Review of Currently Available GP IIb/IIIa Inhibitors and Their Role in Peripheral Vascular Interventions

P. Anondo Stangl, M.D.,[1] and Sara Lewis, M.D.[1]

ABSTRACT

The glycoprotein IIb/IIIa (GP IIb/IIIa) antagonists are the most recent additions to the antiplatelet agents available to the interventional radiologist. The currently available GP IIb/IIIa antagonists are abciximab, eptifibatide, and tirofiban. These medications have demonstrated excellent safety and efficacy in the setting of coronary arterial interventions. The fundamental benefit of the GP IIb/IIIa antagonists lies in their unique mechanism of action: the ability to prevent platelet aggregation, thrombus formation, and distal thromboembolism while preserving initial platelet binding to damaged vascular surfaces. A paucity of data exists regarding the role of GP IIb/IIIa inhibitors in peripheral vascular interventions. The GP IIb/IIIa antagonists would theoretically provide excellent antiplatelet therapy in patients undergoing any of a variety of endovascular interventions during which thrombosis or thromboembolism may endanger distal perfusion in patients with peripheral vascular disease. The goal of this summary is to review the indications for use, pharmacology, and evidence for efficacy of the GP IIb/IIIa antagonists in hopes of translating these data for application in the peripheral arterial circulation. Further research is necessary to determine how these agents may be safely used in combination with other anticoagulants or with stents, efficacy compared with standard regimens, success at preventing distal thromboembolism, and cost effectiveness.

KEYWORDS: Glycoprotein IIb/IIIa antagonist, peripheral vascular intervention, platelet aggregation, thromboembolism, anticoagulation

Objectives: Upon completion of this article, the reader should be able to list the mechanism of action, indications, adverse effects, and evidence for the efficacy of the glycoprotein IIb/IIIa antagonist class of anticoagulants.

Accreditation: Tufts University School of Medicine (TUSM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit: Tufts University School of Medicine designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

[1]Department of Radiology, Mount Sinai Medical Center, One Gustave L. Levy Place, New York.

Address for correspondence and reprint requests: P. Anondo Stangl, M.D., Interventional Radiologist, Department of Vascular Therapy, Kaiser Permanente Colorado, 2045 Franklin Street, Denver, CO 80205 (e-mail: anondostangl@gmail.com).

Pharmacology in Interventional Radiology; Guest Editors, Kimi L. Kondo, D.O. and Charles E. Ray, Jr., M.D.

Semin Intervent Radiol 2010;27:412–421.

DOI: http://dx.doi.org/10.1055/s-0030-1267856.
ISSN 0739-9529.

Endovascular treatment has become a mainstay of treatment for patients with peripheral arterial disease (PAD) and symptomatic limb ischemia. Available treatment options are diverse and include percutaneous transluminal angioplasty, stent placement, atherectomy, thrombolysis, and thrombectomy. Significant risks associated with peripheral vascular intervention are thrombus formation and distal thromboembolism, which may prove disastrous in patients with preexisting PAD or poor collateral circulation. These risks highlight the importance of periprocedural administration of anticoagulant medications to help prevent thrombus formation. An understanding of the clotting cascade and the role of fibrin, thrombin, and platelets have led to the development of many useful pharmacologic agents including aspirin, warfarin, heparin, clopidogrel, and ticlopidine.

The study of a rare bleeding diathesis, Glanzmann thrombasthenia, first described in 1918, led to a greater understanding of platelet activation and aggregation mechanisms, including the function of the glycoprotein (GP) IIb/IIIa complex, which allowed the development of a new class of medications.[1] Patients with Glanzmann thrombasthenia inherit an absence or deficiency of GP IIb/IIIa in an autosomal recessive pattern. Their platelets are of normal size and undergo normal activation-related secretion and shape changes; however, they do not bind fibrinogen and cannot form aggregates.[2,3] The pharmacologic agents that temporarily mimic this pathologic state, the GP IIb/IIIa antagonists, are the topic of this review.

Currently, there are three of these high potency antiplatelet agents: abciximab; eptifibatide; and tirofiban. All the GP IIb/IIIa antagonists function by preventing platelet aggregation, which contributes to acute thrombus formation and distal platelet thromboembolism.[4] These medications are administered parenterally, and to date no oral or subcutaneous agent has been developed, limiting their use to the periprocedural period or the time of an acute event.

MECHANISM OF GP IIB/IIIA RECEPTOR ANTAGONISTS

Platelet activation occurs when an event, including vascular injury, results in the binding of any number of agonists, including serotonin, epinephrine, platelet-activating factor (PAF), adenosine diphosphate (ADP), thromboxane A2 (TXA2), vasopressin, or collagen to a variety of receptors on the platelet cell surface. Agonist binding results in cell receptor activation, which subsequently causes platelet adherence to an area of injury. Once bound to damaged tissue, platelets are activated and undergo a conformational change at the GPIIb/IIIa receptor site, which allows binding to fibrinogen and von Willebrand factor. Multiple binding sites for fibrinogen and von Willebrand factor are present on each platelet, which results in the binding and cross-linking of multiple platelets, known as aggregation. Additionally, a positive feedback loop between platelets exists and causes progressive amplification of platelet activation and aggregation. Existing antiplatelet medications interfere with platelet activation mechanisms such as TXA2 in the case of aspirin, or ADP with the thienopyridines ticlopidine and clopidogrel.[5,6] These medications block only one of many activators of platelets and thus they are inherently weak and provide partial inhibition of platelet aggregation at best.

