Effects of GP IIb/IIIa Inhibitors on Vascular Inflammation, Coronary Microcirculation, and Platelet Function

Dean J. Kereiakes, MD, FACC

The Heart Center of Greater Cincinnati and The Lindner Center at The Christ Hospital, Cincinnati, OH, The Ohio State University Department of Medicine and Division of Cardiology, Columbus, OH

The platelet glycoprotein (GP) IIb/IIIa inhibitors differ markedly in their pharmacokinetics, pharmacodynamics, and differential receptor affinities. Abciximab and the small-molecule GP IIb/IIIa inhibitors (eptifibatide, tirofiban) have separate, distinct binding sites on the GP IIb/IIIa receptor complex. The affinity of abciximab for the platelet GP IIb/IIIa integrin receptor, together with non-platelet-receptor mediated effects achieved through its affinity for the $\alpha V\beta_3$ and CD11b/18 receptors, most likely contribute to the clinical benefit associated with the use of abciximab as adjunctive pharmacotherapy during primary percutaneous coronary intervention for the treatment of ST-elevation acute myocardial infarction.
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Key words: GP IIb/IIIa inhibitors • Abciximab • Percutaneous coronary intervention • Platelet aggregation • Coronary microvascular function • Vascular inflammation

The therapeutic class of platelet glycoprotein (GP) IIb/IIIa inhibitors has been rather arbitrarily defined based on a shared affinity of these agents for the platelet GP IIb/IIIa integrin receptor. Collectively, GP IIb/IIIa inhibitors block the final common pathway for platelet aggregation and have demonstrated efficacy for reducing platelet-mediated adverse ischemic clinical outcomes when administered during percutaneous coronary intervention (PCI) or to patients with acute coronary syndromes (ACS). The currently available US Food and Drug Administration–approved platelet GP IIb/IIIa inhibitors, however, differ markedly in pharmacokinetics, pharmacodynamics, and specific receptor affinity.

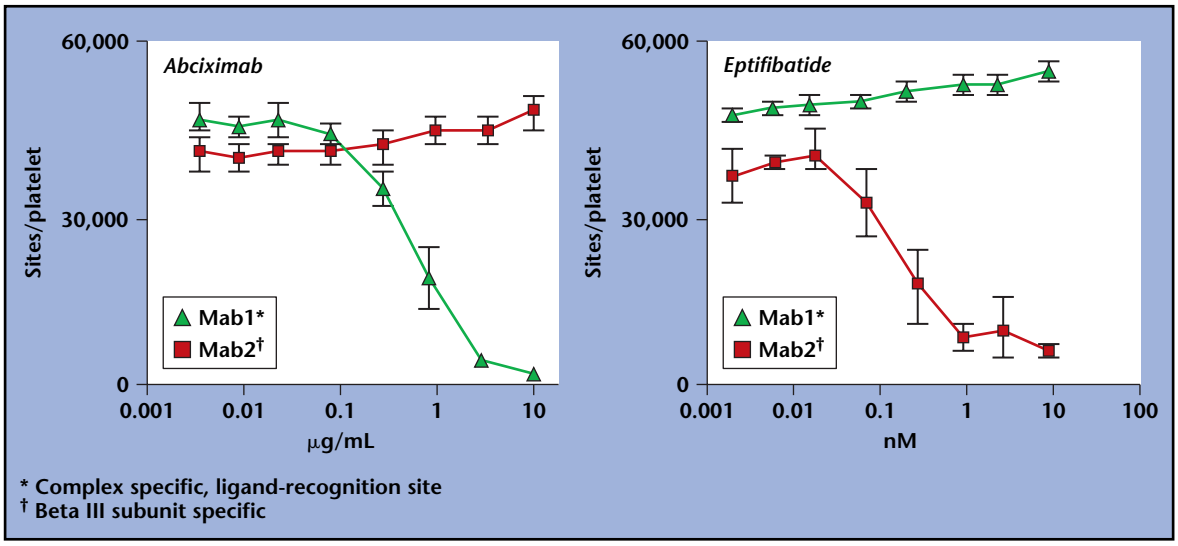
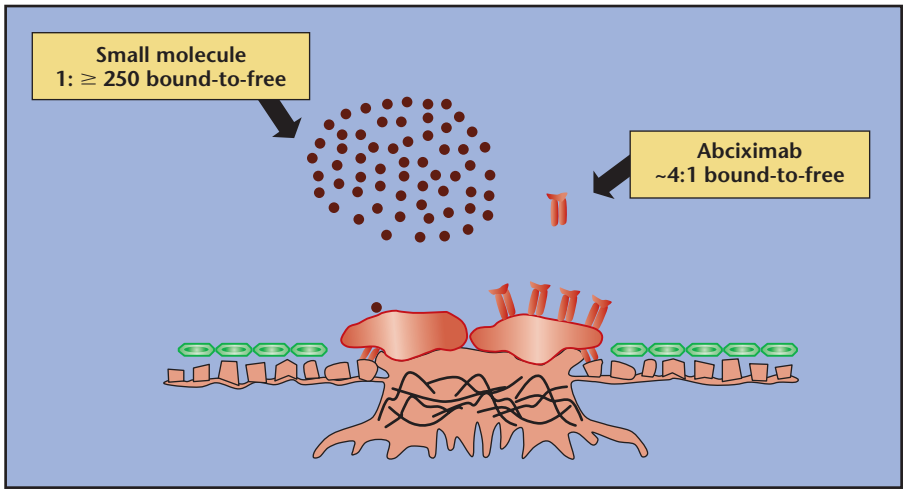


