The Relationship of Platelet Reactivity to the Occurrence of Post-Stenting Ischemic Events: Emergence of a New Cardiovascular Risk Factor

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The reactivity of platelets to agonists plays a central role in the genesis of thrombosis following percutaneous coronary intervention (PCI) and spontaneous plaque rupture. Antiplatelet therapy has reduced the occurrence of thrombotic events following PCI, including myocardial infarction and stent thrombosis. Because the platelet is a fundamental component in the generation of an arterial thrombus and the stimulus for thrombosis is marked in PCI, it is logical to predict that patients with superior platelet inhibition would have the best outcomes with respect to ischemic events post PCI. However, until recently there was little information linking measurements of high ex vivo platelet reactivity to the occurrence of ischemic events. An emerging body of data, mostly from small studies, supports the pivotal link between periprocedural platelet physiology and increased risk of adverse thrombotic events. This review explores the available information linking platelet reactivity during and after PCI to the occurrence of adverse events, including myocardial infarction, recurrent ischemia within 6 months, and stent thrombosis.

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Key words: Platelet reactivity • Platelet aggregation • Platelet inhibition • Thrombosis

Platelet activation by various agonists is critical to the generation of platelet aggregates and subsequent thrombotic complications. In the setting of de novo plaque rupture and rupture induced by percutaneous coronary intervention (PCI), initial platelet activation follows adhesion to the exposed subendothelial matrix via platelet collagen and glycoprotein (GP) Ib–IX-V receptors

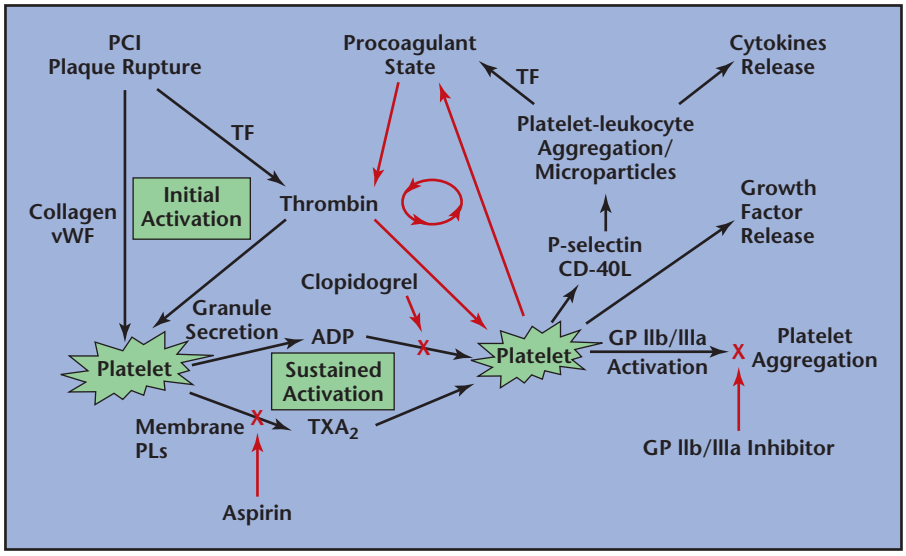


Figure 1. *Platelet response to vascular injury. vWF, von Willebrand factor; GP, glycoprotein; ADP, adenosine diphosphate; 5-HT, 5-hydroxytryptamine (serotonin); TXA_2, thromboxane A_2; TF, tissue factor; PL, phospholipid; CD, clusters of differentiation.*

(Figure 1).[1] The small amount of thrombin generated at the site of vascular injury from release of tissue factor also amplifies platelet activation.