Taking advantage of the distinct mechanisms of activation and aggregation, the GP IIb/IIIa inhibitors interfere with platelet activity at the final common pathway of platelet-induced thrombosis. The benefit of this mechanism of action is that platelet blockade occurs independently of the specific platelet activating agonist and that initial platelet adherence to damaged vascular surfaces is maintained, whereas the subsequent platelet aggregation is prevented. Accordingly, inhibition of this final common pathway to platelet aggregation has much greater antiplatelet activity than aspirin with or without clopidogrel at normal doses.[7]

In addition to preventing platelet aggregation, GP IIb/IIIa antagonism has the ability to induce dissolution of platelet-rich clot by disrupting fibrinogen-platelet interaction, an action termed *dethrombosis*.[8,9] Clot that is resistant to fibrinolysis with plasminogen activators may have a large component of platelet aggregates that are unresponsive to the lytic agent, or may present a dynamic situation in which initial fibrinolysis results in exposure of platelet activating tissue and thrombus components that induce rapid replacement of the lysed clot with platelet aggregates. Further, fibrinolytic agents themselves function as platelet activators and activated platelets produce plasminogen activator inhibitors that contribute to thrombolytic resistance and rethrombosis.[10] These phenomena of fibrinolytic-platelet interactions raise several intriguing possibilities regarding the application of GP IIb/IIIa inhibitors in thrombolysis, either alone or in combination with fibrinolytic agents, to accelerate clot dissolution, improve lysis of resistant clot, and reduce severe hemorrhagic complications associated with prolonged or high-dose plasminogen activator administration.

CURRENTLY AVAILABLE DRUGS

The three currently available GP IIb/IIIa antagonists are abciximab (ReoPro®; Centrocor, Malvern PA and jointly marketed with Eli Lilly, Indianapolis, IN), eptifibatide (Integrilin®; Cor Theraputics, South San Fransciso, CA and Schering-Plough, Kenilworth, NJ), and tirofiban hydrochloride (Aggrastat®; Merck, Deerfield, IL). All three are administered intravenously as a bolus

followed by a variable duration infusion. Abciximab is a murine-human chimeric monoclonal antibody previously referred to as c7E3. Eptifibatide is a circular hexapeptide, a synthetic copy of a component of pigmy rattle snake venom, barbouin. Tirofiban is a nonpeptide tyrosine derivative designed to mimic the natural ligand of the GP IIb/IIIa receptor.

PRIOR APPLICATIONS IN CORONARY INTERVENTIONS

GP IIb/IIIa antagonists are widely applied during percutaneous coronary interventions (PCI), and their safety and efficacy have been well established in multiple trials and registries. The Food and Drug Administration (FDA) has approved the GP IIb/IIIa antagonists for use in the treatment of acute coronary syndromes (ACS), including unstable angina (UA) and non-Q-wave myocardial infarction, and in PCI, including angioplasty, atherectomy, and stent placement. In addition, the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) have made recommendations for the application of GP IIb/IIIa inhibitors based on available data from prior studies in the coronary circulation. The class I recommendations for use of GP IIb/IIIa antagonists include UA/Non-ST Elevation MI (NSTEMI) patients undergoing PCI who cannot tolerate clopidogrel.[11] The class IIa recommendations include use in patients who receive clopidogrel at the time of their procedure to augment platelet inhibition in higher risk situations or in patients who have an absolute contraindication to aspirin.[12]

Several large, prospective, randomized clinical trials have compared GP IIb/IIIa antagonists to standard heparin and aspirin therapy in the treatment of ACS or during PCI, the results of which are summarized in Table 1. As a whole, these studies have shown use of GP IIb/IIIa antagonists to be safe and associated with decreased rates of myocardial infarction, death, and need for target vessel revascularization over heparin and aspirin alone. The addition of GP IIb/IIIa antagonists during PCI also decreases heparin requirements, reaching activating clotting time (ACT) targets and clinical endpoints at lower doses. Interestingly, several of these trials demonstrated long-term clinical benefits that persisted for months to years after PCI.[13–15]

PRIOR APPLICATIONS OF GPIIB/IIIA ANTAGONISTS IN PERIPHERAL ARTERIAL INTERVENTIONS

There remains a relative paucity of data examining the use of the GPIIb/IIIa antagonists during peripheral arterial interventions despite years of use by coronary interventionalists. Of the studies available, most pertain to the use of abciximab and examine its use in combination with other pharmacologic agents. Several authors have examined the use of GP IIb/IIIa antagonists during the treatment of acute peripheral arterial thrombosis to enhance thrombolysis, and to a lesser extent, in chronic lesions and critical limb ischemia.

