Integrin $\alpha_{I\beta_3}$ and Its Antagonism

Martin J. Quinn, Tatiana V. Byzova, Jun Qin, Eric J. Topol, Edward F. Plow

Abstract—$\alpha_{I\beta_3}$, the major membrane protein on the surface of platelets, is a member of the integrin family of heterodimeric adhesion receptors. The $\alpha_I$ and $\beta_3$ subunits are each composed of a short cytoplasmic tail, a single transmembrane domain, and a large, extracellular region that consists of a series of linked domains. Recent structural analyses have provided insights into the organization of this and other integrins and how a signal is initiated at its cytoplasmic tail to transform the extracellular domain of $\alpha_{I\beta_3}$ into a functional receptor for fibrinogen or von Willebrand factor to support platelet aggregation and thrombus formation. These functions of $\alpha_{I\beta_3}$ have been targeted for antithrombotic therapy, and intravenous $\alpha_{I\beta_3}$ antagonists have been remarkably effective in the setting of percutaneous coronary interventions, showing both short-term and long-term mortality benefits. However, the development of oral antagonists has been abandoned on the basis of excess of mortality in clinical trials, and the extension of therapy with existing $\alpha_{I\beta_3}$ antagonists to broadly treat acute coronary syndromes has not fully met expectations. An in-depth understanding of how antagonists engage and influence the function of $\alpha_{I\beta_3}$ and platelets in the context of the new structural insights may explain its salutary and potential deleterious effects. (Arterioscler Thromb Vasc Biol. 2003;23:945-952.)

Key Words: platelets • acute coronary syndromes • aggregation • platelet function inhibitors

In what is considered to be the first description of platelets, the Italian physician Bizzozero noted that these tiny elements of the blood could aggregate and that this propensity might contribute to thrombosis.1 By the early 1900s, the Swiss physician Glanzmann had identified a group of patients in whom abnormal platelet aggregation was associated with a bleeding tendency.2 Thus, the pathological importance of platelet aggregation has long served as a driving force to understand the molecular and cellular basis of this response. In the 1960s to 1970s, platelet aggregation was shown to be agonist induced, and fibrinogen and divalent cations were identified as cofactors.3−5 As investigators began to characterize the membrane proteins of platelets by gel electrophoresis, they observed that the patterns of Glanzmann’s platelets were abnormal,6 and 2 glycoproteins, GPIIb ($\alpha_{IIb}$) and IIIa ($\beta_3$), were missing from the surface of these platelets.7 Fibrinogen was found to bind to platelets with the characteristics of a receptor-mediated interaction, platelet aggregation was a consequence of this interaction, and this binding function was markedly diminished with Glanzmann’s platelets.8−11 Within the first 5 years of the 1980s, ligands other than fibrinogen were shown to bind to $\alpha_{IIb}\beta_3$,12,13 and peptides and antibodies that inhibited binding of these ligands and platelet aggregation were identified.14−18 These latter observations established the principle that blockade of $\alpha_{IIb}\beta_3$ could be an antithrombotic target.

During the past 20 years, research on $\alpha_{IIb}\beta_3$ branched into 3 broad directions. First, fundamental analyses of the structure and function of the receptor have gained momentum. About 1 year ago, a breakthrough in these structure-function relations was provided with the report of the crystal structure of the extracellular domain of $\alpha_{IIb}\beta_3$,19 an integrin that shares...
the same β-subunit with αIIbβ3. Second, the entire concept of bidirectional signaling across integrins in general and across αIIbβ3 in particular has emerged as a dominant theme. Activation of αIIbβ3 to become a competent receptor to bind ligand depends on transmission of a signal from within the cell to the extracellular domain, and occupancy of integrins generates signals that initiate numerous cellular responses.20–24 Third, αIIbβ3 has been explored intensively and extensively as a target for antithrombotic therapy. These efforts led to US Food and Drug Administration (FDA) approval of 3 αIIbβ3 antagonists by 1999 and the expectation that additional antagonists and indications would soon follow.25 To comprehensively address all aspects of αIIbβ3, in a brief review, we shall focus on recent advances relating to αIIbβ3 structure, ligand recognition, activation, and antagonism.