After primary activation, the release of dense-granule contents, including adenosine diphosphate (ADP), and the generation of thromboxane (TX) A_2 further amplifies platelet activation and aggregation processes and stabilizes the mass of the platelet aggregate. Moreover, the formation of coagulation factors on the activated platelet surface further generates more thrombin that further enhances platelet activation and coagulation processes. The interaction of ADP with platelet receptors, particularly the $P2Y_{12}$ receptor, and of TXA_2 with thromboxane receptors plays a critical role in transforming the GP IIb/IIIa receptor to an activated state. The binding of fibrinogen and von Willebrand factor (vWF) to activated GP IIb/IIIa receptors facilitates irreversible platelet aggregation and stable clot generation.[2-4] Elevated platelet function immediately following PCI has been correlated to the occurrence of myocardial necrosis and recurrent ischemic complications.[4-7]

The rationale for antiplatelet therapy during and following PCI is to prevent thrombus formation, to arrest procoagulant activity and inflammatory processes, to promote disaggregation of platelets, and finally to facilitate the perfusion of occluded blood vessels. The determination of optimal platelet inhibition is based on maximizing antithrombotic properties while minimizing bleeding and is critically dependent on individual patient risk.

Synergy Between Pharmacologic Strategies for Blocking Platelet Activation and Blocking Aggregation

Platelet activation is a complex process involving multiple redundant pathways (Figure 2).[8] Strategies that involve simultaneous blockade of cyclooxygenase (COX) by aspirin, of the $P2Y_{12}$ receptor by thienopyridines (eg, clopidogrel), and of activated GP IIb/IIIa receptors by GP IIb/IIIa inhibitors during PCI have proved effective in attenuating the development of in-hospital and thrombotic complications.[4,9,10] The occurrence of postdischarge stent thrombosis is lower for dual antiplatelet therapy than for aspirin therapy alone.[11]

Antithrombotic effects of aspirin in addition to its COX-1 blockade include antioxidant, anti-inflammatory, and anti-atherosclerotic effects on endothelial cells and leukocytes.[12] Aspirin is a comparatively weak inhibitor of platelet function, since other agonists such as ADP, collagen, or thrombin can still activate platelets, as measured by ex vivo tests in patients during aspirin treatment.[13]

Compared with aspirin, clopidogrel is a moderate inhibitor of platelet function. In ex vivo measurements, platelet aggregation induced by ADP, collagen, and thrombin is decreased after clopidogrel treatment. Little information is available on the effect of clopidogrel treatment on arachidonic acid metabolism or on arachidonic acid–induced platelet aggregation.[13] By attenuating ADP-induced platelet activation, clopidogrel also inhibits expression of P-selectin and CD-40L and formation of heterotypic aggregates (platelet-leukocyte aggregates).[14,15] The latter effects result in attenuation of inflammatory processes, as indicated by reduced release of C-reactive protein and tumor necrosis factor.[14] Attenuation of thrombin generation by clopidogrel has also been reported.[16,17]

Because aspirin and $P2Y_{12}$ receptor blockers partially inhibit platelet function, the efficacy of aspirin and clopidogrel may be limited, depending on the agonist concentrations in the local environment where thrombosis occurs. Thus, pharmacologic agents that directly block the GP IIb/IIIa receptor are more effective in inhibiting in vivo platelet aggregation and have been uniformly associated