The Tübingen group initially examined the safety of the use of abciximab with urokinase in the treatment of peripheral arterial occlusion in a small series ($N = 14$).[16] The same group subsequently completed a larger randomized controlled trial evaluating patients undergoing urokinase pulse spray thrombolysis with or without abciximab. Success rates were similar, but adjunctive GPIIb/IIIa antagonist treatment reduced the time of thrombolysis and rates of amputation or open surgery. No significant difference in bleeding complications between the groups was demonstrated.[17]

In a small series by Drescher et al, 15 patients with lower extremity arterial thrombosis underwent catheter-directed thrombolysis using reteplase in conjunction with abciximab. Thrombolysis and limb salvage was achieved in 93% of subjects, and no significant bleeding complications occurred.[18]

Although the RELAX trial (PhosphodiesteRasE-5 Inhibition to Improve Quality of Life And EXercise Capacity in Diastolic Heart Failure; comparing reteplase with and without abciximab) was geared toward safety and dosage determinations, there were no statistically significant differences between the two groups in terms of length of thrombolytic administration, frequency of open surgery, or survival. There was, however, a significant reduction in the rate of distal embolization during thrombolysis with the addition of abciximab.[19]

The APART (The Antibodies of Platelet Receptors and Reteplase for Thrombolysis) Study compared the use of reteplase and abciximab to urokinase and abciximab in patients with acute arterial occlusion and demonstrated excellent safety and low bleeding complication rates, with no other significant difference between the study groups.[20]

In a larger series by Schweizer et al ($N = 84$), patients undergoing intraarterial thrombolysis were given either recombinant tissue plasminogen activator (rt-PA) and aspirin, or rt-PA and abciximab. The patients who received abciximab were shown to have shorter duration of lysis. Further analysis demonstrated that patients who received adjunctive abciximab rather than aspirin or heparin alone had reduced rates of rehospitalization, reinterventions, and amputation.[21]

McNamara et al evaluated 26 patients undergoing thrombolysis utilizing a reduced dose of reteplase (0.25 U/h) and the standard dose of abxicimab. Adjunctive heparin was administered in two of the patients. Overall, the mean treatment time was 8 hours, and no significant bleeding complications occurred. However, a

Table 1 Review of the Clinical Trials of the Glycoprotein IIb/IIIa Antagonists in the Coronary Circulation

			Dosage Regimen			Overall Outcomes (%)			
Agent	**Trial**	**Indication**	**Bolus (μg/kg)**	**Infusion (dose/min)**	**Infusion Duration (h)**	**Death**	**MI**	**Urgent Intervention**	**Major Bleeding***
Abciximab	EPIC	High risk for abrupt closure during PTA	250	10 μg	12	1.7	5.2	3.2	14.0
	EPILOG	Elective or urgent PTA	250	0.125 μg/kg to a maximum dose of 10 μg	12	0.4	3.8	2.3	3.5
	CAPTURE	PTA for UA	250	10 μg	18–24	1.0	4.8	7.8	3.8
	EPISTENT	Elective or urgent PTA or stent placement for UA, post-MI, stable angina	250	0.125 μg/kg to a maximum dose of 10 μg	12	Post-stent 0.3 (30 d), 1.0 (1 year), Post-PCI 0.8 (30 d), 2.1 (1 year)	4.5 (30 d), 5.9 (1 year) 5.3 (30 d), 7.7 (1 year)	1.3 (30 d) 1.9 (30 d)	1.5 1.4
Eptifibatide	IMPACT-II	PTA for UA, post MI, stable angina	135	0.5 μg/kg	20–24	0.5	6.6	4.7	5.1
			135	0.75 μg/kg	20–24	0.8	6.9	5.4	5.2
	ESPIRIT	Elective or urgent stent placement	180 × 2, every 10 minutes	2 μg/kg	18–24	0.1 (48 h), 0.4 (30 d), 0.8 (6 m)	5.4 (48 h), 6.2 (30 d), 7.0 (6 m)	0.6 (48 h), 1.9 (30 d), 8.6 (6 m)	1.3
Tirofiban	RESTORE	PTA within 72 h of UA or MI	10	0.15 μg/kg	36	0.8	4.2	7.6	5.3

*Major bleeding is defined as intracranial or retroperitoneal hemorrhage, need for surgical intervention, reduction of hemoglobin <5 mg/dL, transfusion greater than 2 U of blood.
MI, myocardial infarction; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty; UA, unstable angina

small number of complications occurred including thrombocytopenia ($N=1$) and distal embolization ($N=2$).[22] In a smaller series by McGuckin, 11 patients were given a higher dose of reteplase (0.5 U/h) and the standard dose of abciximab for peripheral arterial thrombolysis. Technical success was reported as 100% and the mean treatment time was 16.4 hours. Bleeding complications were seen more frequently for the higher infusion rate of reteplase combined with abciximab.[23]