Figure 1. *Differential displacement of site-specific monoclonal antibodies Mab1 (LYP18), a complex specific, ligand-recognition site, and Mab2 (4F8), a beta III subunit–specific site.* **(Left)** *Abciximab binds the complex specific, ligand-recognition site, whereas* **(Right)** *eptifibatide, a small-molecule platelet GP IIb/IIIa receptor inhibitor, binds the beta III subunit–specific site. Reproduced with permission from Quinn M et al.*[1]

Separate and distinct binding sites on the GP IIb/IIIa receptor complex have been defined for abciximab and for the "small-molecule" GP IIb/IIIa inhibitors (eptifibatide, tirofiban) by means of differential displacement of site-specific monoclonal antibodies: Mab1 (LYP18), a complex specific, ligand-recognition site (bound by abciximab), and Mab2 (4F8), a beta III subunit–specific site (bound by the small-molecule GP IIb/IIIa inhibitors).[1] In addition to binding a separate site on the GP IIb/IIIa receptor (Figure 1), abciximab has a unique pharmacokinetic and pharmacodynamic profile. Abciximab has a high affinity (low K_d), and the small-molecule inhibitors a relatively low affinity (high K_d), for binding to the GP IIb/IIIa receptor.[2] This difference is reflected in the ratio of platelet-bound to free (in serum) drug (Figure 2). The vast majority of abciximab molecules are platelet-bound (bound-to-free ~4:1),[3] whereas the converse is true for the small-molecule inhibitors (~1: ≥ 250).

Similarly, the pharmacokinetic off-rates of these 2 types of agents are markedly different. Recovery of platelet aggregability is much more rapid (4-8 hours) following discontinuation of the small-molecule GP IIb/IIIa inhibitors than following abciximab (Figure 3).[4] Recovery of aggregability after discontinuation of abciximab is ≤ 50% complete at 24 hours. The gradual "redistribution" of abciximab across GP IIb/IIIa receptors reflects the high-affinity, reversible binding of this agent, with receptor occupancy rates of 30% at 8 days and 10% at 15 days following an abciximab intravenous bolus.[5] The durable presence of abciximab far exceeds the average lifespan (7-10 days) of an individual platelet. Abciximab has cross-affinity for the additional integrin

Figure 2. *Differential pharmacokinetics. Marked differences in the relative affinity for the platelet GP IIb/IIIa receptor and in the ratio of platelet-bound to free (in serum) drug between abciximab and small-molecule GP IIb/IIIa inhibitors. Abciximab has a bound-to-free ratio of ~4:1; the small-molecule inhibitors have a bound-to-free ratio of ~1: ≥ 250.*