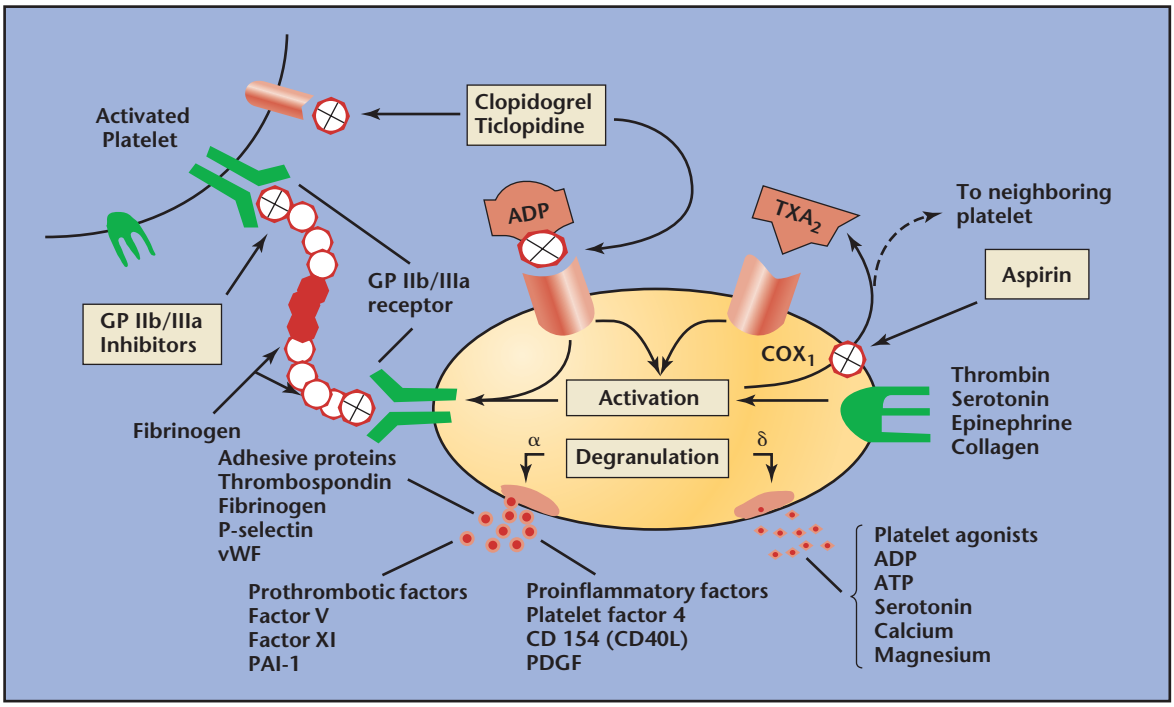


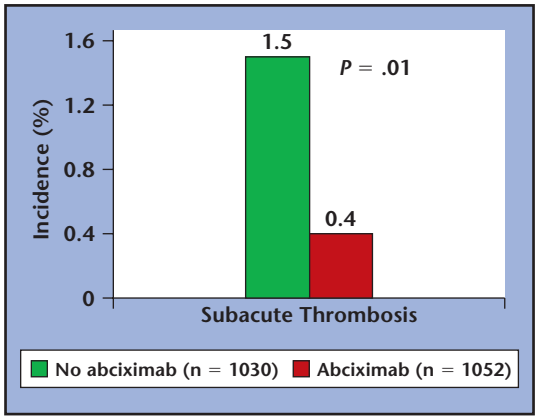
Figure 2. *Platelet activation and mechanism of action of antiplatelet agents. GP, glycoprotein; TXA_2, thromboxane A_2; COX, cyclooxygenase; vWF, von Willebrand factor; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; CD40L, CD40 ligand; ADP, adenosine diphosphate; ATP, adenosine triphosphate. Adapted with permission from Mehta SR, Yusuf S.*[8]

with superior early clinical outcomes for patients with acute cardiac syndrome and patients undergoing PCI. The GP IIb/IIIa blockers markedly inhibit ex vivo platelet aggregation and "outside-in" signaling, but have no effect on platelet adhesion involving GP Ia/IIa–collagen and GPIb-IX-V-vWF interactions. In addition to inhibiting platelet aggregation, GP IIb/IIIa inhibitor treatment is also associated with induction of platelet disaggregation and attenuation of microembolization of distal blood vessels, release of vasoconstrictive mediators, and release of microparticles.[18,19] Thus, the coadministration of a $P2Y_{12}$ inhibitor with a GP IIb/IIIa inhibitor has the rationale of providing superior reduction in thrombotic events compared with GP IIb/IIIa inhibitor therapy alone for patients exposed to a potent thrombogenic stimulus such as PCI. This may have particular relevance in patients undergoing urgent/emergent PCI. For patients presenting with ST-elevation acute myocardial infarction (STEMI) and other acute coronary syndromes, there may not be adequate time to achieve a sufficient antiplatelet effect with orally administered agents, even in high bolus dosing, by the time of the PCI procedure. In this scenario, administration of an intravenous GP IIb/IIIa inhibitor may be particularly useful. In the case of STEMI, abciximab has been found to reduce clinical event rates, including subacute thrombosis (Figure 3).[20,21]