In a small retrospective series of patients with acute peripheral arterial occlusion, Yoon and Miller et al examined the use of either intraarterial or intravenous eptifibatide in combination with rt-PA and heparin, compared with rt-PA and heparin alone. There were no significant differences between the two groups in terms of successful outcome, incidence of major complications, duration of therapy, and overall total dose of rt-PA. It was also shown that a smaller dose of rt-PA was needed to achieve thrombolysis in patients who received intraarterial eptifibatide.[24]

Various combinations of available thrombolytic and antiplatelet medications have also been investigated. A study of 16 patients undergoing peripheral arterial or venous lysis with tenecteplase and eptifibatide demonstrated safety and feasibility, with technical success rates of 91% for arterial and 80% for venous lysis. Mean lysis time was just over 12 hours, but no control group was included for direct comparisons.[25] Schweizer compared the use of abciximab to tirofiban as adjuncts to peripheral arterial lysis with rt-PA, heparin, and aspirin in 60 patients. No significant differences were found in patency rates, outcomes, or complications.[26]

The economic implications of the addition of GP IIb/IIIa inhibitors to peripheral arterial lysis were examined in the PROMPT (Platelet Receptor Antibodies in Order to Manage Peripheral Artery Thrombosis) Trial population. Seventy patients receiving urokinase thrombolytic infusions for peripheral arterial occlusions were randomized to receive either abciximab or placebo. Although the immediate procedure-related costs were significantly higher with the additional medication, improved outcomes led to fewer repeated interventions and hospitalizations, and decreased direct costs at 3-month follow-up.[27]

In the treatment of peripheral arterial thrombosis, the GP IIb/IIIa antagonists appear to improve outcomes over standard fibrinolytic, heparin, and oral antiplatelet regimens. No specific combination of plasminogen activator and anti-GP IIb/IIIa agent has demonstrated superiority, as many of the available options appear effective and may be cost effective as well.

The glycoprotein IIb/IIIa antagonists have also been used in the endovascular management of chronic peripheral arterial lesions, with the goal of treatment being prevention of early thrombosis and improved long-term patency. The evidence for application of GP IIb/IIIa inhibitors during infrainguinal interventions is mixed. One study examining abciximab as an adjunct to endovascular treatment of femoropopliteal disease was encouraging.[28] Ninety-eight patients were randomized to abciximab or placebo prior to treatment of long femoropopliteal lesions. Although the GP IIb/IIIa antagonist group had more minor bleeding complications, patency and clinical outcomes were significantly better, and the benefit persisted for 6 months of follow-up.[28] A subsequent similar trial evaluated abciximab administration during stent placement for complex superficial femoral artery disease. Among 51 patients randomized to receive the drug or placebo, there was no difference in patency or clinical parameters up to 9 months after the intervention.[29] In a separate study, Feiring et al examined the use of various GP IIb/IIIa antagonists and various stent types in patients with critical limb ischemia undergoing angioplasty and stent placement in the infrapopliteal circulation. Excellent safety was demonstrated as there were no significant bleeding complications and no subacute thrombotic effects.[30] Multiple additional studies are currently underway to further examine the role of these medications in the endovascular management of critical limb ischemia.

The existing preliminary studies have uniformly demonstrated safety of the use of GPIIb/IIIa antagonists in lower extremity peripheral arterial interventions without a significant increase in major bleeding complications. Evidence for a beneficial effect during peripheral arterial thrombolysis is building, but not entirely conclusive. Data supporting the application of GPIIb/IIIa antagonists in endovascular management of chronic peripheral arterial lesions are mixed and may not prove to correspond to the coronary experience. Further research is necessary as distal thromboembolism is an infrequent enough event during peripheral endovascular interventions that large studies may be required to show a significant decrease in these relatively rare complications.

PHARMACOLOGY AND DOSE INFORMATION FOR THE CURRENTLY AVAILABLE DRUGS

Table 2 summarizes the pharmacodynamics of each of the GPIIb/IIIa antagonists.

Abciximab

Pharmacology: Abciximab is comprised of a large monoclonal antibody that binds noncompetitively with high affinity to the GP IIb/IIIa receptor. The binding half-life is 2 hours, resulting in a short plasma half-life and long receptor blockade.[31,32] Dissociation from the GP IIb/IIIa complex occurs through proteolysis, resulting in slow elimination with resultant profound platelet

Table 2 Selected Pharmacodynamic Parameters for the Currently Available Glycoprotein IIb/IIIa Antagonists

Agent	Molecule	Mechanism of IIb/IIIa Receptor Blockade	Specificity	Biologic Half-Life (h)	Restoration of Normal Hemostatic Function (h)	Reversibility	Clearance	Dose	Dose Adjustment in Renal Insufficiency	Provoke Antibody Response
Abciximab	Monoclonal antibody	Agent binding causes steric hindrance and conformational changes	+++	8–12	72	Platelets	Platelet binding, protease degradation	0.25 mg/kg bolus followed by 0.125 μg/kg/min infusion for 12 h	No	Yes
Eptifibatide	Peptide	Mimics native protein sequence in receptor	+++	2.5	3–4	Time	Renal (98%), partially metabolized	180 μg/kg bolus followed by 2.0 μg/kg/min infusion and additional 180 μg/kg bolus 10 minutes after first bolus for 18–24 h	Yes	Yes or no???
Tirofiban	Nonpeptide	Mimics native protein sequence in receptor	+++	2	4	Time	Renal (60–70%), Biliary (20–30%)	0.10 μg/kg bolus followed by 0.10 μg/kg/min infusion for 18–24 h	Yes	Yes or no??