Structure of αIIbβ3
αIIbβ3 is restricted primarily to platelets and megakaryocytes, although it is found occasionally on tumor cells as well.26 On platelets, αIIbβ3 is present at the highest density of all of the membrane proteins, ∼80 000 copies per resting platelet.27 The membranes of platelet α-granules also contain αIIbβ3,28 which becomes externalized on platelet secretion to increase the surface expression of αIIbβ3 by 25% to 50%.29,30 As a typical integrin, αIIbβ3 is a noncovalent complex of an α- and a β-subunit (see Figure 1). Each subunit spans the platelet membrane once in a type I orientation. Both αIIb and β3 are glycosylated, and each is the product of a single gene located on chromosome 17.31 αIIb consists of 1008 amino acids. It is proteolytically processed into a heavy and a light chain (Figure 1). The light chain contains a 20-amino acid cytoplasmic tail, a transmembrane helix, and an extracellular segment that is disulfide linked to the heavy chain, which is entirely extracellular. The β3 subunit, 762 amino acids long, has a cytoplasmic tail of ∼48 amino acids.

The model in Figure 1 and the following commentary rely heavily on the crystal structure of αcβ1.19 Each subunit consists of a series of linked domains. At the N-terminal aspects of the α-subunits, a “β-propeller,” a large domain composed of a series of ∼60 amino acid repeats, which are arranged to form 7 “blades” that extend outward from a central core. This structure, first observed in G proteins, was predicted to be present in integrin α-subunits by Springer.32 Within the blades at the base of the β-propeller in the αIIb subunit are 4 divalent binding motifs, in which oxygenated amino acids within short hairpin loops coordinate cations. The remainder of the α-subunit consists of 1 “thigh” and 2 “calf” domains. Between the thigh and the first calf module is a “genu,” a bend that allows the molecule to compact. Not present in the crystallized molecule were the transmembrane and cytoplasmic tail regions. The structure of the cytoplasmic tail peptide of αIIb was solved by nuclear magnetic resonance (NMR)33 and was found to be composed of a membrane-proximal helix that terminates in a bend. Six of the last 8 residues of αIIb are acidic and form a divalent cation–binding site.34,35

The N-terminal aspect of β3 was not present in the crystal structure. Notable features of this region are Cys5, which forms a long disulfide loop to Cys435,36,37 and position 33, the site of the PL A1/2 polymorphism, which has been linked to an increased risk of coronary artery disease in some studies.38 The first identifiable domain in the β3 subunit, the A domain, homologous to I domains within several integrin α-subunits, contains 2 or 3 divalent cations sites, including a MIDAS motif that is prominently involved in ligand binding. A hybrid and a PSI domain, implicated in integrin activation, follow and connect to a protease-resistant region, in which a series of disulfide repeats are arranged into 4 endothelial growth factor (EGF)–like domains that were resolved by NMR.39 The final structural motif discerned in the crystal structure was the βTD. Molecular modeling suggested that a transmembrane helix might extend into the cytoplasmic tail.40 Circular dichroism34,40 and NMR41 support the propensity of the β3 tail to form an extended helix and a turn motif.

Rotary shadow images developed a number of years ago visualized αIIbβ as 2 “stalks” extending from a globular head,42 whereas the crystal structures of the extracellular domain of αβ are compact structures.19,43 This disparity led to considerable discussion in the literature (eg, Liddington44). Most recently, it has been suggested that these conformational differences might be biologically relevant (see following section); they might represent the extremes in a series of
conformational states between resting and activated forms of the β₁ integrins.⁴⁵