Evidence for Synergy of a Combination of Aspirin and Clopidogrel with GP IIb/IIIa Inhibitor

The TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Outcome

Figure 3. *CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) study: incidence of 30-day subacute thrombosis with and without abciximab treatment. From Tcheng JE et al.*[20]



Trial) study was an international, multicenter, double-blind, double-dummy, prospective, randomized trial designed to compare the safety and efficacy of the GP IIb/IIIa inhibitors tirofiban and abciximab, in the setting of percutaneous coronary revascularization.[22] The incidence of the primary endpoint—death, myocardial infarction (MI), or urgent target vessel revascularization at 30 days—was 7.6% in the tirofiban group and 6.0% in the abciximab group, a relative difference of 27% (P = .038). MI occurred in 6.9% of the tirofiban group and 5.4% of the abciximab group (P = .04). Whether the superior results of abciximab were related to the reduced levels of platelet inhibition achieved with the dose of tirofiban used or were an effect independent of GP IIb/IIIa inhibition is open to speculation.

A subanalysis of data derived from the TARGET study lends support for the potential synergistic effect of $P2Y_{12}$ and GP IIb/IIIa inhibition.[23] This analysis found a lower 30-day composite ischemic endpoint, sustained at 6 months, in patients pretreated with clopidogrel and subsequently treated with GP IIb/IIIa inhibitors. Furthermore, at 1 year there was a lower mortality rate in this patient cohort. In the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) trial, however, a benefit of ticlopidine pretreatment was not observed.[24]

The CLEAR PLATELETS (Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets) and CLEAR PLATELETS-Ib studies found superior attenuation of platelet aggregation, myocardial necrosis, and inflammation marker release in PCI patients treated with clopidogrel and eptifibatide, compared with clopidogrel therapy alone.[4,25] In the PEACE (Platelet Activity Extinction in Non-Q-Wave Myocardial Infarction with Aspirin, Clopidogrel, and Eptifibatide) study, addition of eptifibatide therapy to aspirin and clopidogrel provided increased inhibition of activated GP IIb/IIIa expression and fibrinogen binding.[26]

The recent ELISA-2 (Early or Late Intervention in Unstable Angina) trial comparing dual and triple antiplatelet therapy during PCI found a nonsignificant reduction in enzymatic infarct size, a significantly better initial perfusion of the culprit vessel, and a trend toward better survival (death or MI as endpoint) in patients receiving a GP IIb/IIIa inhibitor in addition to dual antiplatelet therapy.[9] The superior inhibition (> 90%) with GP IIb/IIIa inhibitors during PCI was associated with significant early benefits, which were sustained for up to 3 years. In the TOPSTAR (Troponin in Planned PTCA/Stent Implantation with or without Administration of the Glycoprotein IIb/IIIa Receptor Antagonist Tirofiban) trial, addition of tirofiban reduced periprocedural elevation of troponin T in patients pretreated with aspirin and clopidogrel.[10]

Taken together, these studies suggest that addition of a GP IIb/IIIa inhibitor to dual oral antiplatelet therapy during PCI is more effective in reducing periprocedural infarction than dual therapy alone. These findings may be particularly relevant to patients at high risk.

Definition of Clopidogrel and Aspirin Resistance

Laboratory investigations of platelet function after clopidogrel therapy have demonstrated a wide variability in response. A certain percentage of patients exhibit complete nonresponsiveness. Other terms used to describe this phenomenon include "resistance" and "hyporesponsiveness." Based on these observations, it was suggested that such patients may be the least protected from thrombosis. The optimal definition of resistance to clopidogrel is based on its inhibition of the $P2Y_{12}$ receptor. Thus, persistent activity of $P2Y_{12}$ as reflected by ADP-induced aggregation or ADP-stimulated intracellular signaling events, shown by inhibition of adenylyl cyclase activity, would serve as evidence for nonresponsiveness to clopidogrel.[27] In the case of aspirin resistance, there would be residual post-treatment COX-1 activity. Since thrombosis involves multiple signaling pathways, treatment failure is not synonymous with drug resistance.

