine-glycine-aspartic acid sequence[3,16] and also at a glycoprotein Ib/V/IX receptor complex, enhancing platelet adhesion.[12]

Glycoprotein IIb/IIIa antagonists vary in their specificity for the glycoprotein IIb/IIIa ligand binding sites and their ability to block other receptors (*e.g.*, vitronectin receptor and Mac 1). Near total inhibition of aggregation (induced by 20 μM adenosine diphosphate [ADP]) is achieved when 80% or more of the receptors are blocked.[17]

Classification of Glycoprotein IIb/IIIa Antagonists

The development of a new class of drugs that block fibrinogen binding to the platelet glycoprotein IIb/IIIa receptors (the "final common pathway" of platelet activation) has raised the possibility that these potent agents may reduce thrombotic complications in acute coronary syndromes or after percutaneous coronary interventions (fig. 1). Abciximab (ReoPro®; Centocor Inc., Malvern, PA, and Eli Lilly Co., Indianapolis, IN) is a Fab fragment
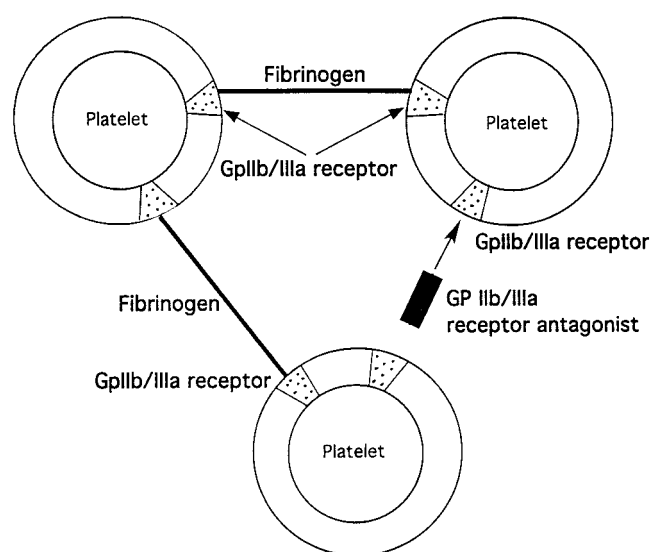

Fig. 1. Schematic overview of action of glycoprotein IIb/IIIa antagonists. GP = glycoprotein.

of a chimeric monoclonal antibody that binds nonspecifically to the glycoprotein IIb/IIIa receptor. Epifibatide (Integrilin®; COR Therapeutics, South San Francisco, CA), a cyclic heptapeptide, and tirofiban (Aggrastat®; Merck & Co., Whitehouse Station, NJ), a nonpeptide, selectively bind to the glycoprotein IIb/IIIa receptor (table 1).

Intravenous Antagonists

The first glycoprotein IIb/IIIa antagonists developed were murine monoclonal antibodies to the glycoprotein IIb/IIIa complex.[18] The structure of the antibody was modified by replacing the constant domain of the murine antibody with the corresponding human sequence, producing a chimeric compound that was less immunogenic. Abciximab is a Fab fragment of the chimeric human–murine monoclonal antibody, chimeric 7E3 immunoglobulin G, that contains murine variable regions

Table 1. Classification of Glycoprotein IIb/IIIa Antagonists

Type	Name	Route	Status
Monoclonal antibodies	Abciximab	Parenteral	ACS, PCI
Peptides	Eptifibatide	Parenteral	ACS, PCI
Small molecules	Tirofiban	Parenteral	ACS
	Lamifiban	Parenteral	ACS (phase III)
	Fradafiban	Parenteral	ACS (phase III)
	Xemilofiban	Oral	PCI (phase III)
	Orbofiban	Oral	ACS (phase III)
	Sibrafiban	Oral	ACS (phase III)
	Roxifiban	Oral	ACS (phase III)
	Lotrafiban	Oral	ACS, CBVD (phase II)
	Lefradifiban	Oral	ACS (phase II)
	SR121787	Oral	ACS (phase II)

ACS = acute coronary syndromes; PCI = percutaneous coronary interventions; CBVD = cerebrovascular disease.

Table 2. Properties of Approved Glycoprotein IIb/IIIa Antagonists

Property	Abciximab	Eptifibatide	Tirofiban
Chemical nature	Fab fragment of antibody	Peptide	Nonpeptide
Receptor specificity	Glycoprotein IIb/IIIa Vitronectin Mac-1	Glycoprotein IIb/IIIa	Glycoprotein IIb/IIIa
Receptor activity	Rapid onset High affinity Slow dissociation	Rapid onset Low affinity Rapid dissociation	Rapid onset Low affinity Rapid dissociation
Molecular weight	48,000 Da	832 Da	495 Da
Plasma half-life	10–26 min	1.5–2.5 h	1.2–2.5 h
Biologic half-life	12–24 h	2–4 h	2–4 h
Elimination	Plasma proteases	Renal	Renal (30–60%) Biliary (40–70%)

and human constant domains. It is prepared by papain digestion of purified chimeric 7E3 immunoglobulin G to produce the Fab fragments and the Fc domain. The Fab fragment is further purified to produce the final abciximab product (molecular weight = approximately 48,000 Da), which contains 439 amino acids comprising 50% murine sequences and 50% human sequences.