**Ligand Recognition by α₁β₃**

A defining characteristic of integrins is the capacity of each family member to bind multiple ligands. The ligand repertoire of αmβ₃ includes fibrinogen, fibronectin, von Willebrand factor (vWF) vitronectin, CD40L, a number of the snake venom disintegrins, and a number of pathogens (reviewed in Plow et al⁴⁶). Fibrinogen and vWF support platelet aggregation. Although fibrinogen is present at substantially higher concentrations than vWF in plasma, initial platelet adhesion to the injured vessel wall is often mediated by vWF’s engaging GPIb on the platelet surface, which may lead to αmβ₃-vWF interactions.⁷⁷ Moreover, in mice rendered deficient in both vWF and fibrinogen, αmβ₃-dependent thrombus formation still occurs,⁴⁸ suggesting that still other ligands can support platelet aggregation. A recent study that also included deficient mice demonstrated that CD40L engagement of αmβ₃ influences the growth and stability but not the initial formation of thrombi.⁴⁹

Two peptides, frequently referred to as the γ-chain and the RGD peptides, define the recognition specificity of αmβ₃ (reviewed in Plow et al⁴⁶); these peptides inhibit the binding of most ligands to αmβ₃ and inhibit platelet aggregation. The dimeric fibrinogen molecule contains 1 set of γ-chain and 2 sets of RGD sequences; mutation of the γ-chain but not the RGD sequences blocks fibrinogen binding to αmβ₃.⁵¹ In contrast, mutation of the RGD sequence in vWF blocks its recognition by αmβ₃.⁵² Recent data suggest that the RGD and γ-chain peptides interact with different but allosterically linked sites in αmβ₃.⁵¹ Accordingly, the αmβ₃ antagonists can bind to different sites in the receptor, which has been demonstrated,⁵⁴ and which implies that their interaction with platelets can have different functional consequences.

In electron photomicrographs, fibrinogen contacted the globular head of αmβ₃.⁴² On the basis of the first crystal structure of αmβ₃, Xiaoang et al¹⁹ suggested that the β-propeller from αm and the A domain from β₃ would form the ligand-binding site and hence, the globular head of the receptor (see Figure 1). In the crystal structure showing an RGD peptide bound to αmβ₃, the Asp in RGD coordinated to the MIDAS-bound metal in the β₃ A domain, and the Arg coordinated with residues in the β-propeller of αm.⁴³ The direct involvement of a β₃ A divalent cation and the αm β-propeller domain establishes a molecular explanation for numerous studies implicating these regions in ligand binding.⁵⁰–⁵² Differences in the structure of the liganded and unliganded forms of αmβ₃ were relatively subtle.

Although the crystal structure allows us to visualize how a peptide ligand binds to the receptor, protein ligand binding to αmβ₃ is more complex. Fibrinogen binding to αmβ₃ is a multistep process; initial reversible contact is followed by irreversible binding, such that the bound ligand no longer readily dissociates.⁶⁴–⁶⁶ Internalization of bound fibrinogen might contribute to this transition in intact platelets⁶⁷ but might also involve formation of additional ligand-receptor contacts. As these contacts form, the conformations of the bound ligand and the occupied receptor change, which lead to the generation of neoepitopes that can be detected by antibodies to ligand-induced binding sites, in the receptor and receptor-induced binding sites, in the ligands.⁶⁸,⁶⁹ Whereas αmβ₃ is required for platelets to retract clots, fibrinogen with mutated γ-chain and RGD sites still retracts clots,⁷⁰,⁷¹ a likely reflection of additional αmβ₃ contact sites.