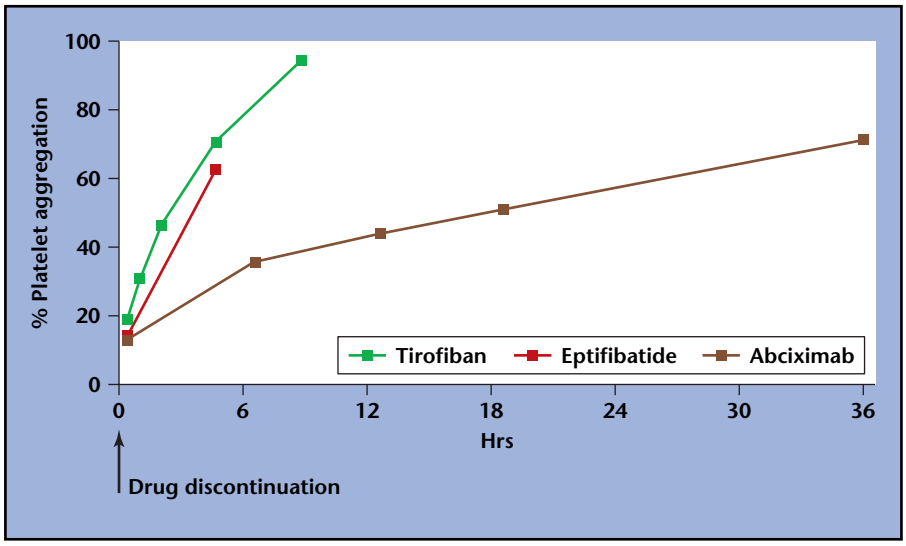


Figure 3. *Reversibility of platelet inhibition. Marked differences in the rate of recovery of platelet aggregability following discontinuation of small-molecule platelet glycoprotein IIb/IIIa inhibitors (tirofiban, eptifibatide) and following abciximab. Recovery of platelet aggregation occurs rapidly (4-8 hours) after discontinuation of small-molecule inhibitors and gradually after discontinuation of abciximab. Adapted from Springer and Drugs of the Future, 15, 2003, 25,* Thrombosis and Thrombolysis, *Mousa SA and Bennet JS,[4] with kind permission from Springer Science and Business Media.*

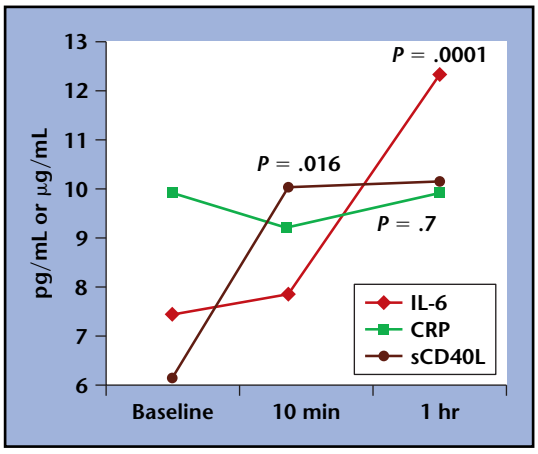
receptors $\alpha V\beta_3$ (vitronectin) and CD11b/18 (MAC1), which modulate multiple functions distinct from platelet aggregation.[6,7] Interest in these abciximab "non-platelet receptor" effects has been heightened by the observations that platelet inhibition alone may not fully explain the magnitude of clinical benefit attributable to abciximab therapy.[8,9]