Eptifibatide, a peptide antagonist, is a small, cyclic heptapeptide (molecular weight = 832 Da) modeled after the Lys-Gly-Asp sequence of the active protein (barbourin) in the venom of the pygmy rattlesnake, *Sistrurus barbouri*. Conceptually, eptifibatide sits in the binding pocket between the IIb and IIIa arms of glycoprotein IIb/IIIa, thus preventing the binding of fibrinogen and thrombus formation.[19]

Tirofiban, a tyrosine derivative, is a nonpeptide molecule (molecular weight = 495 Da).[13] The Arg-Gly-Asp peptide sequence in fibrinogen and von Willebrand factor recognized by several integrins was the starting-point for its design. Lamifiban (molecular weight = 486 Da) is another nonpeptide glycoprotein IIb/IIIa receptor antagonist that is intravenously administered and reversible.[20] It is highly potent and is selective for the glycoprotein IIb/IIIa receptor, with a half-life of approximately 4 h.[21]

Oral Antagonists

Sibrafiban is an orally active prodrug that is converted in two enzymatic steps (by an esterase and an amidoxime reductase) to the active amidine compound Ro 44–3888 and is a selective glycoprotein IIb/IIIa receptor antagonist.[22]

Pharmacodynamics and Pharmacokinetics of the Approved Glycoprotein IIb/IIIa Antagonists

Abciximab inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive molecules to glycoprotein IIb/IIIa receptors on activated platelets. Glycoprotein IIb/IIIa inhibition is mediated by steric hindrance or conformational changes within glycoprotein IIb/IIIa to block access of large adhesive molecules. Abciximab also blocks the vitronectin receptor (located on endothelial cells, smooth muscle cells, and platelets) and the leukocyte receptor macrophage antigen-1 integrin (Mac-1 receptor) located on granulocytes and monocytes. The inhibition of vitronectin receptors interferes with cell adhesion, migration, and proliferation, and helps to transform the highly thrombogenic substrate (consisting of the disrupted plaque and the damaged endothelium with the superimposed thrombus) into a passive surface that does not interact with circulating platelets. The blocking of this vitronectin receptor may prevent restenosis in patients undergoing stenting.[13,23] The inhibition of Mac-1 receptors prevents the recruitment of monocytes to sites of vessel injury and inflammation and may play a role in its antithrombotic activity (table 2).[24]

The binding of abciximab to platelet glycoprotein IIb/IIIa receptor is a rapid high-affinity interaction, and the inhibitory effects are immediate (within minutes).[25,26] All glycoprotein IIb/IIIa receptors are blocked within 15 min with a bolus dose of abciximab (0.25 mg/kg) in humans,[25] and the free drug is degraded by proteases. The concentration of free abciximab is less than 4% of the administered dose 2 h after the bolus.[26] The plasma half-life of abciximab is 10–26 min, and resolution of glycoprotein IIb/IIIa blockade is related primarily to the turnover of platelets. A clinical implication of the pharmacodynamic and pharmacokinetic properties of abciximab is that partial reversal of this agent can be achieved by platelet transfusion.[26] The biologic or effective half-life of abciximab is approximately 12–24 h. Dose adjustment in renal disease is not required.[27] Twenty-four hours after administration of abciximab, 50–60% platelet receptors are still blocked.[25] However, abciximab can be detected on circulating platelets for more than 15 days, indicating platelet-to-platelet transfer, although platelet function recovers over the course of 48 h.[28] Abciximab prolongs the activated clotting time (ACT) by 30–80 s.[29] The activated partial thromboplastin time is

also prolonged as a result of inhibition of thrombin activation.[29]

Eptifibatide (a smaller molecule compared with abciximab) binds to the glycoprotein IIb/IIIa receptor between the IIb and IIIa arms of the extracellular parts of the receptor and prevents binding of fibrinogen. Eptifibatide has a plasma half-life of 2.5 h, with a rapid onset of action and a rapid reversibility of platelet inhibition.[30] Approximately 25% of eptifibatide in plasma is bound to plasma proteins, and the remaining 75% constitutes the pharmacologically active drug. Four hours after termination of an eptifibatide infusion, platelet aggregation recovers to approximately 70% of normal with the return of normal hemostasis.[26] Eptifibatide has a lower affinity for the glycoprotein IIb/IIIa receptor. The pharmacokinetics of eptifibatide are linear and dose-dependent for bolus doses ranging from 90 to 250 μg/kg and infusion rates from 0.5 to 3 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}. The recommended regimens (bolus followed by infusion) produce an early peak concentration, with a steady state achieved within 4–6 h. Doses should be reduced in patients with renal impairment as majority of the drug is eliminated renally. The elimination half-life of eptifibatide is 1.5–2.5 h. Eptifibatide typically prolongs the ACT by 40–50 s. When administered alone, eptifibatide has no measurable effect on prothrombin time or activated partial thromboplastin time.

Tirofiban occupies a binding pocket on the glycoprotein IIb/IIIa receptor and competitively inhibits platelet aggregation mediated by fibrinogen and von Willebrand factor. It has a high affinity for the glycoprotein IIb/IIIa receptor.[12,26] When administered as a 0.4-μg $\cdot$ kg^{-1} $\cdot$ min^{-1} infusion, greater than 90% receptor inhibition is achieved after 30 min. The elimination half-life of tirofiban is approximately 1.5–2.5 h and is cleared from the plasma by biliary elimination ($>$ 70%) and renal excretion. The plasma clearance of tirofiban is significantly decreased ($>$ 50%) in patients with creatinine clearance less than 30 ml/min.[12] It has been shown that the ACT is prolonged by 40–50 s in patients after administration of tirofiban.[26] Tirofiban is removed by hemodialysis.

The glycoprotein IIb/IIIa antagonistic actions of eptifibatide and tirofiban depend on the competitive inhibition of the receptor that occurs when these drugs are in equilibrium with the receptor. Therefore, the blood concentrations of eptifibatide and tirofiban determine the extent of glycoprotein IIb/IIIa antagonism. Platelet transfusions will have little effect to reverse these agents as the free drug in the plasma can effectively block their receptors.[26]

Clinical Trials

The efficacy of the glycoprotein IIb/IIIa antagonists in the treatment of acute coronary syndromes (unstable angina and non–Q wave MI), MI, and percutaneous cor-

onary interventions has been demonstrated in several multicenter trials. Current evidence is largely based on intravenous glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, and tirofiban) administered with aspirin and heparin. The trials have been the subject of several recent reviews,[2,3,12,13,17,24] including a metaanalysis.[31]

