Use of Glycoprotein IIb/IIIa Platelet Inhibitors in Peripheral Vascular Interventions

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With the expanding use of endovascular techniques for the treatment of peripheral vascular disease, consideration of glycoprotein IIb/IIIa receptor inhibitors to enhance the safety and efficacy of these procedures has increased. The scientific literature shows the benefits with the use of these agents in coronary vasculature interventions. However, data evaluating treatment with glycoprotein IIb/IIIa receptor inhibitors during peripheral vascular procedures is limited, with the vast majority of the trials investigating abciximab. With the varied vascular beds and end organs that may be affected by peripheral vascular intervention, the safety and efficacy may need to be studies for each area. The current literature ranging from carotid stenting to thrombolysis and mechanical thrombectomy for acute limb ischemia is reviewed, and recommendations are discussed on the use of these agents. The forthcoming results of controlled clinical trials should further clarify the clinical applications of these agents in peripheral vascular intervention.
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The application of endovascular techniques for the treatment of peripheral vascular disease is rapidly expanding. Although the use of glycoprotein IIb/IIIa receptor inhibitors has a proven efficacy in the coronary vasculature, no large, placebo-controlled trials have evaluated their use in the peripheral vasculature. Until such trials are completed, the clinical practitioner must utilize the findings from small, single-center trials and anecdotal data and extrapolate results from the coronary-artery intervention trials.

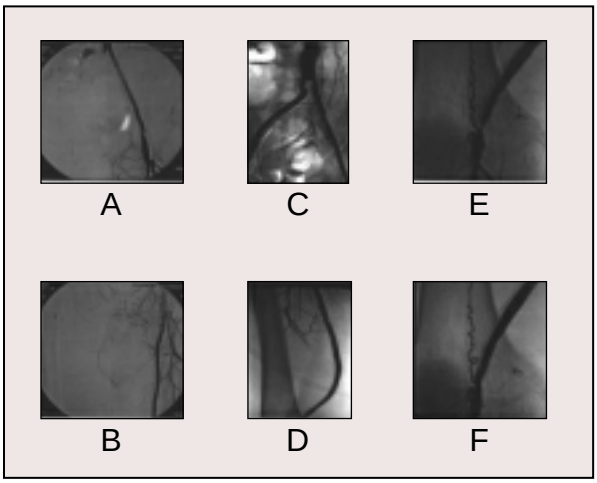

Figure 1. *Angiography from a patient presenting with acute limb ischemia caused by thrombosis of a previously placed aortobifemoral and femoropopliteal bypass.* **A and B:** *pretreatment angiography.* **C and D:** *angiogram 4 hours after treatment with abciximab and low-dose thrombolysis, demonstrating complete thrombolysis of grafts.* **E:** *angiogram demonstrating outflow lesion at distal femoropopliteal bypass.* **F:** *completion angiogram after angioplasty.*

Unlike intervention in the coronary vasculature, interventional therapy in the peripheral vasculature is by definition more heterogeneous because of the variety of vascular beds involved. The safety and possible efficacy of any new therapy must be considered for each individual vascular bed, and that particular end-organ physiology and any unique pathologic conditions that may be present must be taken into account.

As in the coronary vasculature platelet, platelet activation, adhesion, and aggregation play pivotal roles in the body's response to vascular injury by thrombus formation.[1] This arterial damage may occur spontaneously from an atherosclerotic plaque rupture or artificially from the mechanical damage of instrumentation during angioplasty and stent placement. Interruption of the platelet aggregation cascade may be accomplished by a variety of agents (Figure 1 describes the platelet activation cascade). Aspirin-induced inhibition of cyclooxygenase-mediated thromboxane-A2 synthesis and the thienopyridine derivatives (ticlopidine or clopidogrel), which inhibit adenosine diphosphate (ADP)-dependent pathways of activation, partially block platelet activation and aggregation.[2] Their use in coronary intervention has been extensively studied, while knowledge of their effects in peripheral vascular intervention is limited.[3] Although accepted as necessary for peripheral vascular intervention, treatment with these oral agents has never been subjected to randomized, controlled trials.

The coronary use of the glycoprotein IIb/IIIa receptor inhibitors, which inhibit the binding of fibrinogen, the last common pathway of platelet aggregation, has been extensively studied. The observed coronary effects that may also be beneficial in peripheral vascular intervention include decreasing distal microembolization and their impact on that particular organ, decreasing vascular thrombus formation and abrupt closure at the site of intervention, increasing the efficacy of thrombolytic therapy, and decreasing the long-term need for target-vessel revascularization in diabetic subjects.