Vascular Inflammation

Vascular inflammation plays an integral role both in the pathogenesis of ACS and in the vascular response to injury, particularly PCI. Patients with ACS manifest generalized multicentric vascular inflammation with multifocal distribution of complex or ruptured atherosclerotic plaques across a range of vascular beds (coronary, carotid, renal, etc.).[10-12] Histopathology demonstrates an increase in subintimal macrophage and T-lymphocyte density,[12-14] the degree of which seems to be directly correlated with an elevation in systemic serologic "markers" of inflammation, including interleukin-6 (IL-6) and C-reactive protein (CRP).[15,16] In general, patients with many ruptured coronary plaques and/or rupture of carotid plaques have higher levels of CRP.[11,15,16] The genesis of CRP is believed to be, in large part, secondary to monocyte/macrophage production of IL-6 at the site of spontaneous or iatrogenic (PCI) plaque rupture, which subsequently promotes hepatic CRP production.[17,18] Other potential sources of CRP include adipocytes and vascular smooth muscle cells (VSMCs), particularly in response to vascular injury.[19-21]

Many findings exist to support the premise that PCI, particularly stenting, elicits an inflammatory response due to both local stent-vessel injury and distal atheroembolism.[22,23] The inflammatory sequence that follows stent deployment involves platelets as well as leukocytes and is reflected in the temporal sequence of elevated serologic markers, including sCD40L, IL-6, and CRP (Figure 4).[24,25] CD40L resides largely in the alpha-granule of the platelet and is released on platelet activation.[26] Once free, soluble CD40L binds specific receptors on vascular endothelium to promote multiple inflammatory processes (production of tissue factor, cytokines, chemokines, matrix metalloproteinases, reactive oxygen species, and adhesion molecules). White cell adhesion and transmigration across endothelium occur, in rapid sequence, in response to vessel injury and are reflected by the procession of serologic markers. Not surprisingly, as sCD40L reflects the degree of platelet activation, it has

Figure 4. *Time sequence for detection of circulating inflammatory markers sCD40L, interleukin-6 (IL-6), and C-reactive protein (CRP) after coronary stent deployment. A marked increase in sCD40L is detected within 10 minutes of stent deployment, followed by a significant increase in IL-6 within 1 hour of the procedure. Adapted with permission from Aggarwal A et al.[24,25]*



been directly correlated with the incidence of adverse ischemic outcomes in patients with ACS, as well as restenosis following PCI, and is a powerful predictor for clinical benefit associated with abciximab therapy (higher sCD40L predicts greater clinical benefit).[27-29]

Elevated levels of CRP late (≥ 72 hours) after coronary stent deployment have been correlated with subsequent coronary restenosis and with diminished late cardiac event-free survival following stenting.[30] Abciximab shows potent and sustained suppressive effects on IL-6 and CRP levels following PCI, which seems to differ from observations made after small-molecule GP IIb/IIIa inhibitor therapy.[31] For example, a reduction in CRP levels accompanied infusion of eptifibatide for coronary stent deployment, but a substantial increase in CRP was observed following termination of the eptifibatide infusion.[32,33] Similarly, an increment in both sCD40L and CD62 (p-selectin) following initiation of intravenous eptifibatide therapy has been observed, prompting some investigators to propose a proinflammatory/partial agonist effect of eptifibatide.[34-36] In addition to its potent inhibition of platelet aggregation, abciximab's efficacy in suppressing vascular inflammation is multifactorial and most likely involves pleuripotential receptor affinity.

Elevated levels of C-reactive protein late (≥ 72 hours) after coronary stent deployment have been correlated with subsequent coronary restenosis and with diminished late cardiac event-free survival following stenting.

Pleuripotential Receptor Affinity

Abciximab shows affinity for the $\alpha V\beta_3$ receptor equal to that for the GP IIb/IIIa receptor.[6,7,37] The $\alpha V\beta_3$ receptor is expressed in high density on osteoclasts and on certain tumor cells and in variable density on endothelial and smooth muscle cells and on monocytes, T-lymphocytes, and polymorphonuclear leukocytes.[38-41] Only ≤ 500 $\alpha V\beta_3$ receptors are found on the surface of each platelet.[6,37] Endothelial cells exhibit the potential to "upregulate" or increase $\alpha V\beta_3$ expression in regions with underlying atherosclerotic plaque or in response to vascular injury.[39] Although few in number, the $\alpha V\beta_3$ receptors on activated platelets have been implicated in the modulation of platelet adhesion to osteopontin (present in atherosclerotic plaque) and in the suppression of platelet-supported thrombin generation.[42] In fact, in one study, "dual" receptor blockade of the platelet GP IIb/IIIa and $\alpha V\beta_3$ receptors by abciximab provided greater inhibition of platelet-supported thrombin generation than did monoreceptor blockade of either the GP IIb/IIIa or $\alpha V\beta_3$ receptor with specific monoclonal antibodies (10E5 or LM609, respectively) or their combination.[42] This finding may be explained by the interference of abciximab with the binding of factor V/Va to the platelet surface and thus with assembly of the platelet prothrombinase complex.[43]