Abciximab Trials

The Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), the first large-scale trial to show a benefit of abciximab during percutaneous transluminal coronary angioplasty (PTCA) in 2,099 high-risk patients (severe unstable angina, evolving acute MI, or with high-risk coronary morphologic characteristics), reported that the composite rate of death, MI, or recurrent ischemia was reduced by 35% in patients receiving abciximab (a bolus and a 12-h infusion), from 12.8 to 8.3% ($P = 0.008$).[32] Three-year follow-up of patients in this trial demonstrated a sustained benefit with abciximab.[33] In lower-risk patients undergoing PTCA, the Evaluation in PTCA to Improve Long-Term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade (EPILOG) trial reported that the composite endpoint of death, MI, and urgent target vessel revascularization (TVR) at 30 days was reduced from 11.1 to 5.2% ($P < 0.001$), and this persisted through a 1-yr follow-up period.[34,35] The Chimeric Antiplatelet Therapy in Unstable Angina Refractory to Standard Medical Therapy study assessed the value of abciximab administered before PTCA in 1,265 patients with refractory unstable angina who underwent PTCA after receiving an initial 18- to 24-h period of abciximab treatment that was continued for 1 h after the intervention.[36] The rate of death, MI, or urgent TVR at 30 days was reduced from 15.9 to 11.3% with abciximab treatment ($P = 0.01$). Angiographic analysis of the patients in this study showed that abciximab facilitated thrombus resolution and reduced recurrent ischemia.[37,38] The ReoPro® [abciximab] and Primary PTCA Organization and Randomized Trial (RAPPORT) investigated the use of abciximab with PTCA in patients with acute MI of less than 12-h duration and reported that abciximab significantly reduced the incidence of death, reinfarction, or urgent TVR at all time points assessed (3.3 *vs.* 9.9% at 7 days, $P = 0.003$; 5.8 *vs.* 11.2% at 30 days, $P = 0.03$; and 11.6 *vs.* 17.8% at 6 months, $P = 0.05$).[39,40] The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) study, investigating the value of abciximab during coronary stenting, demonstrated that mortality was reduced from 2.4% in the stent placebo group to 1.0% in the stent abciximab group ($P = 0.04$).[41] The benefits of stenting (reducing the need for surgery) and abciximab (reducing death and MI) appeared complementary. The Abciximab with PTCA and Stent in Acute Myocardial Infarction trial examined the effects of abciximab therapy in 299 patients treated for acute MI (presenting within 12 h of the onset of symptoms) with

coronary stenting and showed that the 30-day primary composite clinical endpoint (death, MI, urgent TVR) was significantly reduced in the abciximab group (10.7% *vs.* 20% with placebo).[42] The Strategies for Patency Enhancement in the Emergency Department study was a small dose-escalation trial of the combination of reteplase, a thrombolytic agent, and abciximab in patients with acute MI presenting in the emergency department.[43] The study showed that abciximab in combination with thrombolytic therapy produced rapid improvements in reperfusion after acute MI. The Thrombolysis in Myocardial Infarction (TIMI)-14, a trial that used a combined abciximab, alteplase (half the usual dose), and lower-dose heparin regimen in patients with ST-segment elevation MI, showed that the treatment increased anterograde coronary blood flow without a significant increase in major bleeding.[44]

Eptifibatide Trials

The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT-II) trial, a double-blind, placebo-controlled trial investigating the efficacy of eptifibatide to prevent ischemic complications of percutaneous coronary intervention in patients undergoing elective, urgent, or emergency coronary angioplasty or stent, showed that the composite endpoint (death, MI, unplanned surgical or repeat percutaneous revascularization, or coronary stent implantation at 30 days after enrollment) was not significantly improved (11.4% in the placebo group to 9.2% in the eptifibatide 135–0.5 group [135 μg bolus plus 0.5 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} infusion], P = 0.063; and 9.9% in the eptifibatide 135–0.75 group [135 g bolus plus 0.75 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} infusion], P = 0.22).[45] The Platelet Glycoprotein IIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin Therapy study examined the effect of a combination of eptifibatide, aspirin, and heparin treatment in 10,948 patients with non–ST-segment acute coronary syndromes who presented with ischemic chest pain within the previous 24 h.[46] The primary endpoint (death and nonfatal MI occurring up to 30 days after the index event) was reduced from 15.7 to 14.2% by eptifibatide (P = 0.04). The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis in Acute Myocardial Thrombosis trial, a dose-ranging study combining eptifibatide with heparin, aspirin, and alteplase in 132 patients, reported that the highest eptifibatide dose group had higher TIMI grade 3 flow (normal flow in infarct related coronary artery) compared with placebo-treated patients (66 *vs.* 39%, P = 0.006).[47]

The Enhanced Suppression of Platelet Glycoprotein IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial reported the efficacy of adjunctive double bolus eptifibatide therapy in reducing ischemic complications of nonurgent coronary stent implantation at 48 h and at 30 days.[48] Preliminary results of the ESPRIT study showed that the combined endpoint (death, MI, need for urgent target vessel revascularization, or crossover to glycoprotein IIb/IIIa inhibitor therapy within 48 h) was reduced from 10.5% in placebo patients to 6.65% in the eptifibatide group, a 37% risk reduction with treatment based on analysis of 2,064 patients. At 6 months, eptifibatide reduced the combined incidence of death, MI, or the need for repeat TVR by 22%. There was also a 35% relative risk reduction in the incidence of death or MI over 6 months (from 11.5% in placebo group to 7.5% in the eptifibatide group) after stenting. MI was lowered by 33% (P = 0.00047).

Tirofiban Trials

The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial reported a significant reduction in early ischemic events at 2 days, from 8.7 to 5.4% (P = 0.005), but by 30 days this reduction was no longer significant.[49] The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial reported that the rate of 48-h death, MI, or refractory ischemia was reduced from 5.6 to 3.8% with tirofiban compared with heparin (P = 0.01) in patients with unstable angina.[50] There was no significant difference for the composite endpoint at 30 days. In the PRISM in Patients Limited by Unstable Signs and Symptoms trial, 1,915 patients limited by unstable signs and symptoms were randomized to three groups to receive either tirofiban, heparin, or both tirofiban and heparin over 72 h, during which coronary angiography and angioplasty were performed after 48 h if indicated.[51] The tirofiban group was discontinued early because of increased mortality at 7 days. This unexpected finding was considered to be a result of chance because the number of events was small.[51] Another explanation could be the need for concomitant thrombin inhibition for optimal efficacy of tirofiban.[21] The combined primary endpoint in the tirofiban-plus-heparin group was lower than that in the heparin-only group at 30 days (18.5 *vs.* 22.3%, P = 0.03) and at 6 months (27.7 *vs.* 32.1%, P = 0.02).