**Activation of α₁β₃**

αmβ₃ was the first and remains the most prominent example of an integrin in which activation is pivotal for function.⁷² It is now clear that multiple integrins, including α₁β₃, undergo activation.⁷³,⁷⁴ Integrin activation can influence a change in affinity for ligand, a consequence of a conformational change in the receptor, or, in avidity for ligand, a consequence of receptor clustering.⁷⁵ Both mechanisms can lead to activation of αmβ₃ (Figure 2), but affinity modulation appears to be dominant.⁷⁶ Activation of αmβ₃ can be induced by a wide variety of physiologic agonists, which interact with I or more receptors on the platelet surface. The complex network of intracellular signaling events that lead from the agonist receptors to activation of αmβ₃ have been considered in other reviews.⁴³,⁷⁷ From studies of other receptor systems, it was anticipated that tyrosine phosphorylation of the cytoplasmic tails of integrins might play a key role in activation of αmβ₃. With stringent efforts to inactivate phosphatases, Law et al⁷⁸ showed that 2 tyrosines in the cytoplasmic tail of β₃ do undergo phosphorylation, but at a postreceptor occupancy event. Serine/threonine phosphorylation in the β₃ cytoplasmic tail does occur, although the stoichiometry may be low.⁷⁹,⁸⁰

Studies with peptides and molecular biology approaches suggested that the cytoplasmic tails of αmβ₃ interact with each other,³⁴,³⁵,⁸¹–⁸³ and mutational analyses suggested that this complex might regulate activation.⁸²,⁸³ Earlier attempts
by NMR to detect the complex between the cytoplasmic tails had been unsuccessful.41,84 but 2 recent studies did detect such a complex.85,86 In the most recent study, interaction was shown to occur between the membrane-proximal helical regions of the αIIb and β3 cytoplasmic tails (Figure 2). Mutations of residues in the interface that were previously shown to constitutively activate αIIbβ3 disrupted the tail complex, supporting the hypothesis that the complex maintains αIIbβ3 in a resting state and that its dissociation activated αIIbβ3. Therefore, molecules that dissociate the tail complex are predicted to activate αIIbβ3. Consistent with this prediction, incorporation of peptides that duplicated certain portions of the cytoskeletal protein binds directly to αIIbβ3,87,88 and might do so by dissociating the complex or by competing with molecules that bind to the cytoplasmic tails. Recent attention on such binding molecules with αIIbβ3-activating activity has focused on talin. This cytoskeletal protein binds directly to αIIbβ3,89 and overexpression of talin domains in heterologous cells expressing αIIbβ3 induces activation.90,91 Modifications of talin, such as its cleavage by calpain, may generate fragments that bind to the β3 tail.91 Consistent with the postulated role of talin, NMR shows that the talin head domain generated by calpain dissociates the complex of αIIb and β3 cytoplasmic tails by displacing the αIIb from the β3 cytoplasmic tail.86 Talin also binds to a second site on the β3 cytoplasmic tail.91 Several molecules that interact with the tails of αIIb and/or β3/β3 have been identified, and the physiologic role of these interactions in integrin activation remains to be established.

Several events, none of which are mutually exclusive, might occur subsequent to dissociation of the cytoplasmic tail complex and lead to ligand binding to αIIbβ3. One possibility raised by Li et al44 is that the αIIb and β3 subunits self-associate through their transmembrane segments (Figure 2). These investigators observed homooligomers of transmembrane plus cytoplasmic tail constructs. Formation of such complexes could represent a physiologic mechanism for integrin clustering. Takagi et al45 suggested that the β3 integrins might activate by transitioning from the compact state observed in the crystal structure through a series of more open formats and ultimately could assume a form with extended stalks as observed in the early photomicrographs. This “switchblade” mechanism was proposed on the basis of microscopic, mutational, and biophysical measurements. Consistent with this model, it has long been known that αIIbβ3 can exist in multiple conformational states on the platelet surface: several different activated and occupied conformers of the receptor, as well as a resting state of αIIbβ3, can be distinguished with specific ligands and antibodies.93

In the extracellular domain of αIIbβ3, it has been suggested that disulfide exchange might be involved in receptor activation.94–96 Reducing agents can induce platelet aggregation97 and activate αIIbβ3. Yan and Smith96 noted that additional sulfhydryls in the β3 subunit can be labeled inactivated compared with resting αIIbβ3. Previously, Essex and Li98 had show that an antibody to protein disulfide isomerase could induce platelet aggregation, whereas O’Neill et al44 suggested that αIIbβ3 might have intrinsic thiol isomerase activity. The possibility that disulfide rearrangement might trigger activation within the ligand-binding domain is intriguing but must be reconciled with crystallography data.