Blockade of the $\alpha V\beta_3$ receptor also inhibits leukocyte transmigration across endothelium, a critical step in the white cell inflammatory response, and inhibits the smooth muscle cell proliferation that may contribute to neointimal hyperplasia and restenosis following PCI.[39,44] In animal models, specific blockade of the $\alpha V\beta_3$ receptor with abciximab, LM609 (as noted above, a specific monoclonal antibody to $\alpha V\beta_3$), or XT199 (a synthetic small-molecule antagonist of $\alpha V\beta_3$) can limit neointimal hyperplasia and late lumen loss following balloon angioplasty or stent deployment.[38,45] This effect seems to require protracted, high-dose exposure to $\alpha V\beta_3$ inhibition—not as yet employed in humans.

The available data do not support the presence of clinically demonstrable antiproliferative-antirestenotic effects of abciximab when infused at currently recommended doses (12-24 hours) following PCI in a global patient cohort, but several intriguing observations in patients with diabetes mellitus deserve mention. In the Evaluation of GP IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) trial, patients receiving an abciximab bolus and 12-hour infusion following coronary stent deployment had an 18% reduction (vs placebo) in target-vessel revascularization (TVR) at 6 months.[46] This observation was driven by a 51% reduction (P = .02), abciximab vs placebo) in TVR in patients with diabetes and was further substantiated by a reduction in late coronary lumen loss/angiographic restenosis demonstrated by quantitative coronary angiography in this specific patient subset. Furthermore, the observation of selective late clinical and/or angiographic benefit from abciximab in patients with diabetes was also made in 2 trials: the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long Term Follow-up (ADMIRAL)[47] and the Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics? (ISAR-SWEET), a placebo-controlled,

randomized trial of abciximab during coronary stenting.[48]

In ADMIRAL, abciximab was administered to patients undergoing coronary stent deployment for evolving ST-elevation acute myocardial infarction (STEMI). By the 6-month follow-up, a 61% reduction in TVR was observed among patients with diabetes who received abciximab, but was not substantiated by a concomitant reduction in obstruction of lumen diameter on late coronary angiography.[47] Conversely, in the ISAR-SWEET trial, patients with diabetes undergoing elective coronary stent deployment who received abciximab had a reduction in both clinical (TVR; $P = .03$) and angiographic ($P = .01$) restenosis.[48] Although isolated platelet GP IIb/IIIa receptor inhibition could be responsible for this benefit—by reducing mural thrombus formation and subsequent release of platelet-derived growth factors—patients with diabetes have demonstrated differences (vs nondiabetics) in $\alpha V\beta_3$ receptor expression, which more likely underlies their apparent differential/preferential response to abciximab.

