Evidence that platelets play a central role in acute coronary syndromes has accumulated over the last several decades and verifies the need for more effective, yet safe, antiplatelet agents. Aspirin continues to be used routinely in coronary angioplasty and to treat patients with myocardial infarction or unstable angina. Mechanistic considerations argue that a more vigorous approach to the inhibition of platelet aggregation should afford greater antithrombotic protection. Glycoprotein (GP) IIb/IIIa (\(\alpha_{\text{IIb}}\beta_{\text{IIIa}}\)) serves as the receptor on platelets that binds plasma-borne adhesive proteins, such as fibrinogen and von Willebrand factor (vWF), to permit platelet aggregation. Aggregation is mediated by this pathway, irrespective of the agonist that stimulates platelets and irrespective of the stimulus-response-coupling pathway that is used to activate GP IIb/IIIa to aggregate platelets. Agents that block this final common pathway by blocking the binding of adhesive proteins to GP IIb-IIIa, termed GP IIb/IIIa antagonists, are currently considered the most powerful specific inhibitors of platelet participation in acute thrombosis. However, the hemostatic function of platelets is also dependent on this pathway. Thus, this novel form of antiplatelet therapy comes with potential safety risks, yet the first fruits of the benefits of this therapeutic approach have begun to emerge.

Various antagonists of GP IIb/IIIa are currently receiving considerable attention from the pharmaceutical industry and clinical cardiologists, and they are being studied in a variety of clinical settings. The first of these agents, the monoclonal antibody abciximab, has been approved for use in percutaneous coronary intervention (PCI). More recently, 2 additional parenteral antagonists have also been approved: tirofiban, a nonpeptide, for treatment of acute coronary syndromes (unstable angina or non-Q-wave myocardial infarction) and eptifibatide, a peptide, for use both in PCI and acute coronary syndromes. In addition, nonpeptide oral antagonists of GP IIb/IIIa intended for long-term use are also in various stages of clinical development and may find application in a broad spectrum of atherothrombotic disease. Although comparisons of the clinical effects of these agents are not yet appropriate, much is known about their comparative biochemical and pharmacological properties. Therefore, the purpose of this review is to summarize the role of GP IIb/IIIa in platelet function and then discuss some of the more relevant issues, concepts, and possibly misconceptions concerning the important pharmacological properties and use of GP IIb/IIIa antagonists.

**Ligand-Binding Properties of GP IIb/IIIa Proteins Involved in Aggregation and Coagulation**

The functions of GP IIb/IIIa in platelet physiology are diverse. Although most functions are manifest after platelet
stimulation, receptor functions have been described for the approximately 80,000 copies of GP IIb/IIIa that exist on the surface of unstimulated platelets in circulation. One is to bind any surface-bound fibrinogen, a property of fibrinogen induced by its immobilization on cells or the vessel wall. GP IIb/IIIa binding to immobilized fibrinogen may assist in the recruitment of platelets to damaged vessel walls or to platelet aggregates, and it may also be involved in the GP IIb/IIIa-mediated uptake of fibrinogen into developing α-granules during megakaryocytogenesis. A second function of GP IIb/IIIa on unstimulated platelets is to bind prothrombin, an interaction that increases the rate of prothrombin conversion to thrombin. Because most GP IIb/IIIa antagonists bind to GP IIb/IIIa, irrespective of its state of activation, these antagonists inhibit the GP IIb/IIIa receptor functions on unstimulated platelets. For example, GP IIb/IIIa antagonists not only inhibit platelet adhesion to immobilized fibrinogen but also decrease fibrinogen uptake into developing platelets. In another example, GP IIb/IIIa antagonists inhibit thrombin generation and fibrin clot formation, a finding that suggests that GP IIb/IIIa antagonists may actually decrease thrombin formation at sites of vascular injury.

As illustrated in Figure 1, platelet stimulation induces new functions of GP IIb/IIIa, inducing it to become a receptor for soluble vWF and soluble fibrinogen, proteins that mediate aggregation. Many agonists are known to stimulate platelets, and all become accessible to circulating platelets on vessel injury (eg, plaque rupture, PCI). One class of agonists is soluble; it consists of thrombin, ADP, collagen, vWF, and immobilized fibrinogen, any of which are capable of stimulating platelets, inducing change in platelet shape, and activating receptor function of GP IIb/IIIa.