**Antagonism of αIIIβ3**

When we reviewed the status of αIIIβ3 antagonists about 3 years ago, their future appeared to be bright.25 The benefit of αIIbβ3 antagonism with intravenous agents in the setting of percutaneous coronary interventions (PCIs) had been truly impressive, and their efficacy in other clinical settings appeared promising. Orally active agents were in the midst of development and provided the potential to extend the benefit of short-term therapy to the long-term secondary prevention of cardiovascular disease. In addition, the use of αIIIβ3 antagonists in conjunction with other antithrombotic or thrombolytic agents was under active consideration. This promising future, which raised the possibility that virtually all patients with ischemic heart disease might receive an αIIIβ3 antagonist, has now been replaced by the realization that the therapeutic niche of αIIIβ3 antagonists may be narrower than anticipated.99

The 3 intravenous αIIIβ3 antagonists that were approved by the FDA were abciximab, a chimeric monoclonal antibody fragment; eptifibatide, a cyclic peptide based on a snake venom disintegrin; and tirofiban, a nonpeptide analogue of an RGD peptide. These agents, together with lamifiban, another nonpeptide antagonist, provide marked protection from ischemic events in patients undergoing PCI, leading to a relative risk reduction of 16% to 56% in 30-day ischemic end points in 6 clinical trials involving >12,000 patients (see Topol et al43 and Figure 4 therein). With abciximab, the agent that has been most extensively studied in this setting, this early protection has translated into a long-term protection from death: in a combined analysis of the 3 major abciximab trials, EPIC, EPILOG, and EPISTENT, involving a total of 5799 patients, there was a 22% reduction in mortality (P=0.03) up to the 3-year follow-up.100

It was hoped that the impressive benefits seen in the PCI setting would extend to the larger population of patients with the acute coronary syndromes of unstable angina or non–ST-segment elevation myocardial infarction. Six large trials of αIIbβ3 antagonism in acute coronary syndromes have been conducted (see Table). Overall, the outcomes in these trials indicated a benefit of αIIIβ3 antagonism, but they did not match that observed in a strict PCI setting. A combined analysis of the 6 trials (N=31,402) revealed a 9% reduction in 30-day ischemic events, from 11.8% to 10.8% (P=0.015).101 The benefit of αIIIβ3 antagonists was most pronounced in patients undergoing PCIs, particularly those with diabetes102 or with elevation of the cardiac marker troponin, suggesting that blockade of αIIbβ3 would be of benefit only in the high-risk acute coronary syndrome patients, a much more restrictive population. In fact, it was the high-risk acute coronary syndrome patient who was the target of therapy in the GUSTO IV trial; 59% of the enrolled patients were troponin-positive.103 Patients were randomized to placebo or a bolus and a 24- or 48-hour infusion of abciximab. However, the drug did not show a benefit in the primary end point of 30-day death or myocardial infarction (8.0% for the placebo vs 8.2% for the 24-hour– and 9.1% for
the 48-hour–treated groups; \( P = 0.19 \)). Unexpectedly, mortality increased significantly during the first 48 hours of drug infusion (from 0.3% in the placebo to 0.9% in the 48-hour abciximab infusion groups; \( P = 0.008 \)). The lack of treatment effect was consistent in all subgroups examined, including the high-risk, troponin-positive population. On the basis of these findings, the updated American Heart Association/American College of Cardiology guidelines for the management of patients with non-ST-segment elevation acute coronary syndromes now recommend the use of GPIIb/IIIa antagonists only in patients at high risk or in those in whom PCI is planned, a considerably restricted population than initially anticipated.

