Platelet aggregation, in fundamental terms, is considered a biological end point that contributes to the occurrence of clinical events among patients with advanced atherosclerotic coronary artery disease. Acute coronary syndrome, including non–ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI), accounts for upward of 733,000 hospital admissions yearly in the United States.1 The primary pathophysiological mechanism responsible for the majority of acute coronary syndromes is endothelial plaque disruption with and subsequent platelet adhesion, activation, and thrombus formation.2 The end result is formation of thrombus within a coronary artery, leading to subtotal vessel occlusion with NSTEMI and complete occlusion of the artery with STEMI. In this review, we provide a contemporary view of platelet adhesion as a highly coordinated and teleologically conserved process achieved by surface receptors, protein ligands, and matrix proteins operating at the platelet–subendothelium interface. We also discuss drugs in development, including monoclonal antibodies, inhibitory peptides, and oligonucleotides; preclinical data; and, where available, clinical trial results, highlighting the potential translation of fundamental constructs in platelet biology to patient care.

Fundamental Concepts in Platelet Biology

Platelets are derived from a hematopoietic bone marrow stem cell precursor.3 Through a highly conserved program of cellular differentiation, this stem cell precursor becomes a megakaryocyte at a rate of approximately 100,000,000 megakaryocytes produced per day.3 Subsequently, each individual megakaryocyte will give rise to approximately 500 platelets via additional developmental steps within the bone marrow that involve a proplatelet intermediate stage.3 Once released into circulation, a mature platelet has an expected life span of 7 to 10 days.3 Platelet maturation and development involve the expression of receptors on the platelet cell surface. These receptors facilitate platelet adhesion and activation, and they promote thrombus development through receptor–ligand interactions, with several ligands expressed on the surface of endothelial cells, within the subendothelial matrix, and as soluble proteins in the circulation. Of particular physiological relevance to platelet adhesion are the GP Ib/V/IX, GP VI, and GP Ia/IIa receptors.4,5 Platelet adhesion occurs in a coordinated manner and is characterized by the following stages: tethering, rolling, activation, and stable adhesion.6 The first step in platelet adhesion is termed tethering. Experimental work has demonstrated that shear forces are generated rapidly as blood circulates over a site of endothelial injury and initiates a transient platelet–endothelium interaction. The key element of this important event is the transient binding of GP Ib to von Willebrand Factor (VWF)7 that occurs via multiple “on-and-off” or “start-and-stop” platelet GP Ib receptor—endothelial VWF interactions involving the formation of multiple platelet membrane extensions referred to as tethers.8 The next stage, referred to as rolling, occurs as a result of relatively low affinity interactions between collagen and GP VI.6 This step is augmented by the GP Ia/Ila receptor4 (Figure). The process of platelet activation follows paracrine- and autocrine-mediated signaling through the release of thromboxane A2 and adenosine diphosphate from platelets, along with thrombin activation by tissue factor from the vessel wall.6 Reinforcement of stable platelet adhesion and subsequent thrombus formation is mediated by the interaction of the integrin GP IIb/IIIa, with fibrinogen and VWF.7 Thrombin acts to convert fibrinogen to fibrin, which serves as a stable lattice for the developing thrombus.9

Platelet Adhesion Ligands

von Willebrand Factor

Structure and Function

VWF, a protein multimer formed from 50 to 100 subunit monomers, is synthesized in vascular endothelial cells and is an integral component of the adhesion step along the pathway to thrombus formation.10 Once activated by high shear forces, VWF undergoes conformational changes and initially binds to the GP Ib receptor as part of the tethering stage of platelet adhesion.10 After platelet activation by VWF–GP Ib/V/IX complex initiated cellular signaling, VWF irreversibly binds with GP IIb/IIIa, leading to platelet aggregation and thrombus formation.10 An additional binding site on the VWF molecule exists for direct interaction with type IV collagen.10 The interaction of VWF with collagen leads to the release of factor VIII, which in turn activates thrombin, leading to thrombus formation through the conversion of fibrinogen to fibrin.10 Thus, platelet adhesion promotes platelet activation...
signaling pathways and, in turn, leads to downstream platelet aggregation.