Results of ongoing trials comparing early and late revascularization in patients with unstable angina treated with aspirin, heparin, and tirofiban (Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival trial) and aggressive lipid reduction therapy (Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation trial) will provide additional insights into the timing of angiography, intervention, and adjunct pharmacology best suited for patients with unstable angina.[52] In the Do Tirofiban and ReoPro Give Similar Efficacy Outcomes trial, the use of tirofiban in percutaneous coronary interventions was ruled out as it was associated with a higher number of adverse cardiac outcomes compared with abciximab.[53]

Lamifiban Trials

The Canadian Lamifiban trial demonstrated that lamifiban infusion over 72–120 h reduced the risk of death, nonfatal MI, or the need for an urgent revascularization during the infusion period, from 8.1 to 3.3% (P = 0.04).[21] The Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network trial compared two dosages of lamifiban, with or without heparin, with placebo, and heparin and showed that low-dose lamifiban appeared to be efficacious in 2,282 patients with unstable angina or non–Q-wave MI.[54] However, the higher dose was not superior to the lower dose, suggesting a narrow therapeutic window for lamifiban. The Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction trial showed no obvious clinical benefits with lamifiban over placebo in patients with ST segment elevation acute MI when combined with streptokinase or tissue plasminogen activator.[55]

Metaanalysis of the Parenteral Glycoprotein IIb/IIIa Antagonist Trials

A systematic overview (metaanalysis) using an empirical Bayesian random-effects model to assess the effect of parenteral abciximab, epifibatide, tirofiban, and lamifiban on death, MI, and revascularization in ischemic heart disease was conducted in 16 randomized controlled trials (involving 32,135 patients) of these glycoprotein IIb/IIIa antagonists.[31] The parenteral glycoprotein IIb/IIIa antagonists significantly reduced mortality at 48–96 h (odds ratio, 0.70; 95% confidence interval, 0.51–0.96; P < 0.03), equivalent to a reduction of 1 death per 1,000 patients treated. However, mortality benefits at 30 days (odds ratio, 0.87; 95% confidence interval, 0.74–1.02; P = 0.08) and 6 months (odds ratio, 0.97; 95% confidence interval, 0.86–1.10; P = 0.67) were not statistically significant. Glycoprotein IIb/IIIa antagonists provided a highly significant benefit for the combined endpoint of death or MI at both time points. There were 20 fewer deaths or MIs per 1,000 patients treated at 30 days. For the composite endpoint of death, MI, or revascularization, there was also a highly significant benefit for the glycoprotein antagonists, with an odds ratio of 0.77 (95% confidence interval, 0.68–0.86; P < 0.001) or 30 fewer deaths per 1,000 patients treated. A sustained absolute improvement was shown as the risk differences for death or MI, and the composite outcomes were similar at 6 months. The metaanalysis concluded that the parenteral glycoprotein IIb/IIIa antagonists provided a consistent and sustained therapeutic benefit on death, MI, and revascularization in the patients with ischemic heart disease.

Oral Glycoprotein IIb/IIIa Antagonists Trials

The Sibrafiban *vs.* Aspirin to Yield Maximum Protection from Ischemic Heart Events Postacute Coronary Syndromes trial showed that there was no reduction in the 90-day primary endpoint (death, nonfatal infarction or reinfarction, severe recurrent ischemia) in 9,233 patients with acute coronary syndromes (randomized to receive aspirin or high–low-dose sibrafiban).[56] The Orbofiban in Patients with Unstable Coronary Syndromes trial was stopped because of excessive mortality in the group receiving orbofiban.[57] The Evaluation of Xemilofiban in Controlling Thrombotic Events trial evaluated the effect of xemilofiban in patients undergoing percutaneous coronary interventional procedures.[58] Mortality was higher in the patients receiving xemilifiban compared with placebo (0.7 *vs.* 0.3%, P = 0.048). The Blockage of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion trial, investigating the effects of lotrafiban (a selective, nonpeptide antagonist) in patients who had a recent MI, unstable angina, transient ischemic attack, or ischemic stroke, or who presented at any time after a diagnosis of peripheral vascular disease combined with either cardiovascular or cerebrovascular disease has been closed after excess mortality was recorded among 9,000 atherosclerotic patients after a 1-yr follow-up period.[59,60] There are several explanations for the lack of efficacy of the oral glycoprotein IIb/IIIa antagonists. The bioavailability of the oral antagonists is limited (5–25%), and many of them have a short half-life with an intermediate-to-fast receptor dissociation rate. Despite a high receptor affinity for the glycoprotein IIb/IIIa receptors, the oral glycoprotein IIb/IIIa antagonists may not achieve the desired 80% inhibition of ADP–induced aggregation. Further low plasma drug concentrations may paradoxically induce aggregation because of a change of the glycoprotein IIb/IIIa receptors from a nonactivated to an activated state, as indicated by the higher expression of P-selectin and thromboxane-A_2 formation.[60]

Thrombocytopenia and Bleeding Associated with Glycoprotein IIb/IIIa Antagonists in the Nonsurgical Setting

Thrombocytopenia may be suspected from bleeding symptoms or discovered by routine blood testing in a person without symptoms. Many large studies have shown that spurious low platelet counts, a phenomenon known as pseudothrombocytopenia, are associated with the anticoagulant EDTA used routinely in hematology.[26] EDTA-dependent pseudothrombocytopenia occurs in 0.1% of a general hospital population. The phenomenon is thought to be the result of an altered conformation of platelet membrane glycoproteins or anionic phospholipids after exposure to EDTA and cold temperature, leading to the binding of various immunoglobulins (immunoglobulin G, M, or A) that promote platelet aggregation. In some patients, antibodies against the IIb fraction of the glycoprotein IIb/IIIa complex have been discovered. It is

Table 3. Bleeding, Thrombocytopenia, and Blood Transfusion in Trials (> 400 Patients)

