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STATE-OF-THE-ART PAPER

Consensus and Update on the Definition of On-Treatment Platelet Reactivity to Adenosine Diphosphate Associated With Ischemia and Bleeding

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Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor blocker is a key strategy to reduce platelet reactivity and to prevent thrombotic events in patients treated with percutaneous coronary intervention. In an earlier consensus document, we proposed cutoff values for high on-treatment platelet reactivity to adenosine diphosphate (ADP) associated with post–percutaneous coronary intervention ischemic events for various platelet function tests (PFTs). Updated American and European practice guidelines have issued a Class IIb recommendation for PFT to facilitate the choice of $P2Y_{12}$ receptor inhibitor in selected high-risk patients treated with percutaneous coronary intervention, although routine testing is not recommended (Class III). Accumulated data from large studies underscore the importance of high on-treatment platelet reactivity to ADP as a prognostic risk factor. Recent prospective randomized trials of PFT did not demonstrate clinical benefit, thus questioning whether treatment modification based on the results of current PFT platforms can actually influence outcomes. However, there are major limitations associated with these randomized trials. In addition, recent data suggest that low on-treatment platelet reactivity to ADP is associated with a higher risk of bleeding. Therefore, a therapeutic window concept has been proposed for $P2Y_{12}$ inhibitor therapy. In this updated consensus document, we review the available evidence addressing the relation of platelet reactivity to thrombotic and bleeding events. In addition, we propose cutoff values for high and low on-treatment platelet reactivity to ADP that might be used in future investigations of personalized antiplatelet therapy. (J Am Coll Cardiol 2013;62:2261–73) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
ADP = adenosine diphosphate
CABG = coronary artery bypass graft
CAD = coronary artery disease
CI = confidence interval
HPR = high platelet reactivity to adenosine diphosphate
HR = hazard ratio
LPR = low platelet reactivity to adenosine diphosphate
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
PFT = platelet function testing/test
PR = platelet reactivity
PRI = platelet reactivity index
PRU = $P2Y_{12}$ reaction units
ROC = receiver-operating characteristic
ST = stent thrombosis
TIMI = Thrombolysis In Myocardial Infarction
VASP-P = vasodilator-stimulated phosphoprotein-phosphorylation

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor blocker to inhibit platelet reactivity (PR) and to prevent ischemic event occurrences is an effective pharmacologic therapy administered to patients with acute coronary syndromes (ACS) or those undergoing percutaneous coronary intervention (PCI) (1–3). Except for recommendations related to some specific demographic variables, for example, the history of transient ischemic attack or stroke that precludes prasugrel use in ACS undergoing PCI, a "one-size-fits-all" approach for $P2Y_{12}$ receptor blockers is mostly employed based on clinical trial results. However, the pharmacodynamic effect of clopidogrel has been shown to be widely variable, whereas prasugrel and ticagrelor are associated with a more uniform antiplatelet response (4–10).

In the past decade, compelling evidence from numerous observational studies has emerged demonstrating a strong association between high platelet reactivity to adenosine diphosphate (HPR) and post-PCI ischemic events, especially stent thrombosis (ST) (4). Earlier, we provided a consensus opinion on the definition of HPR based on various methods reported in the literature (4). Since then, updated American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions and European Society of Cardiology guidelines issued a Class IIb recommendation for platelet function testing (PFT) to facilitate the choice of $P2Y_{12}$ inhibitor in selected, high-risk patients undergoing PCI, although routine PFT is not recommended (Class III, no benefit) (Online Appendix, Box-1) (1–3). Recent prospective randomized trials evaluating personalized antiplatelet therapy based on PFT did not demonstrate clinical benefit, thus questioning whether treatment modification based on the results of PFT can actually influence outcomes (11–13). It should be acknowledged that these randomized trials are associated with major limitations. There are also controversies regarding the low positive predictive value of PFT, which some investigators have proposed has limitations in its clinical utility for individual patients. However, others have argued that an application of diagnostic test statistics is not appropriate for a prognostic test such as PFT (14–16). In this updated consensus document, we aim to review the available evidence addressing the relation of PR to thrombotic and bleeding events. We propose updated cutoff values for HPR and low platelet reactivity to adenosine diphosphate (LPR) that might be used in future investigations of personalized antiplatelet therapy. Finally, we highlight the major limitations of the randomized trials that failed to demonstrate the utility of PFT.