**Parenteral GP IIb/IIIa Antagonists**

The four GP IIb/IIIa antagonists developed for parenteral use that have been examined the most extensively in clinical studies include the monoclonal antibody abciximab, the cyclic peptide eptifibatide, the nonpeptide tirofiban, and the α-granule pool of GP IIb/IIIa is functionally important because thrombin-stimulation of platelets in which the plasma membrane GP IIb/IIIa has been rendered inactive is sufficient to support platelet aggregation.

Much effort has been directed toward characterizing the molecular basis for the binding of the soluble adhesive proteins vWF and fibrinogen to platelets. vWF uses two motifs to bind to distinct receptors. One is the Arg-Gly-Asp (RGD) sequence located at residues 1744 to 1746, which binds to GP Ib/IIa; the other is a large motif, the A1 domain, located at residues 449 to 728, which binds to the GP Ib/V/IX complex. GP Ib/V/IX binding to the A1 domain is facilitated when vWF becomes activated either by its binding to collagen on vessel walls or by conditions of high shear. Whereas the activated A1 domain binds to GP Ib/V/IX on unstimulated platelets, binding of the RGD sequence requires platelet activation. Although fibrinogen contains 2 RGD sequences, these do not seem to be involved in its binding to GP Ib/IIa because recombinant fibrinogen lacking these sequences has normal GP IIb/IIIa binding. Rather, fibrinogen binding occurs primarily through the carboxy terminal hexapeptide sequence located at the carboxy terminus of the fibrinogen γ-chain, Lys-Gln-Ala-Gly-Asp-Val (KQAGDV). This sequence is repeated within both outer nodules of fibrinogen, the structural entity that binds GP IIb/IIIa, which allows fibrinogen to bridge aggregating platelets. The relative importance of vWF and fibrinogen to platelet aggregation seems to be a function of shear, with vWF becoming more important to platelet aggregate stability at the high shear rates believed to be achieved in stenosed coronary arteries. It seems that the dual binding motifs on vWF make it ideally suited to mediate platelet aggregation under conditions of high shear. Relevant to the present discussion, GP IIb/IIIa antagonists inhibit platelet aggregation mediated by either adhesive protein.
Parenteral GP IIb/IIIa Antagonists

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>Supplier</th>
<th>Structure</th>
<th>Reference</th>
<th>$K_D$, nmol/L</th>
<th>Integrin Selectivity</th>
<th>Labeled Indication</th>
</tr>
</thead>
<tbody>
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<td>Abciximab</td>
<td>Centocor/Lilly</td>
<td>Human/murine chimeric monoclonal antibody Fab</td>
<td>9</td>
<td>5</td>
<td>$\alpha_{IIb}\beta_3$, $\alpha_b\beta_3$</td>
<td>PCI</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>Merck</td>
<td>Nonpeptide</td>
<td>4</td>
<td>15</td>
<td>$\alpha_b\beta_3$</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>Eptifibatide</td>
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<td>120</td>
<td>$\alpha_b\beta_3$</td>
<td>PCI, acute coronary syndrome</td>
</tr>
<tr>
<td>Lamifiban</td>
<td>Roche</td>
<td>Peptidomimetic</td>
<td>4</td>
<td>9.4</td>
<td>$\alpha_b\beta_3$</td>
<td>(Phase III)</td>
</tr>
</tbody>
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peptidomimetic lamifiban (Table). The Table lists some of the properties of these agents, many of which will be discussed in subsequent sections.

**Issues, Concepts, and Potential Misconceptions About GP IIb/IIIa Antagonists**

**Potency Versus Affinity**

The term potency refers to the position on the dose-effect curve along the dose axis for a particular drug, reflecting the amount of drug required for a desired therapeutic effect. Potency is influenced by many factors, such as distribution, metabolism, and the ability of an agent to interact with the desired targets. Potency is a fairly unimportant characteristic of a drug as long as an effective, acceptable dose can be administered. Efficacy and potency of a drug are not necessarily correlated, and these 2 characteristics of a drug should not be confused.

Affinity constants (usually represented by the dissociation constant $K_D$) are precise biochemical measurements. The dissociation constant $K_D$ is equal to the rate of dissociation of a pharmacological agent from its receptor ($k_d$) divided by the rate of association of this complex ($k_a$). Agents may have similar affinities, but they associate with (and therefore dissociate from) the receptor at different rates. At equilibrium, $K_D$ is equal to the product of the free (unbound) drug concentration and the free receptor concentration divided by the concentration of the drug-receptor complex (illustrated in the legend to Figure 2). Thus, to achieve the same level of receptor occupancy, drugs that have a high $K_D$ (low affinity) have a large unbound concentration at a steady state, whereas drugs with a low $K_D$ (high affinity) are distributed predominantly receptor-bound, with little unbound in the plasma. This is illustrated in Figure 2 at 80% GP IIb/IIIa occupancy.