Trial	Randomized to	Major Bleeding*		Blood Transfusion		Platelets < 100 × 10⁹/l		Platelets < 50 × 10⁹/l		Platelet Transfusion	
		%	P Value	%	P Value	%	P Value	%	P Value	%	P Value
EPIC	Placebo	7		7		3.4		0.7		3	
	Abciximab bolus	11	0.001	13	< 0.001	3.6				4	
	Abciximab infusion	14	0.001	15	< 0.001	5.2		1.6		6	
EPILOG	Placebo	3.1		3.9		1.5		0.4		1.1	
	Abximab–heparin (std)	3.5	0.7	3.3	0.46	2.6		0.9	0.26	1.6	0.32
	Abximab–heparin (low)	2	0.19	1.9	0.013	2.5		0.4		0.9	0.81
CAPTURE	Placebo	1.9*		3.4†		1.3		0.3		0.3	
	Abciximab	3.8*	0.043	7.1†	0.005	5.6		1.6		2.1	
RAPPORT	Placebo	9.5		7.9‡							
	Abciximab	16.6	0.02	13.7‡	0.04						
EPISTENT	Stent–placebo	2.2		2.2§							
	Stent–abciximab	1.5		2.8§							
	Balloon–abciximab	1.4		3.1§							
TIMI-14	Alteplase	6				3		0.6			
	Abciximab	3				6	0.1	1.2	0.1		
	Alteplase–abciximab	7									
	Streptk–abciximab	10									
IMPACT-II	Placebo	4.8		5.2						1.3	
	Eptifibatide 135/0.5	5.1		5.6						1.5	
	Eptifibatide 135/0.75	5.2		5.9						1.3	
PURSUIT	Placebo	9.1		9.2		6.7		< 0.1			
	Eptifibatide	10.6	0.02	11.6		6.8		0.2			
RESTORE	Placebo	2.1		2.2‖		0.9		0.1			
	Tirofiban	2.4	0.662	3.5‖		1.1		0.2			
PRISM	Heparin	0.4		1.4		0.4		0.1			
	Tirofiban	0.4		2.4		1.1	0.04	0.4	0.04		
PRISM-PLUS	Heparin	0.8		2.8		0.8		0.3			
	Heparin–tirofiban	1.4	0.23	0.4	0.21	1.9	0.07	0.5	0.44		
PARAGON-A	Placebo	0.8		4.4		1.1					
	Lamifiban (low)	0.7		4.4		1.5					
	Lamifiban (high)	1.8		8.7		1.3					
SYMPHONY	Aspirin	3.9		4.6		2.5		0.5		0.9	
	Sibrafiban (low)	5.2		5.9		2.6		0.6		1.1	
	Sibrafiban (high)	5.7		6.3		2.8		0.6		1.2	
OPUS-TIMI 16	Placebo	0.4									
	Orbofiban 50/30	1.2									
	Orbofiban 50/50	0.7									
EXCITE	Placebo	1.4		1.1		4.3					
	10 mg Xemilofiban	3.3	< 0.001	3.2	< 0.001	4.5	0.76				
	20 mg Xemilofiban	4.3	< 0.001	4.5	< 0.001	5.8	0.02				

* TIMI criteria for major bleeding = intracranial hemorrhage or a decrease in hemoglobin of greater than 5 g/dl. † Not including bleeding during coronary arterial bypass graft surgery. ‡ Stated in article as "blood products." § Erythrocytes and platelets (includes bleeding during coronary artery bypass graft surgery). ‖ Only patients receiving more than 2 units of blood.

EPIC = Evaluation of GPIIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications; EPILOG = Evaluation in PTCA to Improve Long-term Outcome with GPIIb/IIIa Blockade; CAPTURE = Chimeric Antiplatelet Therapy in Unstable Angina Refractory to Standard Medical Therapy; RAPPORT = ReoPro and Primary PTCA Organization and Randomized Trial; EPISTENT = Evaluation of Platelet GPIIb/IIIa Inhibitor for Stenting; TIMI-14 = Thrombolysis in Myocardial Infarction 14; IMPACT-II = Integrlin to Minimize Platelet Aggregation and Coronary Thrombosis II; PURSUIT = Platelet GPIIb/IIIa in Unstable Angina Receptor Suppression Using Integrelin Therapy; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis; PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management; PARAGON = Platelet GPIIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network; SYMPHONY = Sibrafiban *versus* Aspirin to Yield Maximum Protection from Ischemic Heart Events Post Acute Coronary Syndromes; OPUS = Orofiban in Patients with Unstable Coronary Syndromes; EXCITE = Evaluation of Xemilofiban in Controlling Thrombotic Events; heparin (std) = initial bolus of 100 U/kg heparin before interventional procedure, with additional weight-adjusted boluses to achieve and maintain an activated clotting time greater than 300 s.

important to differentiate true thrombocytopenia from pseudothrombocytopenia. In 0.1–0.5% of patients, severe thrombocytopenia (platelet count < 20 × 10⁹/l) occurs after intravenous administration of glycoprotein IIb/IIIa inhibitors in the nonsurgical setting (table 3).[26] Abciximab causes thrombocytopenia (< 50 × 10⁹/l) in 0.4–1.6% patients, and this can occur after a single dose. In trials with other glycoprotein IIb/IIIa antagonists, the incidence of thrombocytopenia is generally lower than 1%.[26] Thrombocytopenia usually occurs within hours of exposure and resolves on discontinuation of the drug, rarely requiring platelet transfusion unless accompanied by active bleeding.

Kereiakes *et al.*[61] pooled data from the EPIC, EPILOG, and EPISTENT studies and reported that the factors associated with thrombocytopenia were age greater than

65 yr, weight less than 90 kg, baseline platelet count ($< 200 \times 10^9$/l), abciximab therapy, and enrollment into the EPIC trial. Both bleeding and transfusion events were more frequent in patients with thrombocytopenia. In these trials, patients who developed thrombocytopenia had increased mortality rates. However, among patients with thrombocytopenia, those who received prophylactic abciximab had better clinical outcomes, including survival.