antagonism that lasts for ~6 to 12 hours once the infusion has stopped. Detectable platelet inhibition can be observed for up to 2 weeks after administration.[33]

Dose: An initial bolus of 0.25 mg/kg is administered prior to the intervention. A continuous infusion of 0.125 μg/kg/min is administered over 12 hours. The maximal dose administered is 10 μg/min.[4]

Eptifibatide

Pharmacology: Eptifibatide is comprised of a low-molecular-weight molecule that competitively inhibits the GP IIb/IIIa receptor, resulting in a shorter receptor blockade and longer plasma half-life. The plasma elimination half-life is ~2.5 hours. In comparison to abciximab, eptifibatide has higher binding specificity but lower binding affinity. This medication undergoes renal excretion, and dosing must be adjusted in patients with renal insufficiency.[31,32]

Dose: Prior to intervention, two subsequent bolus administrations of 180 μg/kg are given in 10 minutes, followed by a continuous infusion of 2 μg/kg/min for 18 to 24 hours.[34]

Tirofiban

Pharmacology: Tirofiban is similar to eptifibatide in that it is a low-molecular-weight compound that competitively inhibits the GP IIb/IIIa receptor with high specificity and low affinity. The plasma half-life of tirofiban is also short (1.6 hours). Tirofiban undergoes both renal and nonrenal excretion; therefore, dose must be adjusted in patients with renal insufficiency.[31]

Dose: An initial bolus of 10 μg/kg is administered over 3 minutes, followed by an infusion of 0.15 μg/kg/min for 18 to 24 hours.[4]

Although there are significant pharmacodynamic differences between the three GP IIb/IIIa antagonists, there are no data to suggest that these result in significant differences in clinical outcomes.[35] Table 1 summarizes the major trials examining the GP IIb/IIIa antagonists in coronary applications.

ADVERSE EFFECTS AND CONTRAINDICATIONS

The incidence of life-threatening bleeding associated with the GP IIb/IIIa antagonists has been reported to be as low as <0.2%, and appears to be lower than that of a plasminogen activator.[4,36] A meta-analysis by Memon et al of large trials found that the rate of intracranial hemorrhage associated with GP IIb/IIIa antagonists was not greater than that seen in control groups.[37] When used in combination with heparin and monitoring of ACT, there is generally no increase in the risk of major bleeding complications. Some series, however, have

shown rates of minor bleeding slightly greater than when heparin is used alone.[36]

Thrombocytopenia is a potentially major side effect of GP IIb/IIIa antagonist administration. The large abciximab trials suggest the incidence of thrombocytopenia is on the order of 4.7 to 6.5%.[38] An acute decrease in the platelet count to <100,000 cells/mL or a reduction by 25% of the preintervention value requires further evaluation.[4] There appears to be no significant difference in the rate of thrombocytopenia between the three medications. The mechanism of thrombocytopenia is thought to be mediated by formation of antibodies stimulated by the conformational change in the GP IIb/IIIa receptor induced by the medications.[39,40] Despite being an immune-mediated phenomenon, development of these antibodies does not appear to interfere with the efficacy of subsequent administrations of the medication, and recurrent thrombocytopenia is not observed at a higher rate than that seen upon initial exposure. In general, diminished platelet counts following GP IIb/IIIa antagonist administration is a benign complication without consequences. Rarely the thrombocytopenia may be profound and associated with hemorrhagic complications, particularly in those with low initial platelet counts and in the elderly. Treatment involves close monitoring of platelets before and after drug administration and transfusion of platelets if significant decreases are observed.[41]

No anaphylaxis, allergic reaction, hypersensitivity, or decreased efficacy after drug readministration has been reported.[38] The relative contraindications of the GPIIb/IIIa antagonists are similar to those for thrombolysis.[4] Table 3 summarizes contraindications for the three agents, as stated in the package inserts for the three drugs.