**Epidemiology**

Epidemiological research has shown an association between VWF levels and the risk of recurrent myocardial infarction and death in patients with acute coronary syndromes.11–15 Similarly, there are data demonstrating that the degree of VWF elevation correlates with short-term death, recurrent angina, and need for revascularization at 14 days in patients with NSTEMI16 and death or recurrent myocardial infarction in patients with STEMI.17,18

**Inherited Abnormalities**

In humans, von Willebrand disease is classified as type I, 2A, 2B, 2M, 2N, or 3, in which there is either a qualitative or a quantitative abnormality in VWF depending on the specific subtype.19 Patients with von Willebrand disease come to clinical attention with episodic mucocutaneous bleeding and often have excess bleeding in association with invasive procedures.19 Moreover, an acquired abnormality of VWF, termed von Willebrand syndrome, has been well described in the literature. The von Willebrand syndrome is associated with a variety of different clinical scenarios via disparate mechanisms ranging from medication-induced conditions, aortic stenosis, and immune disorders to malignancies.20 Patients with the von Willebrand syndrome exhibit a similar phenotype as do patients with von Willebrand disease.20

**Experimental Models**

In laboratory studies with VWF knockout mice, arterial thrombosis was not prevented, but the time to clot formation was prolonged and the thrombus size was diminished in experimental thrombosis models.21 The VWF–GP Ib interaction remains a potential therapeutic target for the treatment of acute coronary syndromes, with several agents under investigation.

**Investigational Agents**

The VWF represents a fundamentally attractive target for pharmacological intervention in the treatment of acute thrombotic processes, including acute coronary syndromes. In vitro experiments with genetically engineered fragments of VWF demonstrate altered platelet adhesion via competitive inhibition at the GP Ib binding site.22 Antibody-based approaches to disrupt the interaction of VWF with GP Ib have also been investigated. An experimental monoclonal antibody, AJvW-2, is a mouse antibody that targets the A1 region of human VWF10 (Table). Studies with this antibody in cell-based assays of platelet adhesion and aggregation with platelets obtained from patients with acute coronary syndrome revealed a decrease in adhesion and aggregation as measured by viscometry.23 Moreover, research in animal models of balloon-induced arterial injury with the AJvW-2, and with AJW200, another monoclonal antibody directed against the A1 region of VWF, showed a significant diminution of thrombosis burden without a prolongation of bleeding time.24–26

Another approach to drug development has evolved from advances in oligonucleotide chemistry. These advances have led to the development of aptamer-based pharmaceutical therapies. Laboratory-based in vitro evaluation of anti-VWF ribonucleic acid aptamers experimentally supported the theoretical idea that targeted oligonucleotide against VWF would inhibit platelet adhesion in PFA-100 platelet shear force assays and ristocetin-induced platelet aggregation assays.27 Using a convergent systematic evolution of ligands by exponential enrichment approach, several oligonucleotides (R9.3 and R9.14) with molecular weights in the 8- to 15-kd range were identified that bound to VWF with high affinity having dissociation constants (Kd) <20 nM27 (Table). Furthermore, rational design of complementary oligonucleotides based on deoxyribonucleic acid base-pairing rules to function as active reversal agents, or antidotes, was shown to abolish the in vitro inhibition of platelet adhesion within 2 minutes and in a sustained manner for ≤4 hours after administration.27 An anti-VWF deoxyribonucleic acid aptamer, ARC1779, was evaluated in a Phase I double-blind, placebo-controlled
study of 47 volunteers to establish pharmacokinetic, pharmacodynamic, and safety profiles. No adverse events, excess bleeding, or deaths were reported. A Phase II study of this agent, termed the vITAL-1 trial, in patients with NSTEMI undergoing percutaneous coronary intervention was initiated in October 2007, but it was terminated for unclear reasons according to the most recent information available on the FDA ClinicalTrials.gov website (last update on January 8, 2009).

Glycoprotein Ib/IX/V Receptor

Structure and Function

The glycoprotein Ib/IX/V receptor complex consists of four subunits that span the platelet cell membrane. The specific subunits include GP Ibα, GP Ibβ, GP IX, and GP V proteins. With respect to assembly of the functional receptor, the GP Ibα and GP Ibβ subunits are linked to one another by disulfide bonds involving cysteine amino acid residues, whereas noncovalent interactions contribute to the interaction of GP IX and GP V with the GP Ib heterodimer. Under conditions of high shear forces, VWF binds to the leucine repeat sequences of the GP Ib/IX/V complex. This serves to initiate the platelet adhesion and activation cascade as described above in the discussion of the VWF. Additional ligands for the GP Ib receptor include thrombin, P-selectin, factor XI, factor XII, thrombospondin-1, collagen, and soluble GP VI.

