A Critical Appraisal of Platelet Glycoprotein IIb/IIIa Inhibition

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Despite the success of abciximab in preventing ischemic events after percutaneous coronary interventions, attempts to develop intravenous, small-molecule glycoprotein IIb/IIIa antagonists and diversify the clinical indications for these agents have produced varied results. The 30-day ischemic event reduction in the percutaneous coronary intervention trials has ranged by over three-fold (16% to 56%) and is greater among the acute coronary syndrome trials. The phase III trials exploring the role of oral glycoprotein IIb/IIIa inhibition have been consistently disappointing, with evolving evidence of increased mortality. Mechanisms contributing to these heterogeneous results may include normal variation in platelet or receptor number, differences in receptor activity, interpatient variation in pharmacological dose-response and the possibility of prothrombotic or nonglycoprotein IIb/IIIa effects. Plausibility of “suboptimal” effect is suggested by several recent studies. Trials investigating the role of intravenous small-molecule IIb/IIIa antagonists highlight the importance of effective dosing. The increase in bleeding and mortality observed in the oral glycoprotein IIb/IIIa studies indicate the consequences of suboptimal dosing on safety on one hand, while raising the possibility of important prothrombotic, counterregulatory or other sudden cardiac events. This article will undertake a review of the relevant platelet biology, discuss the mechanisms that may contribute to suboptimal antiplatelet efficacy with these agents and examine insights from the clinical trials supporting these concepts. (J Am Coll Cardiol 2000; 36:2028–35) © 2000 by the American College of Cardiology

Antagonists of the glycoprotein IIb/IIIa receptor block the final common pathway for platelet aggregation (1), and extensive research has brought three of these agents to clinical practice. However, in contradistinction to the evidence supporting cholesterol lowering and angiotensin-converting enzyme inhibition therapy, the experience from over 75,000 patients in glycoprotein IIb/IIIa trials is marked by heterogeneity. Antibody-mediated glycoprotein IIb/IIIa blockade during percutaneous coronary interventions (PCI) has reduced 30-day ischemic outcomes by approximately 35% to 50% (2–4). In contrast, the clinical development of more specific, small-molecule (peptide and peptidomimetic) glycoprotein IIb/IIIa antagonists for PCI has been hampered by the question of dose adequacy illustrated by less consistent benefits (5–7). Moreover, as empiric therapy for acute coronary syndromes (ACS), a therapeutic benefit comparable with the PCI trials, appears to be confined to those patients with evidence of myonecrosis (8,9) (i.e., troponin elevation) or undergoing early PCI (10). Of greater concern is that attempts to extend specific receptor blockade to chronic therapy with oral glycoprotein IIb/IIIa antagonists have demonstrated an approximately 30% increase in mortality (11).

The fundamental concept underpinning effective suppression of ischemic events by these agents is an adequate level of platelet glycoprotein IIb/IIIa receptor inhibition at the time of threatened thrombotic occlusion or atherothrombotic embolization. The apparent divergence in efficacy among various agents and in different clinical settings may be explained by factors that compromise this level of inhibition—variations in dose response, divergence of patient characteristics and evidenced (but not clearly defined) prothrombotic mechanisms. In this article we consider how these factors may contribute to the varied benefits observed with intravenous agents (Fig. 1) and, more recently, oral glycoprotein IIb/IIIa antagonists.

The $\alpha_{IIb}\beta_3$ integrin (glycoprotein IIb/IIIa receptor). The $\alpha_{IIb}\beta_3$ integrin is found exclusively on platelets and megakaryocytes, with 70,000 to 90,000 receptors expressed on each platelet in the resting state (12). These heterodimeric molecules have large extracellular regions for cation-facilitated ligand binding and small intracytoplasmic tails mediating intracellular signal transduction. Several extracellular domains have been characterized, such as the KQAGDV binding site corresponding to the carboxyl-terminal of the fibrinogen $\gamma$-chain and a RGD binding site corresponding Arg-Gly-Asp sequence found in many protein ligands including fibrinogen. Integrin binding affinity is dynamic and dependent on the receptor’s conformational status. In the resting state, affinity for fibrinogen binding is low (13). Platelet agonists, via “inside-to-outside” signals (14), trigger a change in the receptor’s structure, transforming it to a high-affinity state (Fig. 2).