GENERAL RECOMMENDATIONS FOR SAFE ADMINISTRATION

The risk of bleeding can be reduced when single wall arterial entry is achieved. To prevent access site complications, early sheath removal is recommended even in the setting of a patient taking concomitant GPIIb/IIIa antagonist infusion. The vascular access sheath may be safely removed once the ACT normalizes (ACT <150 to 180).[4]

Patients should be monitored in an intensive care setting while receiving infusions of these medications. Recommendations for observation of platelet counts vary and should be obtained before GPIIb/IIIa antagonist administration and either 4 and 24 hours after the infusion has stopped, or 2, 6, 12, and 24 hours after cessation.[4,41]

NEW EVIDENCE AND CURRENT DEBATES

Emerging research examines the efficacy of utilizing additional anticoagulant or thrombolytic agents in conjunction with the GP IIb/IIIa antagonists. For example, in patients undergoing cardiac PCI for ACS, a recent meta-analysis demonstrated that there was no significant improvement in clinical efficacy of GP IIb/IIIa plus fibrinolytic therapy compared with GP IIb/IIIa alone.[42] In the recently published FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) Trial, there was no significant clinical benefit of combination reteplase and GP IIb/IIIa antagonist therapy compared with GP IIb/IIIa antagonism alone. However, a significant increase in bleeding complications was observed.[43] Clearly, there is a need for further study into the role of GP IIb/IIIa inhibitors in acute

Table 3 Contraindications and Precautions for the Glycoprotein IIb/IIIa Antagonists

Applicable to All Three Agents	Specific to Abciximab	Specific to Eptifibatide	Specific to Tirofiban
Hypersensitivity to agent component			
Active internal bleeding or recent significant GI or GU bleed within past 6 months			
History of bleeding diathesis within 30 days			
Severe uncontrolled hypertension			
Major surgery or trauma	Within previous 6 weeks	Within previous 6 weeks	Within previous 4 weeks
	Thrombocytopenia (platelets <100,000)	Thrombocytopenia (platelets <100,000)	
Stroke within previous 2 years	Stroke with neurologic deficit at any time		
Intracranial neoplasm, AVM, aneurysm or tumor	Vasculitis		
			Aortic dissection
			Acute pericarditis

AVM, arteriovenous malformation; GI, gastrointestinal; GU, genitourinary.

arterial occlusions, whether as an alternative to or in combination with fibrinolytic agents.

Several studies have examined the mode and timing of the administration of GP IIb/IIIa antagonists in an effort to reduce bleeding complications. The findings suggest that a bolus administration prior to or at the time of cardiac catheterization or PCI while eliminating the intraprocedural infusion of the GP IIb/IIIa antagonists may reduce bleeding complications.[44–46] Kini et al evaluated cardiac events, bleeding complications, and cost in patients undergoing PCI who received the GP IIb/IIIa bolus alone compared with patients who received GP IIb/IIIa bolus in addition to a 12 to 18 hour GP IIb/IIIa infusion. Both groups demonstrated similar rates of ischemic complications; however, the bolus-only group experienced reduced vascular and bleeding complications and lower overall cost compared with the bolus plus infusion group.[47] Abbreviated infusion times have also been investigated during PCI. The BRIEF-PCI trial evaluated 624 patients randomized to eptifibatide bolus followed by either an 18-hour or a 2-hour infusion at the time of coronary intervention. The shorter infusion was shown to be noninferior for ischemic complications, and hemorrhagic complications were decreased.[48] These findings raise the possibility that a single bolus administration or shorter infusion of GP IIb/IIIa antagonist may provide an equal alternative to a prolonged infusion. Optimum dosing and administration strategies for various clinical indications continue to be investigated.

Efficacy of the use of GP IIb/IIIa in patients undergoing stent placement may depend on the specific GP IIb/IIIa antagonist used and the type of stent employed, i.e., bare metal or drug-eluting. For example, Valgimigli et al showed that tirofiban plus sirolimus-eluting stents resulted in reduced target vessel revascularization compared with abciximab plus bare metal stents.[49] Furthermore, a study examining abciximab with paclitaxel drug-eluting stents demonstrated an increase in cardiac events and vessel failure.[50] No data specific to the interaction of GP IIb/IIIa antagonists with stent placement in the peripheral circulation are available, and ongoing research is needed to further elucidate what combination of therapies would prove safest and most efficacious.

Although limited reports exist, the application of the GPIIb/IIIa antagonists in the treatment of acute peripheral arterial occlusions has been shown to be safe and likely improves short- and medium-term outcomes. However, the role of these medications for the management of critical limb ischemia and chronic occlusions remains to be defined.

CONCLUSION

Thromboembolic and ischemic complications pose a serious risk during and after endovascular procedures. The periprocedural use of anticoagulant medications, and particularly antiplatelet agents, has become the standard of care to minimize these risks. The newest pharmacologic agents to be added to the antiplatelet therapeutic armamentarium are the GP IIb/IIIa antagonists. These agents target the GPIIb/IIIa receptor, the final common pathway to platelet aggregation. This action leaves intact the mechanisms of initial activation and platelet adherence to damaged endothelium intact while preventing further aggregation and the formation of clot at the site. Well established for use in coronary interventions, preliminary studies have demonstrated safety of use of the GPIIb/IIIa antagonists in lower extremity peripheral arterial interventions, with minimal increase in rates of bleeding complications. Although few trials directly comparing the different GP IIb/IIIa antagonists exist, there are no data to suggest that there are significant differences in clinical outcomes associated with any particular medication.[35] Some studies raise the possibility that the GPIIb/IIIa agents offer a degree of protection from distal embolization during thrombolysis, which may in turn result in reduced amputation rates; these findings, however, have not been uniformly reproduced. Further research is necessary to examine ideal dose, timing and mechanism of administration, the role of combination therapy and concomitant stent placement, and whether the GPIIb/IIIa antagonists will be more efficacious than the current anticoagulation regimens administered during peripheral interventions.