Before considering the routine use of these powerful antiplatelet agents during peripheral vascular interventions, one must determine whether the current data support a reasonable safety profile. Certainly, the safety profile from coronary trial data appears acceptable[4]; thousands of enrolled patients showed no increase in the incidence of cerebral bleeding events. The majority of the bleeding events that were seen were associated with problematic hemostasis at the vascular access sites. Severe thrombocytopenia was an unusual event, and the bleeding risk appeared to be low. With this large amount of patient data, it thus appears acceptable to consider the use of these agents in patients undergoing peripheral vascular intervention.

Peripheral Vascular Interventions

Carotid Artery Stenting

Even more than in the coronary circulation, embolization to an important end organ such as the brain can have serious consequences. Microembolization may itself lead to further platelet activation, with propagation of the clot extending the cerebrovascular insult. Thus, decreasing platelet aggregation caused by microembolization is desired. The potential for decreasing carotid stent complications by utilizing glycoprotein IIb/IIIa receptor inhibitors before the completion of controlled trials is certainly appealing.

Although coronary glycoprotein IIb/IIIa receptor inhibitors trials showed no significant increase in intracranial hemorrhage, the patients undergoing carotid intervention may have different characteristics that might affect this risk. Patients undergoing carotid intervention, especially those with a history of transient ischemic attacks or a previous stroke, seem to have an intrinsically increased risk of intracranial hemorrhage. The safety of glycoprotein IIb/IIIa receptor inhibitors has been assessed in a variety of small, uncontrolled trials.[5-11] Each report individually appears to show a low risk of intracranial hemorrhage.

Table 1
Intracranial Hemorrhage with Use of IIb/IIIa Agent During Carotid Stenting

Study (year)	Number of Patients	Incidence of Intracranial Hemorrhage
Qureshi et al[5] (2002)	33	2
McGuckin[6] (2001)	18	0
Cecena et al[7] (1999)	45	0
Qureshi et al[8] (2000)	13	0
Kapadia et al[9] (2000)	70	1
Schneiderman et al[10] (2000)	15	0
Chastain et al[11] (1997)	23	2
Hofmann et al[12] (2002)	34	1
Total	251	6 (2.4%)

When these current, single-center series are viewed collectively, however, there appears to be cause for caution (Table 1). The combined incidence of intracranial hemorrhage for these studies is 2.4%. One small (34 patients), single-center, placebo-controlled trial evaluated bolus-only use of abciximab during carotid stenting.[12] The abciximab group had one minor stroke, one major stroke, and one fatal intracranial hemorrhage. The control group also experienced one major stroke. With a periprocedural event rate of 18% in the abciximab group and 8% in the control group, a trend of increased neurologic events was seen.

The coronary studies that evaluated abciximab showed improved outcomes with bolus-plus-infusion therapy over bolus alone. Whether this would also be analogous in the cerebral circulation awaits further study. We await the results of the current U.S. Food and Drug Administration–approved carotid stent trials utilizing emboli protection devices before recommending the routine use of glycoprotein IIb/IIIa receptor inhibitors. However, in patients who have been adequately anticoagulated and are forming visible intraprocedural thrombus on the stent, some data would appear to justify the use abciximab in this setting.[13,14]

Stroke Intervention

The pathophysiology of acute thrombotic stroke and acute coronary syndromes share some important pathologic similarities, especially the important role of platelet-mediated thrombosis. Trial data evaluating the use of abciximab in refractory, unstable angina showed a significant decrease in mortality and myocardial infarction.[15] Multiple IIb/IIIa agents in several trials have showed significant reduction in major endpoints when utilized during acute myocardial infarction and percutaneous intervention.[16,17,18] In an effort to transfer the IIb/IIIa agent's efficacy to the cerebral vasculature, stand-alone abciximab therapy was evaluated in a pilot study in the treatment of acute ischemic stroke.[19] A total of 74 patients less than 24 hours after the onset of an ischemic stroke underwent randomization; 54 were treated with abciximab and 20 with placebo. In this small patient population, a trend toward improved functional status was seen with the use of abciximab (35% versus 20% for placebo). In this series of 74 nonheparinized patients, no increase in major intracranial hemorrhage was seen.