Acute idiosyncratic as well as delayed immune-mediated mechanisms causing thrombocytopenia have been postulated.[62] It is suggested that thrombocytopenia associated with abciximab occurs because antibodies that recognize epitopes on mouse immunoglobulin G are still present on the chimeric Fab fragments, causing increasing platelet clearance by the reticuloendothelial system. It is suggested that lower-molecular-weight antagonists (*e.g.*, sibrafiban) may cause thrombocytopenia by inducing neoepitopes on glycoprotein IIb/IIIa receptors (the ligand-induced binding sites) that are recognized by the immune system.[24]

A platelet count should be obtained soon after commencing abciximab therapy as acute severe thrombocytopenia can occur within 2 h of drug administration. Pseudothrombocytopenia, caused by constituents of the laboratory reagents, is an important differential diagnosis in the sudden onset of thrombocytopenia in patients treated with abciximab.[63] Steigler *et al.*[64] described a case in which the patient's platelet concentration in blood anticoagulated with edetic acid decreased to 119×10^9/l with a further decrease to 57×10^9/l at the end of a 12-h infusion of abciximab.[64] Platelet aggregates were observed by microscopic examination of the blood smear. However, normal platelet concentrations within the reference range were obtained when repeat platelet counts using citrate-anticoagulated samples were performed. Current recommended management of thrombocytopenia associated with the glycoprotein IIb/IIIa inhibitors includes the immediate cessation of the glycoprotein IIb/IIIa antagonist and, in severe cases, platelet transfusions. In cases with associated bleeding, other anticoagulants and antiplatelet drugs should be stopped and possibly reversed. For cases of immune-mediated thrombocytopenia, there may be a place for intravenous immunoglobulin G.

Catastrophic bleeding associated with glycoprotein IIb/IIIa antagonist treatment does not appear to be an issue.[26] Across all clinical trials, the rates of life-threatening bleeding and intracranial hemorrhage were less than 0.2%, and the most common bleeding site was the vascular access site. In the EPIC trial, treatment with abciximab was associated with rates of bleeding (TIMI trial criteria) from 7 to 14% and blood transfusion from 10 to 21% compared with placebo. Because all patients in this trial received a similar initial dose (10,000–12,000 nU) of heparin, more heparin (on a per-kilogram basis)

was administered as the patient's body weight decreased. Regression analysis indicated that this single factor accounted for the excess in bleeding in the EPIC trial. The high incidence of bleeding (16.6%) associated with abciximab in the RAPPORT study reflects the higher levels of anticoagulation used during and after the procedure, and the long interval between angioplasty and sheath removal.[39] These finding were supported by the results of the eptifibatide (IMPACT II) and tirofiban (RESTORE) trial, in which weight-adjusted heparin doses were used, resulting in rates of major bleeding that were comparable to placebo.[45,49]

Several strategies have been recommended to reduce the risk of major hemorrhage (defined as presence of ≥ 1 of the following: intracranial hemorrhage, reduction of hematocrit greater than 15% baseline, or a decrease in hemoglobin greater than 5 g^{-1}) associated with glycoprotein IIb/IIIa receptor antagonists. There is increasing evidence that the bleeding risk is related more to the dose of heparin administered.[26] Lower doses of heparin (administered on a body-weight basis and closely monitored by ACT or activated partial thromboplastin time) and early sheath removal have now been shown to reduce bleeding complications.[26] In the EPILOG study, major bleeding occurred in 3.1% of patients treated with placebo, but only in 2.0% of patients receiving abciximab and low-dose heparin ($P = 0.19$).[34,35] Only the anterior wall of the femoral artery should be punctured during femoral sheath placement and, before removing the sheath, heparin should be discontinued for 3–4 h with the ACT less than 180 s or the activated partial thromboplastin time less than 45 s. Other arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation, and nasogastric tubes should be minimized. Noncompressible sites (*e.g.*, subclavian veins) should be avoided when obtaining intravenous access.

Monitoring of Platelet Inhibition

Monitoring of platelet inhibition caused by glycoprotein IIb/IIIa antagonists is important for quantifying dose requirements in the acute and chronic administration of these drugs. Template bleeding times are poorly standardized, and recent evidence does not support the use of template bleeding times as a prognostic indicator of hemorrhagic events.[62] It has been shown that the ACT is prolonged after glycoprotein IIb/IIIa administration. However, the ACT may not be the best method of assessing the adequacy of anticoagulation in patients who have received glycoprotein IIb/IIIa antagonists because it is also affected by other factors such as fibrinogen concentrations, platelet count, hemodilution, and hypothermia. Coller[65] reviewed the subject of platelet monitoring during glycoprotein IIb/IIIa antagonist therapy

with respect to measuring plasma drug concentrations, percentage of receptor blockade by the drug, or the effect of the drug on platelet function. Preoperative measurement of the degree of receptor blockade by glycoprotein IIb/IIIa antagonists may help to avoid unnecessary blood product transfusion and prevent excessive bleeding, but this is not routinely available. Plasma concentrations of abciximab do not provide good correlation of platelet inhibition because abciximab has a high affinity to the platelet glycoprotein IIb/IIIa receptor and is rapidly cleared from the plasma.[65] However, plasma concentrations of the orally active glycoprotein IIb/IIIa antagonists may be useful, as demonstrated in the TIMI-12 trial when plasma sibrafiban concentrations were well correlated with the degree of platelet inhibition.[66]

The most widely used method for monitoring the effects of platelet function is turbidometric aggregometry using citrated platelet-rich plasma. This method, which measures the change in light absorbance as the platelets aggregate when activated by agonists such as collagen and ADP, is operator dependent, requires baseline measurements before glycoprotein IIb/IIIa administration to assess the changes in platelet function from baseline, and may be also affected by different preparations of platelet-rich plasma. Calcium ion chelation caused by citrate anticoagulation can artifactually enhance the inhibition observed with some glycoprotein IIb/IIIa antagonists such as eptifibatide in *ex vivo* measurements.[65,67] No data are available on the effects of reduced ionized calcium on the inhibitory actions of abciximab, tirofiban, and lamifiban. Aggregation data involving glycoprotein IIb/IIIa antagonists may be best monitored using blood samples anticoagulated with thrombin inhibitors such as PPACK (D-phenylalanyl-prolyl-arginine-chloromethylketone) or hirudin.[12] Mascelli *et al.*[68] described a simple technique of whole blood aggregometry that measured aggregation by changes in electrical impedance, and this method may be easily used in the perioperative setting.