Many of the earlier studies that attempted to link ex vivo evidence of heightened PR to ischemic events were criticized for the potential introduction of artifacts by the laboratory methods. The findings were regarded as "unconvincing" because the PFT were thought to be poor substitutes for the complex interactions taking place in vivo (17). Correlations between various assays were not robust; moreover, there was poor agreement between tests in discriminating patients

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with and without ischemic events (18,19). A large number of recent observational studies involving more than 20,000 patients demonstrated that HPR during clopidogrel treatment is a strong and independent risk factor for post-PCI thrombotic events (20–23). In addition, the most widely used assays (VerifyNow $P2Y_{12}$ assay [Accumetrics, San Diego, California], Multiplate Analyzer [F. Hoffmann-La Roche Ltd., Basel, Switzerland], vasodilator-stimulated phosphoprotein-phosphorylation [VASP-P] assay [Diagnostica Stago, Biocytex, Asnières, France]) have overcome many of the technical and methodological limitations of previous assays, including conventional light transmittance aggregometry.

Platelet Function Measurement in Patients Undergoing PCI

Recently, the multinational prospective registry study ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) (~50% of patients with ACS) reinforced the independent association between HPR and definite/probable ST (16). In this study, HPR (>208 $P2Y_{12}$ reaction units [PRU]) was independently associated with an ~3-fold increased risk for 30-day definite/probable ST (propensity-adjusted hazard ratio [HR]: 3.00, 95% confidence interval [CI]: 1.39 to 6.49; $p = 0.005$). Furthermore, >208 PRU remained an independent predictor of 1-year definite/probable ST (adjusted HR: 2.49, 95% CI: 1.43 to 4.31; $p = 0.001$) and myocardial infarction (MI) (adjusted HR: 1.42, 95% CI: 1.09 to 1.86; $p = 0.01$). Although significantly more patients with HPR had died at 1-year follow-up, HPR was not an independent predictor of mortality after adjusting for a large number of confounding variables (HR: 1.20, 95% CI: 0.85 to 1.70; $p = 0.30$). The authors observed that HPR had a greater impact in ACS patients than in stable coronary artery disease (CAD) patients (16).

The importance of HPR and treatment with intensified therapy should be interpreted in the context of patient characteristics such as ethnicity and underlying risk. In a study of 1,220 East Asian patients, HPR (>272 PRU) was associated with cardiovascular events at 1-year follow-up among acute MI patients, whereas there was no relation in those without acute MI (24). Similarly, Park et al. (25) demonstrated that HPR >235 PRU was independently associated with the primary composite endpoint of death, MI, ST, or stroke in East Asian patients undergoing PCI with ACS, but not with stable CAD patients.

There is further support for an association between HPR determined ex vivo and coronary atherosclerosis and thrombotic event occurrence in vivo. HPR (>230 PRU) during clopidogrel therapy was independently associated with greater coronary artery atherosclerotic burden and plaque calcification as measured by intravascular ultrasound imaging (26). An association between PR and systemic inflammation/procoagulant marker elevation has also been described in patients with CAD (27–29). In addition to the extensive literature on HPR in clopidogrel-treated patients, recent observational studies suggest that HPR is also relevant to the new $P2Y_{12}$ receptor blockers (6,9,10).

In summary, the evidence that supports the potential utility of PFT as a prognostic marker among patients undergoing PCI includes: 1) the accepted highly platelet-related pathophysiology of atherothrombosis and its clinical phenotypes; 2) the consistent confirmation of an association between HPR and ischemic event occurrence; 3) the results of randomized clinical trials demonstrating lower thrombotic event rates in patients treated with pharmacodynamically more potent agents than clopidogrel; and 4) lack of difference in the final mechanism of action between $P2Y_{12}$ receptor blockers. From a statistical perspective, PFT fulfills several criteria as a robust prognostic marker. In particular, HPR is associated with substantial hazard for thrombotic events (11) and improves net reclassification for major adverse clinical events (16,21).