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What Is the Optimal Test of Platelet Reactivity?

At this time, the optimal measure of platelet reactivity that predicts clinical thrombosis or bleeding risk remains uncertain. A standardized laboratory method that simulates the in vivo platelet response to antiplatelet therapy is also lacking. Given that clopidogrel specifically inhibits 1 of 2 ADP receptors, ex vivo measurement of ADP-induced maximum platelet aggregation by light transmittance aggregometry (LTA) is the most commonly used laboratory method to evaluate clopidogrel responsiveness and is considered the gold standard. Although aggregation as measured by LTA is a reproducible tool in the hands of experienced laboratories, it can be confounded by intrapatient variability.

Flow cytometric measurement of the expression of activated GP IIb/IIIa receptor and P-selectin after ADP stimulation can also identify clopidogrel nonresponsiveness and can be correlated with measures of maximum aggregation stimulated by ADP.[28,29] In addition, assessment of ADP-induced platelet-fibrin clot strength by whole blood thrombelastography (Haemoscope Corporation, Niles, IL) and the VerifyNow™ $P2Y_{12}$ Assay (Accumetrics, San Diego, CA), using ADP as the agonist, can also be used to measure clopidogrel responsiveness as point-of-care assays.[30,31] The phosphorylation state of vasodilator-stimulated phosphoprotein (VASP), a specific intracellular marker of residual $P2Y_{12}$ receptor reactivity in patients treated with clopidogrel, can be measured by flow cytometry. This technique is perhaps the most specific indicator of residual $P2Y_{12}$ activity in patients treated with a $P2Y_{12}$ inhibitor.[32]

By utilizing the above mentioned laboratory techniques, various studies have evaluated clopidogrel nonresponsiveness in patients undergoing stenting and reported a prevalence of 5%-44%.[33] The higher prevalence (> 28%) was unequivocally associated with a 300 mg loading dose of clopidogrel, whereas a lower prevalence (< 10%) was associated with a higher (600 mg) clopidogrel loading dose.[34,35] In addition, the prevalence of non-responsiveness depends on time. For example, in one study, following a 300 mg loading dose administered at the time of elective stenting, 63% of patients were resistant to clopidogrel treatment at 2 hours, 30% at day 1 and day 5 post stenting, and 15% by day 30.[28]

On the basis of various COX-1 specific and COX-1 nonspecific methods, the prevalence of aspirin resistance is reported to be between 0.4% and 54%.[33] The wide range of "resistance" rates is due to the lack of standardized methodology to quantify the aspirin response in platelets and the lack of standardized criteria to define aspirin resistance. Another major reason for the wide range of results is the nonspecificity of some methods in indicating the degree of COX-1 inhibition. Multiple studies have demonstrated residual platelet activity after stimulation by agonists other than arachidonic acid, such as ADP and collagen, and these are COX-1 nonspecific assays. In a recent study, platelet responsiveness to aspirin at different doses was measured by both COX-1 specific and COX-1 nonspecific assays. This important study clearly confirmed a low prevalence of aspirin resistance (≤ 5%) when measured with COX-1 specific assays but a higher prevalence (15% to 32%) with COX-1 nonspecific assays such as ADP- or collagen-induced LTA or the platelet function analyzer-100 (PFA-100; Dade Behring, Miami, FL).[36,37]

At this time, however, there are no uniformly established methods for quantifying ex vivo platelet reactivity after clopidogrel and aspirin treatment or the extent of platelet inhibition by clopidogrel and aspirin. Therefore, specific treatment recommendations have not been established for patients exhibiting high platelet reactivity during clopidogrel or aspirin therapy, or for patients who have poor platelet inhibition by clopidogrel or aspirin. A higher aspirin dose (≥ 325 mg/day), strict compliance with therapy, or dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor blocker may overcome the occurrence of "aspirin resistance" in selected patients.[33] This patient population might derive particular benefit from periprocedural intravenous GP IIb/IIIa inhibitors.