The monoclonal antibody abciximab is a relatively high-affinity, parenteral GP IIb/IIIa antagonist with a reported equilibrium dissociation constant ($K_D$) of 5 nmol/L. The high affinity of abciximab for GP IIb/IIIa allows for a high degree of association of the initial bolus dose with the target receptor when administered to patients. Calculations based on the published data indicate that approximately 67% of the bolus dose of abciximab used clinically binds to platelets, assuming that approximately one third of platelets are in the spleen. Clinical trials of abciximab have used a dose of this drug sufficient to achieve a high degree of platelet aggregation inhibition, well into the predicted maximal plateau of the dose-effect curve. Other parenteral GP IIb/IIIa antagonists, including the cyclic heptapeptide eptifibatide, the peptidomimetic lamifiban, and the nonpeptide tirofiban, reportedly have lower affinities (larger $K_D$ values, 10 to 200 nmol/L; Table) than reported for abciximab. Despite these differences in affinity, the small-molecule antagonists have been found, at appropriate doses, to inhibit platelet aggregation completely and to block thrombosis in animal models.

As discussed below, GP IIb/IIIa antagonists belong to an unusual drug class, in part because platelet stimulation, which occurs during arterial thrombosis, may change the number of functional GP IIb/IIIa complexes on the platelet surface and also because the receptor cannot be saturated, but rather is titrated to optimize antithrombotic activity and minimize antihemostatic activity. Doses of GP IIb/IIIa antagonists selected for most clinical trials target 80% receptor occupancy of unstimulated platelets because receptor occupancy in excess of this amount affords marked prolongation of bleeding times. However, because potent agonists such as thrombin can cause up to a 50% increase in the number of GP IIb/IIIa molecules exposed on the platelet surface, receptor occupancy after stimulation becomes an important consideration to predicting antithrombotic efficacy.

Predicting the activity of the different antagonists is complicated by considerations that suggest the possibility that drugs with lower affinities may have different antithrombotic activities and different safety profiles, even though they
achieve the same receptor occupancy in resting platelets. Although experimental data that address this point in patients are not yet available (directly determined receptor occupancy has only been reported for abciximab), clearance of the unbound pool on cessation of infusion of abciximab allows for restoration in platelet aggregation induced by activation of the PAR-1 (thrombin) receptor on platelets even before changes in basal receptor occupancy have become apparent.29 A similar observation can be noted with the small-molecule GP Ib/IIa antagonist L-738,167, which has a very high affinity for GP Ib/IIa in dog platelets and a corresponding slow off-rate. This antagonist seems to be less antithrombotic in a canine model of arterial thrombosis when the thrombotic injury is initiated at a time when platelets are effectively inhibited by this drug ex vivo but the free concentration of the drug is negligible, compared with conditions in which the unbound pool of antagonist is in excess.20,31 In both instances, platelet aggregation may have been achieved by agonist-induced exposure of the α-granule pool of GP Ib/IIa. These observations raise the possibility that if doses of distinct antagonists with different affinities are selected to achieve similar 80% receptor occupancy in unstimulated platelets, nonequivalent antithrombotic activity may be observed for these distinct agents.

Reversibility and Duration of Effect

The off-rate and affinity of each of the GP Ib/IIa antagonists that have been studied clinically vary considerably. Because the optimal duration of antplatelet effects for these agents has not been clearly defined to date and because it has not been determined whether GP Ib/IIa occupancy in the absence of an unbound pool is antithrombotic, it is unclear whether continued antplatelet activity after termination of administration of GP Ib/IIa antagonists with a slow rate of dissociation from GP Ib/IIa is pharmacologically advantageous. If continued receptor occupancy provides continued inhibition of thrombosis, a slow off-rate is clearly an advantage. A potential disadvantage is that agents with a slow rate of dissociation cannot be rapidly cleared to regain normal hemostasis should a patient bleed or need immediate surgery. For example, ex vivo measurements have shown that abciximab dissociates from GP Ib/IIa at a half-time rate for dissociation of either 40 minutes or 3 to 4 hours.19,26 The slow rate of dissociation from GP Ib/IIa displayed by abciximab, a reflection of its high affinity, allows platelet inhibitory effects to be measured days after drug administration has been terminated.32 Prolonged platelet inhibition seems to be easily overcome by platelet transfusions, which are effective because only the platelet-bound pool of abciximab persists after infusion of the drug; the unbound pool is rapidly cleared and is no longer available to bind the receptors on transfused platelets. These prolonged platelet inhibitory effects are not shared by the rapidly reversible inhibitors eptifibatide, lamifiban, or tirofiban, as shown in Figure 3. For example, [3H]tirofiban reportedly has a $K_d$ of 15 nmol/L to resting platelets and a corresponding dissociation rate constant of 0.062 s$^{-1}$, which corresponds to a half-time for dissociation of 11 s.33 Similarly, lamifiban reportedly has an apparent $K_d$ of 9.4 nmol/L.34 Presumably, lamifiban has a rapid dissociation rate, similar to tirofiban.