Inherited Abnormalities

Much of our understanding of the function of the GP Ib/IX/V complex has been acquired from studies of the Bernard-Soulier syndrome, in which patients lack, or have mutant forms of, GP Ibα, Ibβ, or IX. Clinically, these patients have abnormal platelet numbers and platelet morphology, and they are known to have spontaneous mucocutaneous bleeding and more significant hemorrhage associated with trauma.

Experimental Models

The interaction of the GP Ib receptor with VWF is an early and pivotal step in platelet adhesion. Studies using GP Ib knockout mice revealed that thrombus formation was completely abolished, which is in contrast to observations in VWF knockout mice wherein thrombus formation was delayed and a decrease in thrombus burden was reported. The available data suggest that ligands for the GP Ib receptor, other than VWF, may play a critical role in platelet aggregation and thrombosis. Interestingly, GP V knockout mice have normal bleeding times and do not exhibit a Bernard-Soulier phenotype. Furthermore, conflicting data have been reported in GP V knockout experimental thrombosis models, with both prothrombotic and antithrombotic effects observed. Several agents have been investigated in experimental models systems to inhibit platelet adhesion at the GP Ib/V/IX receptor.

Investigational Agents

Researchers have hypothesized that GP Ib inhibition would lead to decreased platelet adhesion and subsequent thrombosis. Experiments using compounds found in Viperidae, Crotalidae, and Elipidae snake venoms, referred to as C-type lectins, have generated mixed results, with some agents leading to platelet inhibition and others to platelet activation in various experimental settings. In the early stage of

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<th>Receptor/Target and Agent</th>
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scientific inquiry is a technique that uses an inhibitory peptide targeting GP Ib that penetrates the cell membrane. Structurally, this synthetic peptide, R9o6557, contains nine arginine amino acid residues, which facilitate cell entry, and also an 11- to 13-amino acid sequence of the cytoplasmic signaling region of the GP Ib receptor. An experimental approach using a monoclonal antibody to the GP Ib receptor, 6B4, in nonhuman primates resulted in a decrease in thrombus formation on an implanted thrombogenic device without inducing significant thrombocytopenia or a prolongation of bleeding time. At this time, we are unaware of any registered trials with ClinicalTrials.gov for compounds directed at inhibition of the GP Ib receptor.

Glycoprotein VI

Structure and Function

The platelet glycoprotein VI receptor is a transmembrane complex formed by two extracellular immunoglobulin-like domains, a mucin-like core region, a region that spans the cell membrane, and an intracellular domain. Ligands for the GP VI receptor include collagen, collagen-related peptide, and convulxin, a protein found in tropical rattlesnake venom, with collagen being the most relevant ligand for platelet adhesion in vivo. The functional role of the GP VI receptor in platelet aggregation takes place in the early stages of platelet adhesion, and much like the GP Ib/V/IX receptor complex, it is instrumental in facilitating platelet adhesion at sites of endothelial injury. An element of redundancy in platelet adhesion receptors may offer an attractive construct for attenuating or tempering thrombosis while maintaining hemostatic capacity.

Inherited Abnormalities

In the literature, congenital or acquired abnormalities of the GP VI receptor are an extremely rare entity, with only 11 case reports to date. This phenotype is manifested by a variable spectrum of mild to severe bleeding episodes; however, a majority have been relatively mild.

Experimental Models

Data from mouse experiments demonstrated that treatment with a monoclonal antibody targeted to the GP VI receptor resulted in a significant prolongation of bleeding times in comparison with control animals. Animal studies with transgenic knockout mice that do not express the transmembrane and intracellular portion of the GP VI receptor complex (FcRγ7) exhibit variable responses in models of arterial thrombosis. In a ferric chloride injury model, which exposes a significant amount of collagen, there is decreased thrombus formation. However, in a laser-induced injury model, which does not expose a significant amount of collagen molecules, there is no difference in the degree of thrombosis in comparison with wild-type mice. Moreover, knockout mice that do not express the GP VI/FcRγ receptor exhibit a mild decrease in arterial thrombosis with electrolytic or laser-induced arterial injury, but the inhibition of thrombosis is significantly increased when thrombin is inhibited with the pharmacological inhibitor hirudin. This observation suggests that a strategy to inhibit thrombosis via the GP VI receptor may also require or achieve maximal effectiveness with concomitant targeting of thrombin, possibly through the platelet protease activated receptor-1. The future role of the GP VI receptor as a target for clinical therapy is the focus of active investigation.