Current data certainly justify further study of the potential use of IIb/IIIa agents with and without heparin in patients with ischemic stroke. Because of the apparent fragility of the vascular supply in the ischemic brain, careful, well-designed trials are necessary before this approach is widely utilized. Whether the differences in the characteristics of the different glycoprotein IIb/IIIa receptor inhibitors results in differences in efficacy and safety remains to be seen.

Renal Artery Intervention

As for the other vascular systems supplying a solid end organ, decreasing platelet aggregation after microembolization in the renal vasculature should be beneficial. Even with the high angiographic success of renal-artery interventions, over 20% of patients suffer deterioration of their renal function.[20] Significant distal embolization has been described in a small series reporting on renal intervention using emboli protection.[21] With the close interac-

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tion of small arterioles and the kidney's collecting system, even nonaggregated platelet embolization may adversely effect glomerular filtration.

The safety of utilizing glycoprotein IIb/IIIa receptor inhibitors during renal artery intervention appears acceptable from available reports.[22] The use of IIb/IIIa agents may be beneficial even with effective distal emboli protection, because guiding catheter manipulation at the time of arterial cannulation is an important source of emboli, which can occur even before an emboli protection device can be utilized. Similar to the discussion on carotid stenting, IIb/IIIa agents could be recommended when thrombus formation occurs at the time of stent implantation.

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Thrombolysis/Mechanical Thrombectomy for Limb Ischemia

The synergistic effect of thrombolytic agents and antiplatelet therapy has been made clear for more than a decade since the development of strategies to aggressively treat myocardial infarction. What often is not appreciated is that acute limb ischemia carries a similar or higher mortality rate compared to the rate for myocardial infarction. When acute vascular thrombosis is initially treated with thrombolytic therapy, the fibrin component is affected. Unfortunately, thrombolytic therapy can itself lead to platelet activation. In addition, the platelet aggregates resist dissociation from the clot and reaccumulate while, at the same time, they express plasminogen-activator inhibitors and platelet-activating compounds. Reocclusion after an initially successful reperfusion or cyclical reflow, where vessels open and close in a cyclical fashion because of platelet aggregation with embolization, decreases the efficacy of the fibrinolytic agent. Several coronary trials have now shown enhanced and accelerated vascular patency when IIb/IIIa agents were combined with thrombolytic therapy.[23,24] If this improved time-to-reperfusion could be transferred to the peripheral vasculature, one would predict improved limb salvage and function, as well as a decrease in the mortality rate.

Recent data evaluating abciximab combined with reduced-dose thrombolytic therapy confirms a reasonable safety profile in patients presenting with acute myocardial infarction.[25] If the dosage of the thrombolytic agents felt to be responsible for intracerebral hemorrhage (ICH) could be decreased even more, thereby possibly further reducing this complication, the use of this combination therapeutic approach might be more easily accepted. The issue of ICH is particularly important in patients with peripheral vascular disease because of the increased prevalence of concomitant cerebral vascular disease.

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Early peripheral intervention data appeared to show that abciximab was superior to aspirin when both were combined with a tissue-plasminogen activator in patients presenting with acute arterial thrombosis.[26] Importantly, no major hemorrhagic events were noted in the 42 patients receiving abciximab. Two recently published pilot studies evaluated both urokinase and reteplase combined with an abciximab bolus and infusion.[27,28] Trends in both pilot studies appeared to show improved efficacy with the use of abciximab. Although the pilot study of 15 patients with reduced-dose reteplase and abciximab resulted in no major hemorrhagic complications, the pulse-spray urokinase-plus-abciximab pilot study of 50 patients had a major hemorrhagic complication rate of 16%; however, no intracerebral hemorrhages occurred. These hemorrhagic complication rates are similar to those seen in the large, randomized, surgery-versus-thrombolysis trials, which did not utilize any IIb/IIIa agents.[29,30]

Glycoprotein IIb/IIIa receptor inhibitors appears to improve the treatment of acute, profound limb ischemia. Mechanical thrombectomy combined with glycoprotein IIb/IIIa receptor inhibitors and or thrombolysis appears to offer an efficacious as well as safer alternative to surgical therapy for acute limb ischemia.[31] In practice, we as well as other clinicians have seen what appears to be very rapid thrombolysis of long seg-

ments of acute thrombosis when a full-dose IIb/IIIa agent is used with low-dose thrombolysis (Figure 1).[32] Because only streptokinase is currently approved for peripheral thrombolysis, much of today's thrombolytic therapy is delivered with an unapproved agent. Each individual clinician is left to decide what the appropriate therapy is for limb thrombus; which thrombolytic agent to use and at what dose has not been fully defined. Future trials further evaluating combination therapies are planned.