Assessment of glycoprotein IIb/IIIa receptor occupancy can be determined by the use of D3 monoclonal antibody binding assay described by Jennings and White.[69] When the percentage of blocked receptors decreases to less than approximately 80%, the ability of the platelets to aggregate and the bleeding time normalize.[26] This forms the basis for the recommendation that platelets be transfused to reverse the abciximab effect.[2,3,26]

Another method of assessing glycoprotein IIb/IIIa receptor blockade is based on the ability of platelets in whole blood to agglutinate fibrinogen-coated beads when activated by a thrombin receptor-activating peptide.[70] This semiquantitative assay was further improved using a microprocessor-controlled, whole blood, cartridge-based technique that provided a quantitative digital display, with a good correlation with traditional tur-

bidimetric platelet aggregometry (using 20 μM ADP) using citrated platelet-rich plasma and radiometric binding assays of glycoprotein IIb/IIIa receptor occupancy.[71] However, these turbidimetric techniques are complex and may not be applicable in the perioperative setting.

Madan *et al.*[72] recently described the use of a platelet function analyzer (PFA-100®; Dade Behring, Miami, FL) that evaluates platelet function by determining the time needed to close an aperture in a membrane coated with collagen and either adenosine (50 μg ADP) or epinephrine (10 μg) as whole blood flows during shear stress conditions. Platelet aggregation causes aperture occlusion. This simple bed-side test yields results similar to those determined by platelet aggregometry as well as receptor occupancy measurements and may gain applicability for perioperative assessment of platelet function.

Thromboelastography may provide useful information about the interaction between platelet aggregates and the soluble components of the coagulation cascade, including the effects of glycoprotein IIb/IIIa antagonists on this interaction, and is used to monitor treatment with abciximab in heparinized patients.[73,74] However, the relations between the specific levels of platelet inhibition and clinical efficacy and safety have not been fully established.

Glycoprotein IIb/IIIa Antagonism and Coronary Artery Bypass Graft Surgery

Abrupt vessel closure can occur in up to 8% of patients undergoing coronary artery angioplasty, causing the majority of periprocedural deaths and acute MI, and is the main reason for urgent surgical intervention (table 4).[75] The incidence of emergency coronary artery bypass graft surgery after coronary stenting procedures has been less than 1% since 1995.[76] Evidence from the aforementioned trials indicate that, in general, the number of patients that require emergency surgery is actually reduced by glycoprotein IIb/IIIa antagonists. However, if the patients required emergency surgery, they are at increased risk of major bleeding (defined as requiring transfusion $\geq$ 2 units) compared with patients having elective surgery.[75] The incidence of urgent coronary artery bypass graft surgery in the aforementioned trials are outlined in table 3.

Boehrer *et al.*[77] analyzed the 2.8% of patients in the EPIC trial who underwent emergency bypass surgery. Erythrocyte transfusions were administered to 88% of patients who received abciximab, and 79% required platelet transfusions, but this was not statistically different than the placebo group. The median duration from administration of abciximab to surgery was more than 24 h, by which time platelet function would have normalized. It was also observed that the incidence of thrombocytopenia was less in the groups that received

Table 4. Frequency of Coronary Bypass Graft Surgery in Trials of Glycoprotein IIb/IIIa Antagonists

Trial	Randomized to	Urgent CABG (%)	Nonurgent CABG (%)
EPIC	Placebo	3.6	
	Abciximab bolus	2.3	
	Abciximab infusion	2.4 ($P = 0.177$)	
EPILOG	Placebo	1.7	
	Abciximab–heparin (std)	0.9	
	Abciximab–heparin (low)	0.4 ($P = 0.007$)	
CAPTURE	Placebo	1.7	1.4
	Abciximab	1.0 ($P > 0.1$)	0.6 ($P > 0.1$)
EPISTENT	Stent–placebo	1.1	
	Stent–abciximab	0.8	
	Balloon–abciximab	0.6	
IMPACT-II	Placebo	2.8	
	Eptifibatide 135/0.5	1.6	
	Eptifibatide 135/0.75	2.0	
PURSUIT	Placebo		14.3*
	Eptifibatide		13.9*
RESTORE	Placebo	1.4	0.7
	Tirofiban	0.9 ($P = 0.315$)	0.7
PRISM	Heparin		16.5*
	Tirofiban		18.1*
PRISM-PLUS	Heparin	3.4	
	Heparin–tirofiban	2.5	
PARAGON-A	Placebo		11
	Low-dose lamifiban		12
	High-dose lamifiban		12

* Total coronary arterial bypass graft surgery at 30 days.

EPIC = Evaluation of GPIIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications; EILOG = Evaluation in PTCA to Improve Long-term Outcome with Abciximab GPIIb/IIIa Blockade; CAPTURE = Chimeric Antiplatelet Therapy in Unstable Angina Refractory to Standard Medical Therapy; EPISTENT = Evaluation of Platelet Inhibitor for Stenting; IMPACT-II = Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis II; PURSUIT = Platelet GPIIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin Therapy; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis; PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PARAGON-A = Platelet GPIIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network; heparin (std) = initial bolus of 100 U/kg heparin before interventional procedure, with additional weight-adjusted boluses to achieve and maintain an activated clotting time greater than 300 s.

abciximab, suggesting a protective effect of glycoprotein IIb/IIIa blockade against platelet activation during cardiopulmonary bypass.[75] Topol et al.[78] reviewed the requirement for emergency surgery in all 6,595 patients undergoing percutaneous coronary revascularization in the EPIC, EPILOG, and EPISTENT trials, and demonstrated that the need for emergency bypass surgery was reduced by 53% with the use of abciximab. There was no difference in the incidence of major bleeding (defined as a hemoglobin loss of > 5 g) in the two groups (82% in the placebo group vs. 87.5% in the abciximab group; $P = 0.62$)

Heparin requirements during cardiopulmonary bypass should be adjusted in patients who received recent glycoprotein IIb/IIIa inhibitor therapy. Patients on abciximab therapy in the EPIC trial required a 10% reduction in heparin dose to achieve a target ACT between 300 and 350 s. Information of the different heparin regimens on postoperative blood loss associated with glycoprotein IIb/IIIa inhibitor treatment is limited. Kereiakes et al.[61] reported that standard heparin dose before cardiopulmonary bypass resulted in excessive blood loss in abciximab-treated patients. However, Lemmer et al.[79] reported no increased in the frequency of blood transfusion in 12 cardiac surgical patients who received 450 IU/kg heparin before bypass and routine platelet transfusion after protamine administration. Prospective randomized clinical trials are needed to determine the optimal heparin dose for cardiopulmonary bypass after use of glycoprotein IIb/IIIa antagonists.