Investigational Agents

A strategy of monoclonal antibodies directed against the GP VI receptor to interfere with or temper the GP VI-collagen interaction has been reported. One such monoclonal antibody, JAQ1, was evaluated in a mouse model, in which in vitro response to collagen was abrogated, along with a near complete prevention of thrombus generation after injection of collagen and epinephrine in vivo. A prolonged bleeding time in comparison with control animals was observed, but it was noted to be significantly lower than in animals treated with an antibody to the GP Ib/IIIa receptor. Moreover, another monoclonal antibody to GP VI, designated OM2, decreased platelet aggregation in a primate experimental model. This group also reported a mild (1.3 times baseline) increase in bleeding time, which was significantly lower than the 5-times baseline prolongation of bleeding time seen with abciximab. The OM2 monoclonal antibody mechanistically seems to function as a blocking antibody, in contradistinction to the JAQ1 antibody, which causes shedding of GP VI receptors from the platelet surface. Moreover, the rational design of a chimeric soluble GP VI–human immunoglobulin Fc domain competitive-inhibition decoy molecule that targets areas of damaged endothelium was associated with a decrease in platelet adhesion in vitro, thrombus generation ex vivo, and platelet adhesion in vivo at sites of endothelial injury in a mouse carotid artery model system. In a rabbit carotid artery injury model system, delivery of a soluble GP VI–Fc immunoglobulin molecule to the site of injury via a balloon delivery catheter resulted in significant reduction in thrombus formation in comparison with control animals. In contrast to these findings, Gruner et al reported no effect of soluble GP VI on thrombosis in a mouse model. Thus, the potential role for a soluble GP VI inhibitory molecule remains to be determined. Another approach targeting the GP VI receptor with the experimental agent EXP3179 has been reported. EXP3179 is a compound generated from the hepatic metabolism of the angiotensin II type I receptor antagonist Losartan. This experimental compound decreased platelet adhesion after injury to the mouse carotid artery, as assessed by intravital fluorescence microscopy. At present, we are unaware of any registered trials with ClinicalTrials.gov using GP VI antagonists.

Glycoprotein Ia/IIa

Structure and Function

An additional receptor involved in the platelet adhesion process is the glycoprotein Ia/IIa receptor, also referred to in the literature as integrin α2β1, VLA-2, or CD49b/CD29. Similarly to GP VI, GP Ia/IIa binds to collagen, facilitating platelet adhesion. As observed with other integrin receptors, inside-out signaling provokes a conformational change in the receptor complex, which in turn increases ligand affinity—in this particular case, collagen. On binding of collagen to the GP Ia/IIa receptor, a signaling cascade is initiated that
promotes downstream steps in the pathway of platelet adhesion, activation, and aggregation.\textsuperscript{5}

\textbf{Inherited Abnormalities}
In humans, a congenital or acquired abnormality of the GP Ia/IIa receptor is a rare phenotype characterized by prolonged bleeding time and episodes of mucocutaneous bleeding.\textsuperscript{46} Genetic association studies have reported an increased risk of myocardial infarction and stroke among individuals with a specific polymorphism in the GP Ia gene.\textsuperscript{47,48}

\textbf{Experimental Models}
Experiments with knockout mice, in which expression of the \(\alpha_\gamma\) subunit (or in another set of experiments the \(\beta_\gamma\) subunit) of the receptor was abolished, did not show significant abnormalities in bleeding time.\textsuperscript{49,50} However, there was a decrease in platelet aggregation in response to collagen exposure.\textsuperscript{50,51} There are conflicting data in knockout mouse models of vascular injury, with one group reporting normal thrombus generation and another reporting impaired thrombus formation.\textsuperscript{52-54} It is important to recognize that transgenic mice lacking expression of both GP Ia/IIa and GP VI do not form thrombi in response to vascular injury, which is distinctly different from the minor abnormalities in platelet aggregation observed in the absence of either receptor alone.\textsuperscript{55} The available evidence suggests a significant interaction between the GP Ia/IIa and GP VI receptors that promotes platelet adhesion and subsequent aggregation.\textsuperscript{4} In addition, GP Ia/IIa activation and binding of collagen may be contingent on collagen first binding to GP VI.\textsuperscript{50} There is ongoing research with agents to inhibit GP Ia/IIa–mediated platelet adhesion.