A higher clopidogrel loading dose of 600 mg or a maintenance dose of 150 mg/day may be considered for patients exhibiting clopidogrel nonresponsiveness. Alternative therapy for clopidogrel resistance includes new, more effective $P2Y_{12}$ receptor blockers such as prasugrel, AZD6140, and cangrelor.[3,33] At this time, it is uncertain whether a threshold of platelet reactivity exists that would indicate excessive risk for ischemic events or bleeding.

Evidence Linking Periprocedural Platelet Reactivity to In-Hospital and Long-Term Adverse Ischemic Events

Reactivity to ADP

Data are emerging that link high ex vivo platelet reactivity to ADP with the occurrence of thrombotic events (Table 1). The earliest studies looked at the possible relation between pretreatment platelet reactivity and clopidogrel resistance, and it was suggested that the least thrombotic protection occurred in patients with high pretreatment reactivity.[28] A subsequent study further evaluated the relation among pretreatment ADP-induced aggregation, post-treatment aggregation, and clopidogrel responsiveness. The results showed that some nonresponders had low pretreatment reactivity to ADP, while some responders had high post-treatment reactivity.[38] Therefore, the evaluation of thrombotic risk based on clopidogrel responsiveness seemed to be flawed, potentially overestimating or underestimating the thrombotic risk in selected patients. Based on these findings, it was further hypothesized that the most reliable predictor of

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Table 1
Clinical Relevance of Clopidogrel Nonresponsiveness

Study (first author)	n	Results	Clinical Relevance
Post-stent ischemic events and periprocedural infarction			
Matetzky[7]	60	↑ ADP-induced platelet aggregation (4th quartile)	Recurrent cardiac events
Gurbel[5] (PREPARE POST-STENTING study)	192	↑ Periprocedural platelet aggregation	Post-PCI ischemic events (6 months)
Gurbel[4,25] (CLEAR PLATELETS and CLEAR PLATELETS-Ib studies)	120	↑ Periprocedural platelet aggregation	Myonecrosis and inflammation marker release
Gurbel[30]	100	↑ Periprocedural platelet aggregation with chronic clopidogrel	Post-PCI ischemic events (6 months)
Cuisset[6]	106	↑ Platelet aggregation	Recurrent events
Lev[40]	120	↑ Clopidogrel-/aspirin-resistant patients	Post-PCI myonecrosis
Stent thrombosis			
Barragan[41]	36	↑ $P2Y_{12}$ reactivity ratio (VASP levels)	Stent thrombosis
Gurbel[29] (CREST study)	120	↑ $P2Y_{12}$ reactivity ratio ↑ Platelet aggregation ↑ Stimulated GP IIb/IIIa expression	Stent thrombosis
Ajzenberg[42]	49	↑ Shear-induced platelet aggregation	Stent thrombosis

ADP, Adenosine diphosphate; CLEAR PLATELETS Study, Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets: Results of the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets study; CREST Study, Clopidogrel Effect on Platelet Reactivity in Patients with Stent Thrombosis; GP, Glycoprotein; PCI, Percutaneous Coronary Intervention; PREPARE POST-Stenting, Platelet Reactivity in Patients and Recurrent Events Post-stenting; VASP, vasodilator-stimulated phosphoprotein.

thrombotic risk is post-treatment platelet reactivity to ADP.[39]

Matetzky and colleagues,[7] in a study of clopidogrel responsiveness in patients undergoing stenting for acute STEMI, found that patients who exhibited the highest quartile of ADP-induced aggregation had a 40% probability of a recurrent cardiovascular event within 6 months. The prospective PREPARE POST-STENTING (Platelet Reactivity in Patients and Recurrent Events Post-stenting) study included 192 consecutive patients undergoing elective stenting, followed up for 6 months. In this study, Gurbel and colleagues[5] demonstrated a higher rate of recurrent ischemia in patients in the highest quartile of ADP-induced platelet aggregation compared with patients in the lowest quartile. In addition, patients in the highest quartile of platelet-fibrin clot strength generated by thrombin stimulation, as measured by thrombelastography, had the highest rate of recurrent ischemic events.