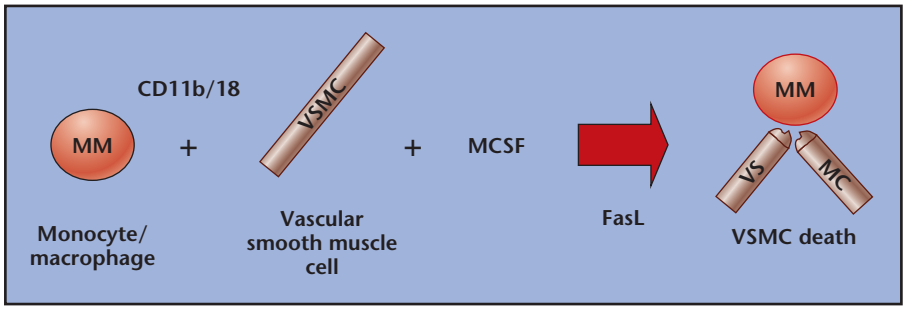
Among platelet GP IIb/IIIa inhibitor agents, only abciximab shows affinity for the CD11b/18 (MAC1) receptor.[6] CD11b/18 contributes to the processes of neutrophil adhesion, leukocyte transmigration, neutrophil aggregation, chemotaxis, and phagocytosis as well as leukocyte-platelet interactions.[6,7] White cell surface expression of CD11b/18 is increased in patients with active coronary heart disease and following PCI.[49-51] In fact, CD11b/18 expression is upregulated following PCI, particularly stent deployment, and is inhibited by abciximab.[49] Consistent with the putative effect of abciximab on the CD11b/18 receptor are the observations that abciximab markedly diminishes both white cell adhesion to the site of stent deployment and circulating monocyte/neutrophil-platelet aggregates.[37,52] Recent data have also implicated CD11b/18 in the process of restenosis following coronary stent deployment.[51] Finally, the CD11b/18 receptor seems to be involved in modulating monocyte/macrophage-mediated VSMC death (apoptosis), which probably influences vulnerability to plaque rupture.[53]

These observations suggest that the anti-inflammatory effects of abciximab, mediated at least in part by an affinity for the CD11b/18 receptor, may provide "cytoprotection" for vascular smooth muscle cells, which in turn confers long-term plaque stability.

Multiple histopathologic observations have suggested inflammation is involved in the instability of atherosclerotic plaque.[54-56] Indeed, plaques implicated in causing sudden cardiac death or myocardial infarction have monocyte/macrophage infiltration of the plaque or fibrous cap and diminished smooth muscle content.[55] A direct assessment of plaque strain (a measure of vulnerability to plaque rupture) by intravascular elastography has found it to be directly correlated with macrophage density and inversely correlated with the smooth muscle cell content of the plaque.[57]

The mechanism of monocyte/macrophage-mediated VSMC apoptosis and the potential plaque-stabilizing effects of abciximab have only recently been described.[53] In vitro incubation of VSMC with monocytes in the presence of monocyte colony-stimulating factor (MCSF) results in VSMC apoptosis. Monocyte attachment to VSMCs seems to require the CD11b/18 receptor and is inhibited by abciximab and by CD18 (a specific monoclonal antibody to CD11b/18) but not by the small-molecule GP IIb/IIIa inhibitors (eptifibatide, tirofiban).[53] Following attachment, the monocyte becomes activated by MCSF and mediates VSMC death (Figure 5). Clinically, blood levels of MCSF are elevated in patients in direct proportion to the acuity of the clinical syndrome.[58,59] These observations suggest that the anti-inflammatory effects of abciximab, mediated at least in part by an affinity for the CD11b/18 receptor, may provide "cytoprotection" for VSMCs, which in turn confers long-term plaque stability. Such a "plaque-stabilizing" effect of abciximab has been implicated as contributing to the

Figure 5. *Mechanism of monocyte/macrophage-induced vascular smooth muscle cell (VSMC) death. Monocyte/macrophage (MM) attachment to a VSMC involves the CD11b/18 receptor. In the presence of monocyte colony-stimulating factor (MCSF), via the FasL pathway, macrophage activation results in VSMC apoptosis. Adapted with permission from Seshiah PN et al.*[53]



long-term survival advantage associated with abciximab therapy following PCI, particularly primary PCI for STEMI.[8,9,60]

Abciximab Effects on Microvascular Function and Myocardial Perfusion

Adjunctive pharmacotherapy with abciximab during primary PCI and stenting has been shown to improve thrombolysis in myocardial infarction blush grade (TMBG) as well as the magnitude of ST segment resolution (> 70% resolution), both of which reflect the adequacy of microvascular flow and the efficacy of myocardial reperfusion.[61,62] One study reported that improvement in these parameters was accompanied by an increase in coronary flow reserve and in peak coronary flow velocity in the stented vessel.[63] Attenuation of coronary microvascular endothelial dysfunction and a reduction in coronary resistance, as reflected by an increase in coronary flow reserve and fractional flow reserve, respectively, add further objective support for the premise that abciximab directly improves small-vessel blood flow with consequent enhancement in myocardial nutritive reperfusion.[64,65]