\textbf{Investigational Agents}
Despite the supportive role the GP Ia/IIa receptor seems to play in collagen-mediated platelet adhesion, there are very few reports in the literature investigating inhibitory strategies targeting GP Ia/IIa with respect to arterial thrombosis. One group used a recombinant protein, \(\alpha_\gamma\)-l, which is the binding site for collagen to the GP Ia component of the GP Ia/IIa receptor complex, to inhibit platelet adhesion to a collagen matrix under high shear stress in vitro\textsuperscript{56} (Table). More recently, an approach using the synthesis of small molecule inhibitors to the GP Ia/IIa receptor showed efficacy in the inhibition of platelet adhesion in vitro and prolonged duration to thrombus formation in a mouse ferric chloride arterial injury model system.\textsuperscript{57} However, to date, we are unaware of any human clinical trials targeting inhibition of the GP Ia/IIa receptor.

\textbf{Glycoprotein IIb/IIIa}

\textbf{Structure and Function}
The glycoprotein IIb/IIIa receptor complex is a heterodimer of integrin molecules.\textsuperscript{58} In its mature form, it is composed of alpha and beta subunits that form the GP IIb/IIIa receptor through noncovalent interactions.\textsuperscript{59} The alpha and beta subunits both have extracellular, transmembrane, and intracellular domains.\textsuperscript{59} Cation-binding sites are found on both the alpha and the beta subunits, which have been demonstrated to be critical for receptor heterodimer formation.\textsuperscript{59} In an environment of platelet stimulation, the GP IIb/IIIa receptor apparatus undergoes a conformational change involving the extracellular domain whereby the affinity for VWF and fibrinogen is markedly increased.\textsuperscript{59} This affinity increase and the conformational change to facilitate ligand binding are affected by a process termed inside-out signaling, whereby the early stages of platelet adhesion trigger intracellular signaling pathways, which in turn activate the GP IIb/IIIa receptor complex.\textsuperscript{59} Furthermore, once VWF or fibrinogen is bound to the GP IIb/IIIa receptor, signaling occurs in a linear outside-in manner to promote the final stages of platelet aggregation and thrombus formation.\textsuperscript{59} Accordingly, the GP IIb/IIIa receptor plays a role not only in platelet aggregation but also in adhesion via interaction with VWF, fibrin, and fibrinogen.

\textbf{Inherited Abnormalities}
From a historical perspective, discovery of the GP IIb/IIIa receptor evolved from observations and further molecular investigation of patients with Glanzmann thrombasthenia, an inherited mucocutaneous bleeding disorder with deficient or abnormal GP IIb/IIIa receptor expression.\textsuperscript{60} Subsequently, investigators hypothesized that inhibition of the GP IIb/IIIa receptor would be an additional efficacious target in the management of atherothrombosis, based on several lines of experimental evidence.\textsuperscript{60}

\textbf{Experimental Models}
Animal studies with the monoclonal 7E3 antibody to the GP IIb/IIIa receptor demonstrated inhibition of platelet aggregation and decreased extent of thrombosis in canine models of myocardial infarction.\textsuperscript{60} Subsequently, human trials with a chimeric version of 7E3, known as abciximab, were performed, leading to approval by the US Food and Drug Administration (FDA) in 1994.\textsuperscript{60} Abciximab is a murine antihuman chimeric monoclonal antibody that is FDA approved for adjunct use at the time of percutaneous coronary intervention.\textsuperscript{60} In subsequent years, eptifibatide and tirofiban were developed and approved for use. Eptifibatide is a synthetic heptapeptide that was synthesized based on the structure found in nature with the KGD sequence in \textit{Sistrurus miliarius barbouri} (barbourin) snake venom.\textsuperscript{61} It is approved for use in percutaneous coronary intervention and in the management of NSTE-IM. Likewise, tirofiban is a nonpeptide antagonist that binds to the RGD sequence of the GP IIb/IIIa complex.\textsuperscript{59} Similarly to eptifibatide, tirofiban is approved for use upstream in the management of NSTE-IM and in the periprocedural period with percutaneous coronary intervention.