REFERENCES

1. Coller BS. Blockade of platelet GPIIb/IIIa receptors as an antithrombotic strategy. Circulation 1995;92(9):2373–2380
2. Hardisty RM, Dormandy KM, Hutton RA. Thrombasthenia: studies on three cases. Br J Haematol 1964;10:371–387
3. Caen JP, Castaldi PA, Leclerc JC, et al. Congenital bleeding disorders with long bleeding time and normal platelet count: I. Glanzmann's thrombasthenia (report of fifteen patients). Am J Med 1966;41:4–21
4. Shlansky-Goldberg R. Platelet aggregation inhibitors for use in peripheral vascular interventions: what can we learn from the experience in the coronary arteries? J Vasc Interv Radiol 2002;13(3):229–246
5. Awtry EH, Loscalzo J. Aspirin. Circulation 2000;101(10): 1206–1218
6. Breddin HK. Antiplatelet agents in cardiovascular and cerebrovascular diseases. Clin Appl Thromb Hemost 1998; 4:87–95
7. Meadows TA, Bhatt DL. Clinical aspects of platelet inhibitors and thrombus formation. Circ Res 2007;100(9): 1261–1275
8. Furman MI, Frelinger AL III, Michelson AD. GPIIb/IIIa inhibitor-induced dethrombosis. J Thromb Thrombolysis 2004;18(1):11–17
9. Gold HK, Garabedian HD, Dinsmore RE, et al. Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without exogenous plasminogen

activators. Observations in animals and humans. Circulation 1997;95(7):1755–1759
10. Coller BS. Platelets and thrombolytic therapy. N Engl J Med 1990;322(1):33–42
11. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). Circulation 2006; 113(7):e166–e286
12. King SB III, Smith SC Jr, Hirshfeld JW Jr, et al; 2005 WRITING COMMITTEE MEMBERS. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. Writing on Behalf of the 2005 Writing Committee. Circulation 2008;117(2):261–295
13. Cohen M. Antiplatelet therapy in percutaneous coronary intervention: a critical review of the 2007 AHA/ACC/SCAI guidelines and beyond. Catheter Cardiovasc Interv 2009; 74(4):579–597
14. Topol EJ, Califf RM, Weisman HF, et al.; The EPIC Investigators. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. Lancet 1994; 343(8902):881–886
15. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336(24): 1689–1696
16. Tepe G, Schott U, Erley CM, Albes J, Claussen CD, Duda SH. Platelet glycoprotein IIb/IIIa receptor antagonist used in conjunction with thrombolysis for peripheral arterial thrombosis. AJR Am J Roentgenol 1999;172(5):1343–1346
17. Duda SH, Tepe G, Luz O, et al. Peripheral artery occlusion: treatment with abciximab plus urokinase versus with urokinase alone—a randomized pilot trial (the PROMPT Study). Platelet Receptor Antibodies in Order to Manage Peripheral Artery Thrombosis. Radiology 2001;221(3):689–696
18. Drescher P, McGuckin J, Rilling WS, Crain MR. Catheter-directed thrombolytic therapy in peripheral artery occlusions: combining reteplase and abciximab. AJR Am J Roentgenol 2003;180(5):1385–1391
19. Ouriel K, Castaneda F, McNamara T, et al. Reteplase monotherapy and reteplase/abciximab combination therapy in peripheral arterial occlusive disease: results from the RELAX trial. J Vasc Interv Radiol 2004;15(3):229–238
20. Tepe G, Hopfenzitz C, Dietz K, et al. Peripheral arteries: treatment with antibodies of platelet receptors and reteplase for thrombolysis—APART trial. Radiology 2006;239(3):892–900
21. Schweizer J, Kirch W, Koch R, Müller A, Hellner G, Forkmann L. Short- and long-term results of abciximab versus aspirin in conjunction with thrombolysis for patients with peripheral occlusive arterial disease and arterial thrombosis. Angiology 2000;51(11):913–923
22. McNamara TO. Combination of ReoPro and Retevase in thrombolysis of peripheral arterial occlusion: preliminary results. (abstract)J Vasc Interv Radiol 2001;12(suppl):S123
23. Drescher P, McGuckin J, Rilling WS, Crain MR. Catheter-directed thrombolytic therapy in peripheral artery occlusions: combining reteplase and abciximab. AJR Am J Roentgenol 2003 May;180(5):1385–1391
24. Yoon HC, Miller FJ Jr. Using a peptide inhibitor of the glycoprotein IIb/IIIa platelet receptor: initial experience in patients with acute peripheral arterial occlusions. AJR Am J Roentgenol 2002;178(3):617–622
25. Burkart DJ, Borsa JJ, Anthony JP, Thurlo SR. Thrombolysis of acute peripheral arterial and venous occlusions with tenecteplase and eptifibatide: a pilot study. J Vasc Interv Radiol 2003;14(6):729–733
26. Schweizer J, Kirch W, Koch R, Müller A, Hellner G, Forkmann L. Use of abciximab and tirofiban in patients with peripheral arterial occlusive disease and arterial thrombosis. Angiology 2003;54(2):155–161
27. Duda SH, Tepe G, Bala M, et al. Economic value of thrombolysis with adjunctive abciximab in patients with subacute peripheral arterial occlusion. Pharmacoeconomics 2002;20(3):203–213
28. Dörffler-Melly J, Mahler F, Do DD, Triller J, Baumgartner I. Adjunctive abciximab improves patency and functional outcome in endovascular treatment of femoropopliteal occlusions: initial experience. Radiology 2005;237(3): 1103–1109
29. Ansel GM, Silver MJ, Botti CF Jr, et al. Functional and clinical outcomes of nitinol stenting with and without abciximab for complex superficial femoral artery disease: a randomized trial. Catheter Cardiovasc Interv 2006;67(2): 288–297
30. Feiring AJ, Wesolowski AA, Lade S. Primary stent-supported angioplasty for treatment of below-knee critical limb ischemia and severe claudication: early and one-year outcomes. J Am Coll Cardiol 2004;44(12):2307–2314
31. 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(4):437–444
32. Kereiakes DJ, Runyon JP, Broderick TM, Shimshak TM. IIb's are not IIb's. Am J Cardiol 2000;85(8A, 8A):23C–31C
33. 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(17):1680–1688
34. ESPRIT Investigators. Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000;356(9247):2037–2044
35. Schrör K, Weber AA. Comparative pharmacology of GP IIb/IIIa antagonists. J Thromb Thrombolysis 2003;15(2):71–80
36. Tcheng JE. Clinical challenges of platelet glycoprotein IIb/IIIa receptor inhibitor therapy: bleeding, reversal, thrombocytopenia, and retreatment. Am Heart J 2000;139(2 Pt 2):S38–S45
37. 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(3):213–217