A direct correlation has been observed between the degree (%) of ST segment resolution and coronary flow velocity reserve following primary PCI with stenting for treatment of STEMI.[66] Furthermore, analyses of paired left ventriculograms and/or SPECT (single photon emission computed tomography) myocardial scintigraphy performed at the time of primary PCI, and at follow-up, have demonstrated a salutary effect of abciximab on global as well as regional (infarct zone) left ventricular functional recovery and a reduction in the extent of infarction within the myocardial distribution designated as "at risk."[52]

These beneficial effects on microvascular function and flow have been attributed to both the platelet-inhibitory and the non-platelet-mediated actions of abciximab. For example, dissolution of platelet thrombus ("dethrombosis") secondary to blockade of high-affinity platelet GP IIb/IIIa receptors has been demonstrated for both abciximab and the small-molecule GP IIb/IIIa inhibitors (Figure 6).[67,68]

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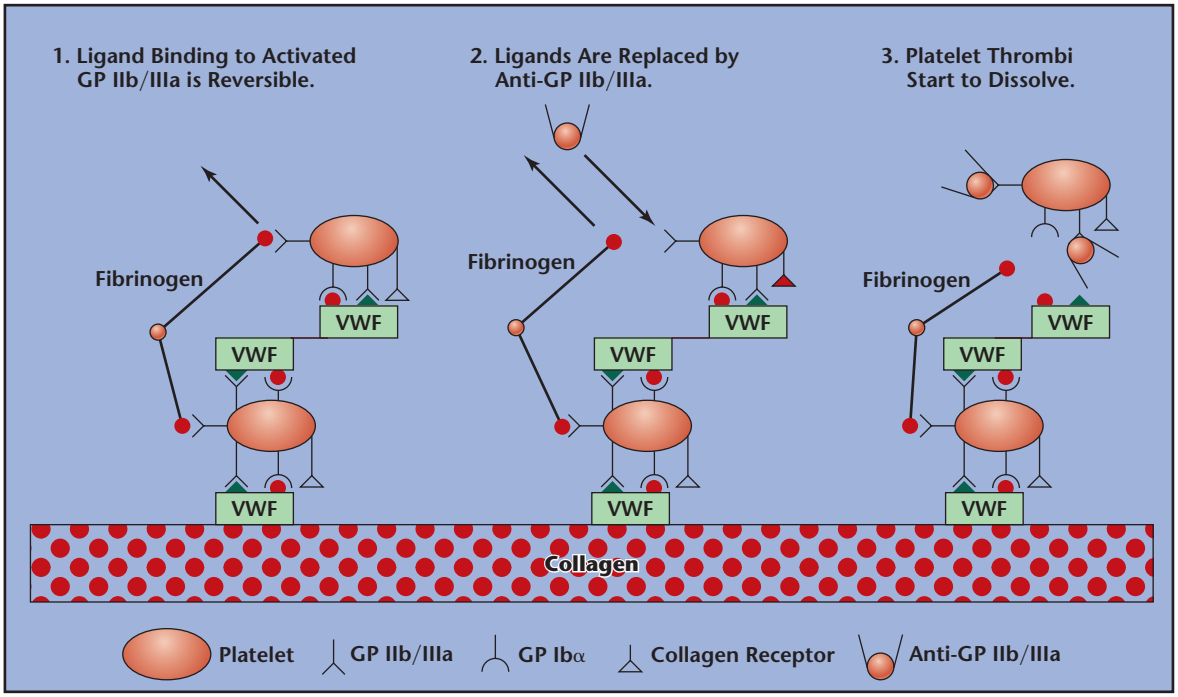
Figure 6. *Mechanism of platelet thrombus dissolution by antiglycoprotein IIb/IIIa receptor agents. High-affinity antiglycoprotein IIb/IIIa receptor agents displace ligands (fibrinogen, von Willebrand factor [VWF], thrombospondin, etc.) that mediate platelet "bridging"/aggregation, resulting in disaggregation. GP, glycoprotein; VWF, von Willebrand factor. Reprinted with permission from Goto S et al[67] and The American College of Cardiology Foundation.*