Conversely, receptor binding by fibrinogen, vWF and synthetic compounds induce postoccupancy events known as “outside-to-inside” signals. These signals modify membrane fluidity, cytoskeletal activity (13), intracellular calcium mobilization (15) and induce new receptor epitopes (16)
Likewise, antagonist-initiated changes in generation (17) and P-selectin expression may be different platelet aggregation similarly, their effects on thrombin be drug-specific. For example, while two agents may inhibit functions induced or inhibited by synthetic inhibitors may dissimilar responses (13). Therefore, the array of platelet grin may, in fact, lead to postoccupancy events that favor inside signals are binding-site specific, such that ligand clot retraction. Platelet responses induced by outside-to- integrin (19) and possibly MAC-1 (20). This agent has almost no renal excretion, but transfer to unoccupied platelets results in a gradual decline in antithrombotic effect (24 to 48 h for 50% recovery of ADP-induced aggregation). Subsequent intravenous agents developed include epitifibatide (peptide-specific for the KGD motif and possibly the fibrinogen γ-chain), tirofiban and lamifiban (peptidomimetics of the RGD site). Compared with abciximab, these small-molecule agents demonstrate exclusive specificity for the αIIbβ3 receptor, have less binding affinity, shorter durations of biological effect (approximately 2 to 4 h) beyond the administration period and predominantly undergo renal excretion. However, like abciximab, binding is not confined to activated receptors. The development of prodrugs with RGD-specificity has provided oral agents, including xemilofiban, orbofiban and sibrafiban, demonstrating longer half-lives (approximately 4 to 11 h) and predominantly renal excretion. The correlation between percentage of receptor occupancy and degree of platelet aggregation inhibition is at the core of safe and effective glycoprotein IIb/IIIa inhibition. Initial studies focused on percentage receptor occupancy, correlating >80% receptor occupancy with >80% inhibition of ADP-induced aggregation (21). While targeting this level of platelet inhibition has provided important reductions in ischemic events, heterogeneity of platelet-specific, patient-specific and agent-specific factors may alter the pharmacologic response and importantly affect clinical outcome.

Factors potentially compromising the glycoprotein IIb/IIIa inhibitor efficacy. Individual variability. Since platelet thrombus formation is subject to the absolute number of glycoprotein IIb/IIIa receptors available for aggregation, individual variation in splenic size, platelet count (22) and numbers of receptors per platelet may influence dose response. For example, the normal range of platelet count (approximately 150,000 to 400,000/µL) and glycoprotein IIb/IIIa receptors per platelet (70,000 to 90,000) provide a four-fold range of total receptor number. Variations in intrinsic platelet competence and receptor number observed with age (23), gender (24) and diabetes (25) may also affect dose response. At the molecular level, the clinical impact of genetic aspects of the glycoprotein IIb/IIIa receptor remains uncertain although recent mechanistic studies suggest that platelet outside-to-inside signaling and response to platelet inhibitors are influenced by PI A polymorphism (26,27). Divergence in clinical effect may be accentuated by the

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(ligand-induced binding sites) and thereby link the glycoprotein IIb/IIIa receptor to other important platelet functions including granule secretion, P-selectin expression and clot retraction. Platelet responses induced by outside-to-inside signals are binding-site specific, such that ligand binding at different sites within the αIIbβ3 integrin induce dissimilar responses (13). Therefore, the array of platelet functions induced or inhibited by synthetic inhibitors may be drug-specific. For example, while two agents may inhibit platelet aggregation similarly, their effects on thrombin generation (17) and P-selectin expression may be different (18). Likewise, antagonist-initiated changes in αIIbβ3 integrin may, in fact, lead to postoccupancy events that favor thrombosis (e.g., activating quiescent receptors). In short, effective inhibition of platelet aggregation does not necessarily equate with effective suppression of secretion or platelet procoagulant activity.
dynamic nature of receptor expression and activity in response to stimuli such as thrombin and fibrinogen. Thrombin increases platelet surface glycoprotein IIb/IIIa expression by approximately 50% (12), possibly supporting platelet thrombosis despite antagonist activity, as evidenced by persistent platelet aggregation during therapy with standard abciximab doses in occasional patients with unstable angina (28). Conversely, low fibrinogen levels, especially after non-fibrin-specific fibrinolysis, may accentuate the antithrombotic effects of glycoprotein IIb/IIIa receptor inhibition (29) and contribute to the approximately 40% increase in bleeding events as observed in the Thrombolysis in Myocardial Infarction-14 study (30).