\textbf{Subendothelial Matrix Protein Ligands}
In addition to VWF and collagen, several other ligands participate in the platelet adhesion process. These include fibronectin, fibrinogen, thrombospondin, and laminin.\textsuperscript{62} Fibronectin is an extracellular matrix protein that binds to platelets via platelet \(\alpha_{\text{IIb}}\) and \(\alpha_{\text{m}}\) Receptors.\textsuperscript{62} Experimental evidence suggests that fibronectin alone plays a minor role in the adhesive process but that it interacts in an additive or synergistic manner with other ligands to facilitate platelet adhesion.\textsuperscript{62} Fibrinogen has been demonstrated to contribute to platelet adhesion via the \(\alpha_{\text{IIb}}\) receptor.\textsuperscript{62} Likewise, the cross-linked form of fibrinogen, fibrin, is also a ligand
involved with platelet adhesion and has been reported to interact in a synergistic manner with VWF to promote adhesion. Lamins 8 and 10 are components of the subendothelial matrix, which have been reported to function as ligands for the platelet integrin α_{IIb}β_{3} receptor and GP VI receptors and to play a role in the adhesive process. The role of the subendothelial matrix ligands in the platelet adhesion process is incompletely understood and will likely be the focus of in vitro and in vivo experiments in the coming years. What role, if any, these molecules may play as targets for pharmacological inhibition of platelet adhesion remains to be determined.

**Novel Direct Collagen Inhibitors**

An alternative approach to direct inhibition of GP VI or GP Iα/IIa to disrupt the platelet–collagen adhesive process has been recently reported, using a novel protein isolated from the saliva of the malaria vector mosquito *Anopheles stephensi* (Table). In this study, the anopheline antiplatelet protein (AAPP) inhibited platelet adhesion in vitro along with ex vivo collagen-induced platelet aggregation in rats. The AAPP seems to inhibit platelet adhesion through a GP VI– and GP Iα/IIa–independent mechanism by direct binding to collagen. Additional investigation in the future will determine whether this agent or other potential inhibitors of collagen may be useful targets to inhibit platelet adhesion.

**Novel Inhibitors of Intracellular Signaling**

Another strategy to inhibit platelet adhesion involves circumventing the cell membrane receptor and targeting downstream intracellular signaling molecules. The type Iα phosphoinositide 3-kinase p110β (PI3K) is an intracellular signaling intermediate that exerts its actions via activation of the well-described second-messenger molecules phosphoinositide (P3) (3,4,5) P5 and P (3,4)P4. In platelets, PI3K activation is linked to GP Iβ/IIa-mediated adhesion under conditions of high shear stress. Experiments in vitro demonstrated that the PI3Kβ isoform specific inhibitor, TGX-221, decreased shear-dependent platelet adhesion. Furthermore, in vivo animal experiments in an arterial thrombosis model system demonstrated nearly complete prevention of thrombus formation in animals treated with TGX-221 without prolongation of bleeding time. At present, we are unaware of any clinical trials registered with the FDA that use inhibitors of PI3K.

The future of antiplatelet therapy, specifically the development of drugs that target platelet adhesion, either through inhibition of surface receptors and/or protein ligands, is one of substantial opportunity. A clear recognition of unmet needs to prevent coronary arterial events among patients at risk, even with a full complement of currently available platelet-directed therapies, must be appropriately tempered by the pivotal role that platelet adhesion assumes in protective hemostasis and vascular repair. Accordingly, targets, mechanisms, and the degree of inhibition must each receive careful consideration, with meticulous Phase I testing that includes pharmacokinetics, pharmacodynamics, and advanced biomarkers to uncover and gauge potential signals suggesting vascular toxicity or bleeding risk. Although the optimal target for inhibiting platelet adhesion is unknown, we postulate that GP VI and GP Iβ-VWF warrant high-level consideration. Last, an aptamer-antidote oligonucleotide platform may provide the means to achieve a graded response or, when the clinical setting dictates, complete reversal of platelet inhibition.

**Disclosures**

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