In the CLEAR PLATELETS and CLEAR PLATELETS-Ib studies, a 600 mg clopidogrel loading dose in patients undergoing elective stenting was associated with superior early platelet inhibition of ADP-induced aggregation compared with a 300 mg loading dose, and this superior platelet inhibition was sustained over 24 hours.[4,25] In turn, increased platelet inhibition was accompanied by a decreased release of markers of in-hospital myocardial necrosis and inflammation. Cuisset and colleagues[6] also demonstrated that patients with high post-treatment platelet reactivity had an increased risk of cardiovascular events. More importantly, these patients were resistant to both clopidogrel and aspirin treatment. Similarly, Lev and colleagues[40] found that the occurrence of creatinine kinase–myocardial band elevations after stenting was more frequent in patients exhibiting aspirin and clopidogrel resistance. Finally, a recent study investigating platelet reactivity in patients already receiving chronic clopidogrel therapy at the time of elective coronary stenting showed that recurrent ischemic events within 6 months of the procedure were significantly associated with higher pre-procedure ADP-induced platelet aggregation.[30] All these findings strongly suggest that a high platelet reactivity phenotype is a risk factor for ischemia in patients undergoing PCI.

Stent Thrombosis

Three small studies have suggested that high platelet reactivity to ADP in patients treated with clopidogrel may also be a risk factor for stent thrombosis. Barragan and colleagues,[41] in an important paper published in 2003, were the first to highlight a potential link between high platelet reactivity to ADP and the occurrence of stent thrombosis, by measuring VASP phosphorylation. The investigators demonstrated that poor clopidogrel responsiveness

indicated by a high $P2Y_{12}$ receptor reactivity ratio—a marker of incomplete receptor blockade in their assay—was associated with stent thrombosis.

In the recent CREST (Clopidogrel Effect on Platelet Reactivity in Patients with Stent Thrombosis) study, Gurbel and colleagues[29] assessed platelet function in 20 patients with a stent thrombosis, compared with 100 consecutive patients without stent thrombosis. Measurements were made using LTA, ADP-stimulated expression of active GP IIb/IIIa measured by flow cytometry, and the $P2Y_{12}$ reactivity ratio measured by VASP phosphorylation, employing the same assay used by Barragan and coauthors. Elevated levels of all these measures were observed in patients with stent thrombosis compared with patients free of stent thrombosis, similarly indicating inadequate inhibition of the $P2Y_{12}$ receptor. In addition, only 1 of the 120 patients studied was aspirin resistant, and that patient had a stent thrombosis.

Finally, Ajzenberg and co-workers[42] observed increased shear-induced platelet aggregation in patients with stent thrombosis compared with patients without stent thrombosis who were receiving dual antiplatelet therapy and to healthy volunteers not receiving dual antiplatelet therapy.

Clinical Relevance of Aspirin Resistance

Grotemeyer and colleagues[43] found that patients exhibiting aspirin resistance, as measured by an elevated platelet aggregate ratio, had a 10-fold increased risk of recurrent vascular events compared with aspirin-sensitive patients (40% vs 4.4%; $P < .0001$) (Table 2). Using whole blood aggregometry to evaluate aspirin resistance, Mueller and colleagues[44] found an 87% increase in the incidence of reocclusion in "aspirin-resistant" patients who underwent balloon angioplasty and were treated with 100 mg of aspirin daily for 18 months. Eikelboom and colleagues[45] employed a more COX-1 specific method that measures urinary 11-dehydro (Tx) B_2 thromboxane metabolite levels in patients enrolled in the HOPE (Heart Outcomes Prevention Evaluation) trial for aspirin responsiveness. They found that the risk of MI, stroke, or cardiovascular-related death was greater in the highest quartile of urinary TXB_2 metabolite levels. These data suggest that suboptimal inhibition of COX-1 or nonresponsiveness to aspirin therapy is a major cardiovascular risk factor.