**Pharmacologic heterogeneity.** Inter- and intraindividual variation in the dose–response can also contribute to suboptimal effects. Pharmacokinetic studies have demonstrated a subtherapeutic effect (<80% aggregation inhibition) after bolus doses of glycoprotein IIb/IIIa inhibition in approximately 10% to 15% of patients undergoing PCI, with an increased frequency among those presenting with ACS (28,31,32). Failure of the maintenance infusion to sustain platelet inhibition ≥80% has also been observed with each intravenous agent, and intrapatient divergence appears to increase with greater infusion duration (32,33).

Age, lean body mass and renal function also contribute to pharmacologic heterogeneity, and these factors have been shown to impact the efficacy and safety of glycoprotein IIb/IIIa inhibition (34). Creatinine clearance is especially relevant to the small-molecule inhibitors since their excretion is almost solely by renal elimination. While most clinical trials have excluded patients with creatinine >2.0 to 2.5 mg/dl (5–7), correlation between increased adverse outcomes and reduced renal function has been observed.

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**Figure 1.** Overview of intravenous glycoprotein IIb/IIIa trials by pooled analysis, with respect to 30-day death or myocardial infarction. Relative risk ratios for treatment with glycoprotein IIb/IIIa inhibitors as adjunctive therapy for percutaneous coronary intervention (PCI) and as empiric therapy for acute coronary syndromes (ACS) with electrocardiographic evidence of ischemia.

**Figure 2.** Platelet glycoprotein IIb/IIIa structure and function. Heterodimeric structure with cation binding sites, RGD, KGD and KQAGDV binding sites and intracellular tail mediating both inside-to-outside and outside-to-inside signaling. Inside-out signals lead to increased platelet glycoprotein IIb/IIIa receptor activation, while outside-in signals increase ligand-induced binding site (LIBS) expression and cytoskeletal responses.
with lamifiban (35), sibrafiban (36) and orbofiban (37). Interestingly, although increased bleeding events might be expected, increased thrombotic outcomes have also been observed. Despite the importance of renal function, the recently completed Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) B and Sibrafiban Versus Aspirin to Yield Maximum Protection From Ischemic Heart Events Post Acute Coronary Syndromes (SYMPHONY) trials, which respectively dosed intravenous lamifiban and oral sibrafiban according to creatinine clearance, did not show improved clinical outcomes relative to previous fixed-dosing trials (38).

**Prothrombotic and toxic mechanisms.** Of perhaps greater concern is the possibility that these agents promote thrombotic events (partial agonist activity). While providing potent antagonism of fibrinogen binding, their capacity to prevent platelet secretion is not ensured and, in some circumstances, may actually be enhanced. Since binding of these antagonists is not confined to high-affinity receptors, binding and stimulation of quiescent receptors may be counterproductive. Peter et al. (39) have demonstrated antagonist-induced receptor activation with both antibody-fragment and small-molecule glycoprotein IIb/IIIa inhibition, and, during trough periods or after drug discontinuation, the platelets may be left more activated than before therapy. These mechanisms may have greater consequence with oral therapy since plasma levels recurrently fall between doses. Demonstrating this, Holmes et al. (40) reported potentiation of platelet P-selectin expression in 15 patients receiving orbofiban for 14 days (40). Enhanced activation and recruitment of circulating platelets may also explain the association between thrombotic events and thrombocytopenia observed in several studies (41,42). Ligand induced binding sites expression also occurs (16,39,43), possibly providing neoepitopes for immune-mediated platelet clearance, while promotion of leukocyte-platelet aggregates has also been reported with small-molecule antagonists (44).

Another intriguing mechanism that may contribute to the varied benefit reported among trials is the finding that RGD peptides can induce cardiomyocyte apoptosis (45). Caspase-3 is a central enzyme of cellular apoptosis. Procaspase-3, the precursor of the active molecule, contains RGD-binding motifs adjacent to sites of processing required for activation. Time and dose-dependent increases in caspase-3 activity and apoptosis have been reported with prolonged incubation with the RGD peptides, xemilofiban and orbofiban, but not with eptifibatide (KGD peptide) or abciximab (Fig. 3). Furthermore, these effects on apoptosis appear augmented in hypoxic conditions and may explain some of the adverse-outcome observations made in the oral glycoprotein IIb/IIIa trials (46).