In a review[80] of 11 consecutive patients who required emergency cardiac surgery after failed angioplasty or stent placement associated with abciximab, the time from the cessation of administration of abciximab to surgery was critical in influencing the degree of bleeding and coagulopathy after cardiopulmonary bypass. On the basis of the pharmacodynamics of abciximab, the patients were classified into early (cardiac operation < 12 h after abciximab administration; n = 6) and late (cardiac operation > 12 h after abciximab administration; n = 5) groups. The median values for postoperative chest drainage (1,300 vs. 400 ml; $P < 0.01$), packed erythrocytes transfused (6 vs. 0 packs; $P = 0.02$), platelets transfused (20 vs. 0 packs; $P = 0.02$), and maximum ACT (800 vs. 528 s; $P = 0.01$) were significantly greater in the early group compared with the late group. Heparin (300 U/kg) was administered during bypass to maintain ACT at greater than 400 s. However, the median

maximum ACT was 800 s in the early group compared with 528 s in the late group. Large quantities of platelets were required to reverse the coagulopathy associated with abciximab. In the six patients who underwent surgery within 12 h of administration, the mean number of platelet transfusions was 34 units. As patients receiving abciximab experience platelet dysfunction for 12–24 h after termination of the infusion, it would seem prudent that surgery should be delayed for at least 12–24 h after abciximab if the patient's cardiac status permits. Surgery should be delayed for 4–6 h to reduce the risk for increased bleeding in patients who have received eptifibatide or tirofiban.

Assessment of platelet function using platelet turbidometric aggregometry or the platelet function analyzer PFA-100[®] may be useful in patients who have received glycoprotein IIb/IIIa antagonists before anesthesia and surgery. Measurements of receptor occupancy may not be reliable because most patients treated with abciximab show normalized platelet function (at 24 h) despite moderate levels of receptor occupancy, suggesting dissociation between occupancy and function.[72] Coronary revascularization surgery using off-pump coronary artery surgical techniques may be beneficial in patients receiving glycoprotein IIb/IIIa treatment to avoid the hemodilution, platelet dysfunction, and changes in glycoprotein IIb/IIIa receptors associated with cardiopulmonary bypass that predispose to postoperative bleeding.

In a recent study, Koster *et al.*[81] reported the combined use tirofiban and unfractionated heparins for anticoagulation during cardiopulmonary bypass in 10 cardiac surgical patients with heparin-induced thrombocytopenia type II, the presence of heparin-induced thrombocytopenia type II antibodies, and renal impairment. A bolus dose of 10 μg/kg tirofiban followed by a continuous infusion of 0.15 μg · kg^{-1} · min^{-1} was administered. Five minutes after the bolus dose of tirofiban (400 IU/kg), unfractionated heparin was administered with a target ACT of approximately 480 s. There was no increase in postoperative bleeding and no thromboembolic complications. The investigators suggested that the combination of unfractionated heparins and tirofiban may be an alternative to other anticoagulation strategies in patients with heparin-induced thrombocytopenia.

The pharmacodynamics of the individual drugs are important in understanding their reversal. The biologic half-life of abciximab is 12–24 h compared with its short plasma half life (10–15 min), because it remains tightly bound to the receptor. Little drug exists in the plasma compartment and unblocked glycoprotein IIb/IIIa receptors on the infused platelets would be available, diluting the effect of abciximab.[25] Rapid redistribution of previously bound abciximab lowers the overall percentage of inhibited platelet glycoprotein IIb/IIIa receptors. Several investigators recommend that an early prophylactic

platelet transfusion may be useful in patients who have received abciximab.[26,75] However, prophylactic platelet transfusion is not effective or useful for patients on eptifibatide or tirofiban undergoing cardiopulmonary bypass.[26] In the setting of emergency bypass surgery and abciximab, reduction in initial heparin dosing is controversial but may be theoretically advisable and should be titrated to the target ACT. Prophylactic platelet transfusion should be considered as the patient on abciximab is weaned off cardiopulmonary perfusion.

Summary

The glycoprotein IIb/IIIa antagonists represent an important new class of drugs with increasing use in acute ischemic coronary syndromes and more recently episodic cerebral ischemia. Emergent surgery may be required after complications or failure of interventional cardiologic procedures for acute coronary syndromes and MI in patients treated with these drugs. Platelet function analyzers may provide a reliable means of assessing residual antiplatelet effects perioperatively. If the patient's clinical condition permits, a delay of surgery for at least 12 h after administration of abciximab and 4–6 h after administration of eptifibatide or tirofiban would appear prudent. Prophylactic platelet transfusion may be useful to reduce bleeding after abciximab but is not efficacious in patients who have received eptifibatide or tirofiban treatment. There are many issues concerning the perioperative risk in patients who have received glycoprotein IIb/IIIa antagonists that remain unresolved. Literature concerning the safety of performing central neuraxial regional blockade (spinal or epidural anesthesia) in these patients is not available. Avoiding spinal or epidural anesthesia in patients recently treated with glycoprotein IIb/IIIa inhibitors would appear wise. The role of antifibrinolytics (*e.g.*, aprotinin) in this setting remains to be defined. An understanding of the pharmacology of the glycoprotein IIb/IIIa antagonists is essential for the optimal perioperative and intraoperative management of patients recently treated with glycoprotein IIb/IIIa antagonists.

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