Aspirin resistance was associated with a significant increase in the composite endpoint of death, myocardial infarction, or stroke.

Gum and colleagues[46,47] found a 5% incidence of aspirin resistance, based on the criteria of ≥ 20% arachidonic acid–induced aggregation and ≥ 70% ADP-induced aggregation, in patients with stable cardiovascular disease treated with 325 mg of aspirin daily for up to 2.5 years. Aspirin resistance was associated with a significant increase in the composite endpoint of death, MI, or stroke. More recently, Chen and co-workers,[48] using the Accumetrics point-of-care device (Ultegra Rapid Platelet Function Assay-ASA) with cationic propyl gallate as the agonist, found that despite treatment with clopidogrel and heparin, aspirin resistance (as defined by this assay) was associated with a ~2.9-fold increase in the occurrence of myonecrosis following PCI.

Conclusion

An emerging body of data, mostly derived from small studies, provides

Table 2
Clinical Relevance of Aspirin Resistance

Study (first author)	n	Patient Type	Method	Results
Grotemeyer[43]	180	Post-CVA	Platelet aggregates	10 × increase in vascular events
Mueller[44]	100	PVD	Platelet aggregation (whole blood)	87% increase in incidence of reocclusion
Eikelboom[45]	976	HOPE trial	Urinary TXB_2	Increase in MI/stroke/death with increase in TXB_2
Gum[46,47]	325	Stable CAD	Platelet aggregation (LTA)	3.12 × increase in MI/stroke/death
Chen[48]	151	PCI	RPFA	2.9 × increase in myocardial necrosis

CVA, cerebrovascular accident; PVD, peripheral vascular disease; TXB_2, thromboxane B_2; CAD, coronary artery disease; LTA, light transmittance aggregometry; MI, myocardial infarction; PCI, percutaneous coronary intervention; RPFA, rapid platelet function analyzer.

evidence that post-PCI patients with the greatest ex vivo platelet reactivity to ADP are at high risk for recurrent ischemic events. Nonresponsiveness to clopidogrel is a recognized entity in post-PCI patients. Whether these patients are at excess ischemic risk should be determined in large-scale prospective trials. Given that GP IIb/IIIa blockade obviates the limitation of oral $P2Y_{12}$ inhibitors that incompletely inhibit platelet aggregation stimulated by multiple agonists, a reluctance to use GP IIb/IIIa inhibitors in favor of oral $P2Y_{12}$ inhibitors alone deserves closer scrutiny. Evidence from PCI trials suggests ischemic events are reduced by adding GP IIb/IIIa inhibitors for patients pretreated with dual oral antiplatelet therapy. Future prospective investigations of pre- and post-PCI platelet reactivity that clearly identify thrombotic risk will solidify the position of platelet reactivity as the new measurable cardiovascular risk factor. Most importantly, high platelet reactivity is a modifiable risk factor that can be addressed by alternative antiplatelet strategies. ■

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Main Points

- Platelet reactivity is emerging as a new measurable and modifiable cardiovascular risk factor.
- Elevated platelet function immediately following percutaneous coronary intervention (PCI) plays a central role in the genesis of post-PCI thrombotic events.
- The rationale of antiplatelet therapy during and following PCI is to prevent occlusive thrombus formation, arrest procoagulant activity and inflammatory processes, promote platelet disaggregation, and facilitate perfusion of occluded blood vessels.
- Simultaneous blockade of cyclooxygenase (COX) by aspirin, of the $P2Y_{12}$ receptor by thienopyridines (clopidogrel), and of activated glycoprotein (GP) IIb/IIIa receptors by GP IIb/IIIa inhibitors during PCI attenuates the development of thrombotic complications.
- Patients exhibiting nonresponsiveness to clopidogrel, as defined on the basis of its inhibition of the $P2Y_{12}$ receptor, or aspirin resistance, as defined by residual post-treatment COX-1 activity, are at increased risk of recurrent vascular events after PCI.

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