**Insights and questions from clinical trials. PCI.** As adjunctive therapy for PCI, the primary objective of the randomized trials with intravenous glycoprotein IIb/IIIa inhibitors was to reduce a 30-day ischemic composite end point (death, MI and urgent revascularization). While substantial benefits have been reported in many trials, significant reductions in ischemic end points have not been uniformly observed, with relative risk reductions ranging by over three-fold, from 16% to 56% (2–7,10,47–49). Of the 17,200 patients enrolled in large-scale studies (2–7,10,47–49), the most compelling support for glycoprotein IIb/IIIa therapy and the largest dataset (n = 9,038) comes from the abciximab trials. Collectively, these trials underscore several aspects of antibody-mediated glycoprotein IIb/IIIa inhibition: 1) a clinically important reduction (approximately 40%) in early (30-day) ischemic events; 2) sustained benefits at long-term (one-year) follow-up (2–4,50) and 3) benefits extending similarly to all interventional devices, lesion complexities (51) and patient acuities (3,4).

Not all aspects of the early abciximab data are consistent, however. Some differences among the 30-day primary end...
Stenting. Blockade; EPISTENT PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa 5 the Prevention of Ischemic Complications; EPILOG 5 the Prevention of Ischemic Complications; EPILOG and EPISTENT. CAPTURE = C7E3 FAB Anti Platelet Therapy in Unstable Refractory Angina; EPIC = Evaluation of c7E3 for the Prevention of Ischemic Complications; EPILOG = Evaluation in PCTA to Improve Long-term Outcome with Abciximab GP IIb/IIIa blockade; EPISTENT = Evaluation of IIb/IIIa Platelet Inhibitor for Stenting.

Figure 4. Divergence in platelet inhibition with abciximab with increasing time. Divergence in platelet inhibition with increasing infusion duration (52). Late variation in platelet inhibition may contribute to increased periprocedural events as seen in CAPTURE when compared with EPIC, EPILOG and EPISTENT. CAPTURE = C7E3 FAB Anti Platelet Therapy in Unstable Refractory Angina; EPIC = Evaluation of c7E3 for the Prevention of Ischemic Complications; EPILOG = Evaluation in PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa blockade; EPISTENT = Evaluation of IIb/IIIa Platelet Inhibitor for Stenting.

point reductions are evident, bringing into question the timing of PCI and the optimal duration of the postprocedural drug infusion. In particular, the c7E3 FAB Antiplatelet Therapy in Unstable Refractory Angina trial (CAPTURE) reported a relative risk reduction in death, myocardial infarction (MI) and urgent revascularization of 23% (p = 0.012) using 18 to 24 h of preprocedural abciximab but only a 1-h postprocedural infusion. In comparison, a 35% (p = 0.008), 56% (p < 0.001) and 51% (p < 0.001) reduction in the same end point was seen in the Evaluation of c7E3 for the Prevention of Ischemic Complications trial (EPIC), Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome With Abciximab Glycoprotein IIb/IIIa Blockade (EPILOG) and Evaluation of IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT), respectively, employing a 12-h postprocedural infusion. This distinction is consistent with the evidence of subtherapeutic inhibition in up to 10% to 15% of patients after ≥8 to 12 h of abciximab infusion (32,52) (Fig. 4) and underscores the value of “adequate” inhibition during and after PCI. Thus, compared with the EPI-trials, not only were CAPTURE patients’ platelets more likely to be under 80% inhibited at the time of PCI, but they also returned to normal function sooner after PCI. Another seeming inconsistency is the reduction in clinical restenosis by abciximab, which is suggested by lower rates of target-vessel revascularization at six months in EPIC (26% reduction, p = 0.007) (3) and in the diabetic patients of EPISTENT (51% reduction, p = 0.002) (4). This reduction in restenosis has not been confirmed in other abciximab trials and angiographic studies (53).