The development of orally active \( \alpha_{IIb}\beta_{3} \) antagonists provided the potential for long-term therapy in the secondary prevention of cardiovascular disease. However, to the surprise of many, none of the 5 large trials of oral \( \alpha_{IIb}\beta_{3} \) antagonism was successful; rather, a consistent increase in adverse events was demonstrated. A combined analysis confirmed this lack of efficacy and revealed a highly significant (35% relative, or 0.7% absolute) increase in the risk of death in the 45 523 patients studied.\(^1\)\(^6\)\(^4\) These disappointing results halted further investigations into the use of these oral agents, and it now seems unlikely that oral \( \alpha_{IIb}\beta_{3} \) inhibition will play a role in the secondary prevention of cardiovascular disease.

The combination of \( \alpha_{IIb}\beta_{3} \) antagonists and thrombolytic agents showed the potential for faster, more durable, and more complete reperfusion in patients in phase II trials and pilot studies. These observations led to 2 larger phase III trials, GUSTO V and ASSENT III. In GUSTO V (\( N = 16 \, 588 \)), patients were randomized within 6 hours of an evolving ST-segment elevation myocardial infarction to a standard dose of the intravenous thrombolytic agent reteplase or the combination of abciximab and half-dose reteplase.\(^1\)\(^0\)\(^5\) Combination therapy failed to influence the primary end point of 30-day mortality, 5.9% in patients receiving standard therapy and 5.6% in the combination arm (\( P = 0.43 \)). The combination of reteplase and abciximab reduced the incidence of ischemic complications of myocardial infarction but was associated with increased bleeding, particularly in patients >75 years of age.\(^1\)\(^0\)\(^6\) ASSENT-III compared the efficacy of the thrombolytic agent tenecteplase in combination with various heparins and abciximab in patients within 6 hours of the onset of acute ST-segment elevation myocardial infarction (\( N = 6095 \)).\(^1\)\(^0\)\(^7\) The primary end point of 30-day death/myocardial infarction or refractory ischemia was reduced in the abciximab and low-molecular-weight heparin arms: abciximab 11.4%, \( P = 0.0002 \); low-molecular-weight heparin 15.4%; and unfractionated heparin 11.1%, \( P < 0.0001 \), but major bleeding, particularly in diabetics and older patients, increased. Whether the benefits of combination therapy will outweigh the risks and/or costs and compare favorably to catheter-based reperfusion therapy remains uncertain.

The reason why the \( \alpha_{IIb}\beta_{3} \) antagonists have not lived up to expectations outside the setting of PCIs and might have induced deleterious effects has been the subject of considerable speculation. Potential mechanisms receiving particular attention have been (1) paradoxical \( \alpha_{IIb}\beta_{3} \) antagonist–induced platelet and inflammatory cell activation and (2) the level of platelet inhibition targeted or achieved in the trials. \( \alpha_{IIb}\beta_{3} \) antagonist–induced platelet and inflammatory cell activation has been demonstrated both ex vivo, as an increase in expression of markers of platelet activation,\(^1\)\(^0\)\(^8\),\(^1\)\(^0\)\(^9\) and in vitro, as the induction of fibrinogen binding.\(^1\)\(^1\)\(^0\) calcium transients,\(^1\)\(^1\)\(^1\) thromboxane A\(_2\) production,\(^1\)\(^0\)\(^8\) platelet-leukocyte aggregates,\(^1\)\(^1\)\(^2\) and release of the inflammatory mediator CD40L.\(^1\)\(^1\)\(^3\) However, the reports of in vitro \( \alpha_{IIb}\beta_{3} \) antagonist–induced activation have been conflicting and in some cases might have been attributed to prothrombin activation within the plasma.\(^1\)\(^1\)\(^4\) Furthermore, it is unclear whether all \( \alpha_{IIb}\beta_{3} \) antagonists possess partial agonist effects. There is growing evidence that antagonists interact with a number of sites on \( \alpha_{IIb}\beta_{3} \), resulting in distinct functional consequences. Thus, paradoxical platelet activation may only be a problem with certain \( \alpha_{IIb}\beta_{3} \) antagonists.