Rapid reversibility should not be assumed to be a general property for all small-molecule GP Ib/IIa inhibitors because the very potent oral GP Ib/IIa inhibitor L-738,167 reportedly has a dissociation rate constant of 0.0047 s$^{-1}$, which translates into a half-time for dissociation of 25 minutes from unactivated platelets, with a correspondingly long-term half-life in vivo of 107 hours in dogs.35 This property of slow release from platelets by L-738,167 dictates the extended vascular compartment residency of this antagonist.30,31 The effects of the short-acting antagonists eptifibatide or tirofiban (Figure 3) on platelet function are minimal several hours after discontinuation of infusion.36 However, rapid reversibility also depends on intact clearance mechanisms. For example, when the renal blood flow decreases in a patient with cardiogenic shock who has been treated with a GP Ib/IIa antagonist that is solely cleared by renal mechanisms, the duration of action of this agent would be markedly prolonged. It is still unclear whether the property of rapid reversibility, an important distinguishing feature of many of the small peptide and nonpeptide GP Ib/IIa antagonists as a class, will give these agents any advantage in settings in which patients require emergency surgical procedures and the need to restore hemostasis rapidly is desired. Currently available data that address this issue are limited.37,38

Another issue related to reversibility is the ability of certain GP Ib/IIa antagonists to cause conformational changes within the GP Ib/IIa complex that can be detected by using ligand-induced binding site (LIBS) antibody reagents that report these conformational changes.39 It has been suggested that LIBS epitope expression may report partial agonist activity of certain GP Ib/IIa antagonists and that this effect should be considered when evaluating these antagonists.40–43 It has also been suggested that LIBS expression in vivo may
facilitate the production of antibodies against GP IIb/IIIa and cause subsequent immune thrombocytopenia.\textsuperscript{44} Nearly all GP IIb/IIIa antagonists have been found to induce LIBS antibody binding.\textsuperscript{45} LIBS epitope expression seems to be a normal function of GP IIb/IIIa, as evidenced by observations showing that fibrinogen binding to GP IIb/IIIa also induces this effect.\textsuperscript{39} LIBS epitopes are fully reversed after the removal of GP IIb/IIIa antagonists. Thus, although the clinical data concerning this issue are limited to a few agents, the available data do not indicate that GP IIb/IIIa antagonist-induced expression of LIBS epitopes is linked to platelet stimulatory events in vivo. The association between LIBS expression and the potential to induce immune thrombocytopenia has not yet been adequately studied.

**Antagonist Specificity**

Most peptide and nonpeptide GP IIb/IIIa antagonists have been designed to inhibit platelet GP IIb/IIIa without altering the adhesive protein binding of related integrins. In contrast, the monoclonal Fab fragment abciximab is not specific because it also inhibits the cellular vitronectin receptors $\alpha_\beta_3$, most likely because of the cross-reactivity of the antibody, whose $\beta_3$ subunit is shared with GP IIb/IIIa.\textsuperscript{46} Abciximab may also interact with the neutrophil-associated integrin Mac-1 (CD11b/CD18), although the mechanism and importance of this interaction are unknown.\textsuperscript{47} The vitronectin receptor $\alpha_\beta_3$ is upregulated several days after angioplasty is performed and may modulate smooth muscle cell and endothelial cell replication.\textsuperscript{48} In separate studies, it has been shown that inhibitors of $\alpha_\beta_3$ have effects on vascular cells because they block proliferation of smooth muscle cells in experimental vascular injury–induced intimal hyperplasia models, induce apoptosis in proliferating endothelial cells, and are vasodilators.\textsuperscript{49–51}