The clinical trial results with small-molecule glycoprotein IIb/IIIa antagonists in PCI are varied and reinforce the importance of adequate drug dosing. The Integrin to Manage Platelet Aggregation To Combat Coronary Thrombosis-II trial (IMPACT II) (48), the initial PCI study of eptifibatide, demonstrated a relative risk reduction in death, MI or urgent revascularization at 30 days of 17% (p = 0.08). There was no significant reduction in target-vessel revascularization or overall benefit at six months. Reassessment of the dose found that reduction of the serum calcium levels by EDTA (sample anticoagulant) lowered fibrinogen-binding affinity and facilitated eptifibatide binding. Therefore, the percentage inhibition of platelet aggregation for these doses (135 μg/kg bolus + 0.5 μg/kg or 0.75 μg/kg infusion) was estimated to be only 40 to 50% (roughly half the planned target level) (54). Patients undergoing PCI in the PURSUIT trial, with a higher eptifibatide dose (180 μg/kg bolus + 2.0 μg/kg infusion), experienced a 31% (p = 0.001) relative risk reduction in death or MI at 30 days (55). Likewise, a 43% (p = 0.0017) reduction in the same end point at 48 h has been preliminarily reported in the Enhanced Suppression of the Platelet Glycoprotein IIb/IIIa Receptor Using Integrelin Therapy trial (ESPRIT), using a high-dose double-bolus and infusion regimen (180 μg/kg bolus + 2.0 μg/kg infusion + a second 180 μg/kg bolus after 10 min). Whether these dose increases will provide durable benefit and long-term mortality reductions as observed in EPISTENT awaits follow-up. For now, further support for the dose-benefit gradient comes from the 55% relative risk reduction in major adverse cardiac events with platelet inhibition >95% at 10 min after glycoprotein IIb/IIIa inhibitor bolus (p = 0.006) observed in the recent GOLD (Au-Assessing Ultegra) study (56). These findings each highlight the fact that the optimal level of platelet inhibition at the time of PCI is still incompletely defined although a greater understanding of this issue has been enabled by the advent of rapid platelet function testing (57).

Issues of adequate dosing also cloud the experience with tirofiban in PCI. The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis trial (RESTORE) demonstrated a 24% (p = 0.052) reduction in 30-day death MI, urgent revascularization and bailout stenting using EPIC end point definitions (47). However, initial dose-defining studies with tirofiban used 5 μM ADP-induced platelet aggregation compared with 20 μM ADP used in both abciximab and eptifibatide dose-defining studies. Therefore, efficacy of this dose may not be comparable with that of abciximab or eptifibatide in the face of clinically relevant stimuli, as evidenced by a small direct-comparison study (33). Relative clinical efficacy of this agent is even more difficult to assess since this trial collected and adjudicated creatine-kinase data only for patients with suspected ischemic events. True comparative data awaits the results of
the ongoing Do Tirofiban And Reopro Give Similar Efficacy Outcomes Trial (TARGET), a randomized double-blinded, double-dummy trial comparing tirofiban with abciximab in approximately 5,000 patients undergoing coronary stenting.

**ACS.** Contrasting the substantial benefits experienced by ACS patients within the PCI trials, integration of glycoprotein IIb/IIIa antagonist therapy into the empiric management of ACS has observed a lesser magnitude of effect. Collectively, with over 24,000 patients studied, the ACS trials demonstrate an approximately 12% relative risk reduction in 30-day death or MI. However, when considered individually, these trials report risk reductions ranging from 8% to 27% (5–7). Heterogeneity in these results may stem from the inherent diversity of patient acuity and the uncertain timing of thrombo-occlusive events within these populations. The “timing of injury” concurrent with the period of maximal platelet inhibition distinguishes the PCI trials from the trials of glycoprotein IIb/IIIa inhibition therapy in ACS patients. While the precise time, and at least to some extent, the degree of vessel injury are known for patients undergoing PCI, these factors are far less predictable in patients considered at risk for spontaneous coronary events. Thus, when PCI is undertaken at the time of greater and more consistent platelet inhibition (i.e., early in the treatment period), more substantial benefits may be provided. This is evidenced by the 31%, 35% and 42% relative risk reductions in 30-day death or MI observed in patients undergoing early PCI in the PURSUIT study (55), PARAGON B and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms trial (PRISM PLUS) (6), respectively. These outcome reductions are greater than the 6%, 7% and 12% reductions in the same end point for those patients not undergoing PCI in the respective trials.