Low levels of platelet inhibition have been associated with adverse outcomes. This factor undoubtedly played an important role in the failures of long-term oral therapy, as lower levels of platelet inhibition were targeted in these trials to limit bleeding side effects. In these trials, moderately fluctuating levels of platelet inhibition were seen owing to short half-lives and variable bioavailabilities of the oral compounds.\(^1\)\(^1\)\(^5\) Loss of platelet inhibition might also have been important in the apparent early untoward effect of abciximab in the GUSTO IV trial. Here, the usual abciximab bolus and 12-hour infusion were extended to 24 and 48 hours in the hope of prolonging platelet inhibition. However, this might not have been the case, as a loss of platelet inhibition demonstrated between 12 and 24 hours was observed with a 36-hour abciximab infusion.\(^1\)\(^1\)\(^6\),\(^1\)\(^1\)\(^7\) Partial agonist effects of \( \alpha_{IIb}\beta_{3} \) antagonists discussed in the preceding paragraph also

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**Summary of ACS Trials (30 Day Death/MI) Using \( \alpha_{IIb}\beta_{3} \) Antagonists**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>No. of Patients</th>
<th>Placebo</th>
<th>( \alpha_{IIb}\beta_{3} )</th>
<th>OR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRISM</td>
<td>Tirofiban</td>
<td>3232</td>
<td>7.1</td>
<td>5.8</td>
<td>0.80 (0.61–1.05)</td>
<td>0.11</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>Tirofiban</td>
<td>1915</td>
<td>11.9</td>
<td>8.7</td>
<td>0.70 (0.51–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>Eptifibatide</td>
<td>10 948</td>
<td>15.7</td>
<td>14.2</td>
<td>0.89 (0.79–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>PARAGON A*</td>
<td>Lamifiban</td>
<td>2282</td>
<td>11.7</td>
<td>12.1</td>
<td>0.96 (0.70–1.32)</td>
<td>0.82</td>
</tr>
<tr>
<td>PARAGON B</td>
<td>Lamifiban</td>
<td>5225</td>
<td>11.4</td>
<td>10.6</td>
<td>0.92 (0.77–1.09)</td>
<td>0.35</td>
</tr>
<tr>
<td>GUSTO IV†</td>
<td>abciximab</td>
<td>7800</td>
<td>8.0</td>
<td>9.1</td>
<td>1.1 (0.94–1.39)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

* Treatment arm includes all patients who received lamifiban.
† Treatment arm refers to patients in 48-hour abciximab group.
must depend on the level of platelet inhibition. Hence, the 2 explanations for the undesirable outcomes obtained with \( \alpha_{IIb}\beta_3 \) antagonists are clearly interrelated.

In summary, the clinical development of antagonists of \( \alpha_{IIb}\beta_3 \) has been far from straightforward. The initial promise has been replaced by the realization that potent platelet inhibition with \( \alpha_{IIb}\beta_3 \) blockade does not necessarily translate into a dramatic improvement in clinical outcomes. At present, the indication of \( \alpha_{IIb}\beta_3 \) antagonists appears limited to short-term therapy at high levels of platelet inhibition in patients undergoing PCIs or initial medical therapy in high-risk patients with acute coronary syndromes. Patients receiving these agents with PCIs derived a pronounced benefit of mortality reduction and protection from myocardial infarction. With >1.5 million procedures per year worldwide, this is a substantial clinical benefit in the field of ischemic heart disease. In the future, further refinements in therapy might be possible. Needed is the ability to integrate recent structural information developed on the integrins and their activation. With 10. Bennett JS, Vilaire G. Exposure of platelet fibrinogen receptors by ADP

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In the June 2003 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, in the article by Quinn et al (Integrin $\alpha_{\text{IIb}}\beta_3$ and Its Antagonism; pp 945–952), Figures 1 and 2 were incorrectly numbered, so their order should be reversed. The legends are correct as they are. The authors apologize for this error.