Circumstantial evidence implying a benefit of vitronectin-receptor blockade by abciximab was initially based on the results of the EPIC trial.\textsuperscript{10,52–54} In EPIC, a 26% reduction in repeat percutaneous transluminal coronary angioplasty (PTCA) was noted at 6 months in patients treated with bolus and infusion of abciximab compared with bolus alone or placebo.\textsuperscript{54,55} This reduction in “clinical restenosis” was believed to be a clinical indicator of reduced arterial narrowing after PTCA.\textsuperscript{53} Two additional clinical trials with abciximab, the CAPTURE and EPILOG studies,\textsuperscript{55,56} and a study of abciximab in nonhuman primates\textsuperscript{57} have not provided confirmation of a long-term reduction in restenosis. Thus, the desirability for integrin specificity or lack thereof for efficacy reasons remains an open question. Although specific data concerning specificity and safety are lacking, the pharmaceutical industry, because of uncertainty, for the most part has focused its initial attention toward developing the first generation of oral GP IIb/IIIa antagonists intended for long-term use to be highly specific for GP IIb/IIIa. Ongoing investigation of nonspecific integrin antagonists in animal models of disease may ultimately provide additional answers to questions of specificity and identify new disease targets for integrin antagonists.\textsuperscript{50}

**Platelet Monitoring: Pharmacodynamic Surrogates**

The subject of platelet monitoring has been recently reviewed in detail.\textsuperscript{58} Therefore, the discussion of the pharmacodynamic assessment of blood samples from patients undergoing GP IIb/IIIa antagonist therapy will focus on several key issues. The pharmacological effects of GP IIb/IIIa antagonists can be assessed in a number of different ways. The most widely used method is turbidometric aggregometry, which was used in the dose selection for the larger trials conducted to date.\textsuperscript{27,36,59,60} Although the relative ease of measuring ex vivo platelet aggregation might suggest that this measurement would be appropriate for these purposes, platelet aggregation is highly variable within patient populations, is highly dependent on the skill and experience of the investigators performing the measurements, and may be affected by preparation and handling of blood samples.\textsuperscript{58} Although most laboratories assess the extent of platelet aggregation by the maximal change in percentage of light transmission, it is also possible, and perhaps equally valid, to measure the initial slope of the aggregation response.

Controversy also exists concerning the issue of whether inhibition of platelet aggregation should be normalized for a baseline state before the administration of the antplatelet agent. On the one hand, the ability to express platelet aggregation (and its inhibition) as a percentage of a baseline value minimizes the differences between various laboratories; on the other hand, it links all subsequent determinations to a single measurement performed at a single point in time and ignores physiological changes that may have occurred, such as the activation state of platelets and the number of GP IIb/IIIa molecules expressed on the platelet surface. This issue is particularly important when platelet inhibition is studied for prolonged periods of time (ie, with oral agents).

Other factors that influence platelet aggregation measurements are the number of receptors on platelets at the time of blood sampling, the variability of the binding constants determined for specific inhibitors, the specific anticoagulants used to obtain the required platelet-rich plasma for aggregation measurements, the final ionized calcium concentration of the plasma sample, and the agonist and concentration of the agonist used to stimulate aggregation.\textsuperscript{29,53,61,62} For example, citrate anticoagulation reduces the ionized calcium concentration normally found in blood and has been found to artificially enhance the apparent activity of eptifibatide in ex vivo measurements.\textsuperscript{61} It has been suggested that this phenomenon led to underdosing with eptifibatide in the IMPACT II trial,\textsuperscript{63} which was subsequently corrected with the higher dose chosen in the PURSUIT trial,\textsuperscript{64} as demonstrated by aggregometry studies performed on blood samples anticoagulated with $\alpha$-phenylalanyl-prolyl-arginine-chloromethylketone (PPACK), a direct thrombin inhibitor. Although calcium chelation is known to affect other GP IIb/IIIa antagonists,\textsuperscript{65} no data have been published on the calcium effects of the inhibitory activities of abciximab, tirofiban, or lamifiban. Until data are established, aggregation data using GP IIb/IIIa antagonists might best be monitored in blood samples anticoagulated with thrombin inhibitors such as PPACK or hirudin. In another example, activation of platelets through the thrombin receptors or through the collagen receptor will...
induce additional GP IIb/IIIa molecules to the platelet surface, some with prebound fibrinogen, which increases the concentration of GP IIb/IIIa antagonist required to achieve a given level of inhibition of aggregation compared with that achieved when ADP is used to activate the platelet. Because of these variables in platelet aggregometry measurements, it is unclear which combination of conditions best reflects the effects of inhibitors in vivo.