Limb Occlusive-Disease Intervention

The possible role of IIb/IIIa agents in the routine intervention for atherosclerotic occlusive disease is less clear than for other peripheral vascular uses For aortoiliac occlusive disease, where angioplasty and stenting have high clinical success rates and few complications, additional clinical benefit with the use of glycoprotein IIb/IIIa receptor inhibitors has not been established. However, a theoretical benefit may be present for infrainguinal and infrapopliteal disease. Safety should not be a significant issue, as there is no organ system downstream from the intervention that may lead to excessive bleeding as long as wire manipulation has been uncomplicated. Infrainguinal intervention has been associated with a significantly higher restenosis rate than that seen in the aortoiliac region. Whether the anti-inflammatory effect or the decrease in platelet aggregation at the intervention site will effect this is unknown. Currently, there is an ongoing feasibility study ("Bilateral leg artery stent therapy employing ReoPro–BLASTER," Cordis Endovascular, Miami, Florida) evaluating the effect of abciximab on stenting for long lesions in the superficial femoral artery.

With no predictable down side and a multiplicity of theoretical benefits, only financial considerations would appear to restrict use of these agents during peripheral vascular procedures in the tibial vessels.

The routine use of IIb/IIIa agents may be more justifiable in the infrapopliteal arteries, where intervention is usually undertaken for limb salvage. The ischemic foot may not be as tolerant of microembolization as a nonischemic foot is. Improved limb salvage may be seen if the IIb/IIIa agent improves postprocedural microvasculature flow and decreases early closure of the intervention site. The prevalence of diabetes in this patient population is high, and diabetes is the one comorbidity in which abciximab appears to decrease reintervention. The tibial vessels in the diabetic population are also associated with diffuse occlusive disease. This extensive disease usually makes both surgical bypass and percutaneous intervention difficult. Anecdotal series have reported successful utilization of rotational atherectomy during use of abciximab in these diffusely diseased vessels.[33] The coronary literature supports this therapeutic combination with studies showing significantly improved outcomes when IIb/IIIa agents are utilized with the rotational atherectomy device.[34] With no predictable down side and a multiplicity of theoretical benefits, only financial considerations would appear to restrict use of these agents during peripheral vascular procedures in the tibial vessels.

Summary

The practice of medicine is often a combination of art and science. At times it may be unreasonable to insist on the results of randomized, placebo-controlled trials before using medications or medical devices for unapproved uses when data or experiences are available to support their use. Certainly, safety must be established and monitored during any unapproved use. However, by utilizing the available scientific evidence and sound medical judgment, physicians can make effective decisions. The glycoprotein IIb/IIIa receptor inhibitors appear to be clear examples of agents whose unapproved usage is in some circumstances reasonable. The use of these agents in the coronary vascular bed has been extensively evaluated, the mechanisms of benefit have been defined, and their benefit has been proven. Their use—particularly of abciximab where most of the experience has occurred—in noncoronary, ie, peripheral vascular intervention, has in certain circum-

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stances, such as a visible thrombus forming on a stent, or to hasten thrombolysis in severe, acute limb thrombotic ischemia, seems justified. The broader and routine use of these agents during peripheral vascular interventions may be clarified following further clinical use and the results of ongoing and future clinical trials. ■

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Main Points

- Clinical trials have shown that platelet aggregation and clot formation are decreased by the use of glycoprotein IIb/IIIa receptor inhibitors in coronary vasculature interventions.
- The beneficial effects of these agents observed in coronary vasculature trials—for example, the reduction of distal microembolization, the decrease in vascular thrombus formation, and the increase in the efficacy of thrombolytic therapy—would be vital in peripheral vasculature interventions. However, there have been no large, placebo-controlled trials on the use of these agents in the peripheral vasculature.
- Because peripheral vasculature is so varied and little is known about the effects of the various glycoprotein IIb/IIIa receptor inhibitors on the vascular beds and end organs, each of these agents must be individually studied for safety and efficacy.
- Abciximab is the most extensively studied glycoprotein IIb/IIIa receptor inhibitor, and it has shown positive implications for peripheral vascular intervention in multicenter coronary vasculature and other small clinical trials.
- Future results from ongoing, randomized, controlled studies will clarify whether glycoprotein IIb/IIIa receptor inhibitors are indeed efficacious and safe to use in a range of peripheral vasculature interventions.