38. Kleiman NS, Tcheng JE. Safety issues surrounding use of platelet GPIIb/IIIa antagonists: reversibility and readministration. Eur Heart J 1999;1(suppl E):E36–E42
39. Nurden AT, Poujol C, Durrieu-Jais C, Nurden P. Platelet glycoprotein IIb/IIIa inhibitors: basic and clinical aspects. Arterioscler Thromb Vasc Biol 1999;19(12):2835–2840
40. Bougie DW, Wilker PR, Wuitschick ED, et al. Acute thrombocytopenia after treatment with tirofiban or eptifibatide is associated with antibodies specific for ligand-occupied GPIIb/IIIa. Blood 2002;100(6):2071–2076
41. Said SM, Hahn J, Schleyer E, et al. Glycoprotein IIb/IIIa inhibitor-induced thrombocytopenia: diagnosis and treatment. Clin Res Cardiol 2007;96(2):61–69
42. Keeley EC. Abciximab following clopidogrel reduces post-PCI complications in patients with acute coronary syndromes. Nat Clin Pract Cardiovasc Med 2006;3(12):650–651
43. Ellis SG, Tendera M, de Belder MA, et al; FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358(21): 2205–2217
44. Marmur JD, Mitre CA, Barnathan E, Cavusoglu E. Benefit of bolus-only platelet glycoprotein IIb/IIIa inhibition during percutaneous coronary intervention: insights from the very early outcomes in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial. Am Heart J 2006; 152(5):876–881
45. Fischell TA, Attia T, Rane S, Salman W. High-dose, single-bolus eptifibatide: a safe and cost-effective alternative to conventional glycoprotein IIb/IIIa inhibitor use for elective coronary interventions. J Invasive Cardiol 2006;18(10): 487–491
46. Marmur JD, Poludasu S, Agarwal A, et al. Bolus-only platelet glycoprotein IIb-IIIa inhibition during percutaneous coronary intervention. J Invasive Cardiol 2006;18(11): 521–526
47. Kini AS, Chen VHT, Krishnan P, et al. Bolus-only versus bolus + infusion of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention. Am Heart J 2008;156(3): 513–519
48. Fung AY, Saw J, Starovoytov A, et al. Abbreviated infusion of eptifibatide after successful coronary intervention The BRIEF-PCI (Brief Infusion of Eptifibatide Following Percutaneous Coronary Intervention) randomized trial. J Am Coll Cardiol 2009;53(10):837–845
49. Valgimigli M, Bolognese L, Anselmi M, et al. Two-by-two factorial comparison of high-bolus-dose tirofiban followed by standard infusion versus abciximab and sirolimus-eluting versus bare metal stent implantation in patients with acute myocardial infarction: Design and rationale for the MULTI-STRATEGY trial. Am Heart J 2007;154:39–45
50. Teirstein PS, Kao J, Watkins M, et al. Impact of platelet glycoprotein IIb/IIIa Inhibition on the paclitaxel-eluting stent in patients with stable or unstable angina pectoris or provocable myocardial ischemia (a TAXUS IV substudy). Am J Cardiol 2005;96(4):500–505