Measurement of the degree of receptor occupancy by various agents of the GP IIb/IIIa inhibitor class has been proposed to be an alternate surrogate, but it has not been uniformly adopted. Although receptor occupancy measurements are comparatively straightforward for the percentage of GP IIb/IIIa occupied by abciximab because of its slow rate of dissociation, techniques suitable for direct measurement of receptor occupancy in clinical trials by low-molecular-weight GP IIb/IIIa inhibitors that dissociate more rapidly from platelet GP IIb/IIIa have been difficult to achieve and remain to be developed. The receptor occupancy by eptifibatide is measured indirectly by the expression of a LIBS epitope by the D3 monoclonal antibody. Although dose-response curves for GP IIb/IIIa antagonist inhibition of platelet aggregation reaches a plateau at ~80% receptor occupancy, a value achieved in many clinical trials, it is not yet known whether the 80% receptor occupancy level optimizes the antithrombotic efficacy of this class of drugs. It has also been argued that the extent of platelet aggregation is dependent on the absolute number of unoccupied receptors rather than the percentage receptor occupancy by an antagonist. The relationship between efficacy and receptor occupancy by antagonists remains to be elucidated clearly, as does the possibility that alternative mechanisms of inhibition may be operating that do not rely on mass action law.

Although it is difficult to state with certainty which pharmacodynamic surrogate(s) most accurately predict antithrombotic activity, the data available indicate that inhibition of platelet aggregation may have the widest current applicability. However, one real limitation of aggregometry is the inability to discriminate among high levels of blockade (ie, >90%) using ADP as the platelet agonist. To some extent, this limitation may be overcome by stimulation with more-potent agonists, such as the thrombin receptor–activating peptides.

Implications for Development and Clinical Practice
As accumulated data from the various clinical trials with this class of drugs grow, the temptation naturally arises to compare the various agents in terms of their relative safety and efficacy in clinical practice. Similar scrutiny of the various thrombolytic agents has occurred over the last decade and has illustrated the treacherous nature of indirect (ie, interstudy) comparisons. Comparisons of these agents can be made directly only in trials that use optimized protocols for each agent, and these have not yet been performed. Although it is logical to expect that higher doses of GP IIb/IIIa antagonists will lead to greater levels of inhibition of platelet aggregation and greater clinical efficacy, it is of interest that the available data from clinical trials that have studied multiple doses have neither refuted nor supported this concept.

The use of GP IIb/IIIa antagonists in clinical investigation and practice has only just begun, not only in terms of identifying the clinical indications for which these agents will be efficacious with acceptable safety margins, but also in terms of moving this novel approach from short-term–use paradigms to potential long-term indications. Testing of the parenteral inhibitors in short-term indications, such as angioplasty and in acute coronary syndromes, has generally targeted high-grade GP IIb/IIIa inhibition, with treatments continuing for as long as 96 hours. Testing oral agents in these settings is considerably more complex and may not target the same degree of high-grade receptor inhibition. The risk of serious, as well as less clinically serious but equally troublesome, bleeding predicts that with long-term indications, such as in secondary prevention of ischemic events after myocardial infarction or after stroke, the desirable levels of inhibition of platelet aggregation are likely to be considerably lower than those targeted for acute short-term use. Determining an appropriate degree of GP IIb/IIIa blockade with these agents that will be both effective and safe is perhaps the greatest challenge in the development of these oral agents.

The other major challenge in the development of the oral antagonists will be the nature of the pharmacokinetic and pharmacodynamic variability that they display in patients. Higher variability in drug effect is often associated with lower bioavailability drugs. What will be the acceptable low-end bioavailability and corresponding acceptable variability for these agents? Will lower levels of platelet inhibition through this potent mechanism yield a clear therapeutic benefit that is devoid of serious and less serious bleeding effects associated with their antithrombotic action? Are each of these small molecules competitive inhibitors or do they bind to distinct sites on GP IIb/IIIa? Will these agents be used with or without aspirin? What will happen when patients are given, either intentionally or inadvertently, other nonsteroidal anti-inflammatory drugs? What are the effects of oral antagonists after antecedent administration of abciximab? These are some of the more difficult issues that will need to be addressed if the oral GP IIb/IIIa antagonists are to proceed from novel concept to bona fide therapeutic advance.

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Platelet Glycoprotein IIb/IIIa Antagonists: What Are the Relevant Issues Concerning Their Pharmacology and Clinical Use?
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