Likewise, within the ACS population a marked heterogeneity in patient acuity occurs. While early PCI “localizes” the time of injury, evidence of myonecrosis “defines” the population at greatest risk for which the early institution of glycoprotein IIb/IIIa therapy provides incremental benefit over aspirin and heparin alone (Fig. 1). Validation of this concept comes from the impressive reductions in death or MI of 42% (p = 0.018), 67% (p < 0.001) and 70% (p = 0.002) observed in the troponin positive patients of PARAGON B, Platelet Receptor Inhibition in Ischemic Syndrome Management trial (PRISM) (9) and CAPTURE (8), respectively, many of whom underwent early PCI. In short, clinically important reductions in ischemic events can be expected when therapeutic glycoprotein IIb/IIIa inhibition and the time of increased risk correspond.

Additional questions have been raised by the ACS trial experience. Treating patients with very high levels of glycoprotein IIb/IIIa therapy has not consistently had favorable outcome, with increased ischemic events, bleeding events or both seen with several small-molecule antagonists (6). The effect of concurrent heparin therapy in ACS patients adds a further level of complexity. Increased adverse events observed in the absence of concurrent heparin in some trials (6,58) provide support for the clinical relevance of differences in thrombin inhibition documented among the agents. These observations may also suggest the possibility of important prothrombotic mechanisms, especially considering the oral glycoprotein IIb/IIIa experience.

The lack of benefit with oral glycoprotein IIb/IIIa inhibition. Despite clinical trial experience with over 33,000 patients, variations in patient populations and study designs and the study of three different oral glycoprotein IIb/IIIa agents (sibrafiban [38], xemilofiban [59] and orbofiban [37]), no reduction in ischemic events with these drugs is evident. Moreover, trends towards an increased mortality with the oral glycoprotein IIb/IIIa antagonists were observed in each trial and are statistically significant for both the Orbofiban in Patients With Unstable Coronary Syndromes Thrombolysis In Myocardial Infarction 16 trial (OPUS-TIMI 16) trial (37) and the second SYMPHONY study (60). In keeping with the evidence of increased P-selectin expression with orbofiban (40), analysis of the cause of death in OPUS-TIMI 16 revealed an excess of thrombotic events. Pooled analysis of the oral glycoprotein IIb/IIIa inhibitor trials shows a 33% increase in mortality (p = 0.002) with long-term follow-up (11). Bleeding rates were increased in all active treatment arms attesting to the antplatelet efficacy of these agents at the doses studied.

This stark disparity between the intravenous and oral glycoprotein IIb/IIIa antagonist experience is perplexing and is not reconciled by subtherapeutic dosing alone. While the lack of sustained platelet inhibition between doses is an obvious limitation of oral therapy, suboptimal plasma levels cannot account for the results from the second SYMPHONY trial where the highest mortality rate was observed with high-dose sibrafiban. Nor does a dependence of concurrent aspirin therapy fully explain these findings since increased mortality was observed in the OPUS TIMI-16 trial and the low-dose sibrafiban arm of the second SYMPHONY trial, both of which included concurrent aspirin. Considered in combination with the phase II trial experience (36,61–63), these data lend strong support to the existence of clinically relevant prothrombotic mechanisms. Alternatively, the increased mortality observed raises the possibility of toxic mechanisms, such as the effect on ischemic apoptosis recently reported with RGD peptides (45,46). Confirmation of the mechanisms involved in these adverse events may enable the design of agents with improved profiles.

**Conclusions.** Unquestionably, intravenous platelet glycoprotein IIb/IIIa inhibition has proven to be an important, clinically effective adjunct therapy during PCI and in the management of ACS. This benefit is most apparent in those patients with ACS with evidence of troponin elevation or who are undergoing early PCI (Fig. 1). However, adverse outcomes among treated patients persist, and heterogeneity among the clinical trials is marked. Current weight-based
dosing strategies do not adequately account for diversity in platelet and patient-related factors, and the potential for bleeding or triggering prothrombotic or toxic mechanisms are increasingly being appreciated. These issues are highlighted by the difficulties in establishing a clear dose-response relationship and suggest that greater benefits may be achieved with more patient-specific dosing. Potential prothrombotic effects and the dependence on concurrent antithrombin therapy will require further clarification. Rapid platelet function testing may help define a safe and effective level of glycoprotein IIb/IIIa inhibition and allow the optimization of doses in all patients. Likewise, ongoing head-to-head trials comparing agents will provide important new insights into the extent of class effect and relevance of the various ancillary actions of the glycoprotein IIb/IIIa inhibitors.

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