Platelet "disaggregation" is one proposed mechanism by which microemboli are reduced and small-vessel/capillary blood flow improves. Recent data suggest that white cells and white cell platelet aggregates may contribute to impaired microvascular function and thus to the subsequent extent of myocardial infarction. Studies have shown a direct correlation of the presence and level of neutrophil byproducts (leukotrienes) with both the acuity of the clinical syndrome (stable vs unstable angina vs STEMI) and the degree of microvascular coronary resistance.[69,70] Furthermore, blockade of the CD11b/18 receptor with a specific monoclonal antibody (CD18) reduces coronary microvascular resistance and improves flow.[70] In an animal model, a reduction in polymorphonuclear leukocyte accumulation within zones of experimental infarction has been demonstrated for abciximab, but not for the small-molecule GP IIb/IIIa inhibitor lamifiban.[71] Similarly, studies show a reduction in monocyte and neutrophil-platelet aggregate formation following abciximab administration (in vitro), but not following eptifibatide or tirofiban.[72,73] These observations suggest that non–GP IIb/IIIa receptor activities of abciximab may contribute to the objectively measured improvements in coronary microvascular function and flow, and to the limitation of the size of myocardial infarction that accompanies abciximab administration for primary PCI.

Conclusion

Although this class of therapeutic agents—the GP IIb/IIIa inhibitors—has been simplistically defined by a common affinity for the platelet GP IIb/IIIa receptor, marked differences exist among the members of this "class" with respect to pharmacokinetics, pharmacodynamics, and differential receptor affinities. The specific affinity of abciximab for the $\alpha V\beta_3$ and CD11b/18 receptors, in combination with the pharmacokinetic phenomenon of gradual redistribution, contributes to a more profound and protracted anti-inflammatory effect of this agent. Thus, specific platelet- and non-platelet-mediated effects of abciximab probably contribute to the magnitude of the clinical benefit associated with its use as adjunctive pharmacotherapy during primary PCI with stenting for treatment of STEMI. ■

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Main Points

- The currently available platelet glycoprotein (GP) IIb/IIIa inhibitors, abciximab and the "small-molecule" inhibitors (eptifibatide, tirofiban), have distinct binding sites on the GP IIb/IIIa receptor complex.
- Abciximab has a higher affinity (vs the small-molecule inhibitors) for binding to the GP IIb/IIIa receptor, and more gradual recovery of platelet aggregability after discontinuation of the drug.
- Abciximab has cross-affinity for the $\alpha V\beta_3$ and CD11b/18 receptors, which may contribute to its "non-platelet receptor" effects, including potent and sustained suppression of interleukin-6 and C-reactive protein levels following percutaneous coronary intervention (PCI).
- Blockade of $\alpha V\beta_3$ receptors by abciximab inhibits both the white cell inflammatory response and smooth muscle cell proliferation that may contribute to restenosis following PCI.
- Through its affinity for the CD11b/18 receptor, abciximab diminishes both white cell adhesion to the site of stent deployment and circulating monocyte/neutrophil-platelet aggregates following PCI.
- The anti-inflammatory effects of abciximab, mediated in part by its affinity for the CD11b/18 receptor, may provide a "plaque-stabilizing" effect, which could contribute to the long-term survival advantage associated with abciximab therapy following PCI, particularly for ST-elevation myocardial infarction.
- Adjunctive pharmacotherapy with abciximab during primary PCI and stenting improves TIMI myocardial blush grade and the magnitude of ST segment resolution, both of which reflect the adequacy of microvascular flow and the efficacy of myocardial reperfusion.

treatment demonstrates prolonged platelet inhibition with gradual recovery from GP IIb/IIIa receptor blockade. *Circulation*. 1998;97:1680-1688.
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