Platelet Function Measurement in Medically-Managed Patients

Although prognostic utility of HPR is robust in patients undergoing PCI, its clinical relevance in medically-managed ACS patients or in stable CAD patients is less clear. In a recent study, antiplatelet drug responsiveness assessed by several assays did not add any incremental predictive value

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over common risk factors for the occurrence of major adverse cardiovascular events at 3-year follow-up in stable patients (n = 771) with symptomatic atherothrombotic disease managed medically with aspirin and/or clopidogrel (30).

In the TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) platelet function substudy (n = 2,564), the greater platelet inhibition provided by prasugrel versus clopidogrel did not translate into an improved event-free survival in the overall study (7). In an unadjusted analysis, HPR (PRU >208) was associated with the occurrence of the primary composite endpoint (cardiovascular death, MI, or stroke) through 30 months. However, in an adjusted analysis including a large number of demographic and clinical characteristics, HPR did not remain an independent predictor of adverse events (7). Some limitations merit discussion regarding the TRILOGY study. Patients were not-randomized and platelet function was not measured during the initial period of potentially highest thrombotic risk (patients were enrolled and randomized 4 to 10 days after the index event). The TRILOGY study enrolled a significant proportion of patients who did not have proven evidence of significant CAD in whom PR to adenosine diphosphate (ADP) may not have influenced outcome. Finally, the adjusted analysis included multiple risk factors and covariates that may influence thrombotic outcomes by their effect on platelet physiology and thereby could have masked the independent association of HPR on ischemic events. Although multivariable adjustment is important to suggest causal relationships between risk factors and events, univariate associations may be more important for the treating physician who is unable to adjust test results for multiple variables at the bedside. Indeed, HPR has been associated with several prognostic variables including ACS, diabetes, high body weight, older age, reduced left ventricular ejection fraction, or elevated C-reactive protein (31,32), whereas smoking has been associated with a lower frequency of HPR in some studies (33,34).

Treatment intervention based on platelet function measurement was used to reduce post-PCI thrombotic events in the GRAVITAS (Gauging Responsiveness With a VerifyNow Assay–Impact on Thrombosis and Safety) trial. PCI patients with HPR (≥235 PRU) were randomly assigned to either standard dose clopidogrel or a repeated 600-mg loading dose of clopidogrel followed by 150 mg daily (high dose). High-dose clopidogrel treatment was ineffective in reducing the 6-month composite ischemic event occurrence of cardiovascular death, nonfatal MI, and ST. Notably, the event rate was low (2.3% vs. 5% used for power calculation); therefore, the study was substantially underpowered (11). In addition to being underpowered, there are other potential explanations for the neutral results of GRAVITAS trial (35). In a time-dependent analysis of GRAVITAS, <208 PRU was independently associated with the 60-day primary endpoint (HR: 0.23, 95% CI: 0.05 to 0.98; p = 0.047) and tended to be an independent predictor at 6 months (HR: 0.54, 95% CI: 0.28 to 1.04; p = 0.06) (36). Only a minority of patients receiving high-dose clopidogrel achieved <208 PRU, indicating that the high-dose clopidogrel regimen may have been suboptimal. A more potent intervention that reduces HPR to a greater extent would have had greater potential to improve clinical outcomes given the very low event rate. In support of this hypothesis, the ELEVATE–TIMI 56 (Escalating Clopidogrel by Involving a Genetic Strategy–Thrombolysis In Myocardial Infarction 56) trial showed that up to 225 mg of clopidogrel might be necessary to overcome HPR in patients carrying 1 loss-of-function cytochrome *2C19* gene (37). The GRAVITAS trial enrolled a population at low absolute risk for ischemic events despite displaying HPR. The majority of patients had stable angina and were successfully treated with PCI, and periprocedural events were not included in the primary endpoint. The tested pharmacologic intervention was administered more than 12 h after PCI, and the associated acute vessel injury/stent deployment, which may have been too late to blunt a platelet-related incipient lesion. Finally, it is possible that a single PFT will not reliably reflect the effect of clopidogrel on ADP-induced PR in all patients (35).

In the ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting) study, 2,440 patients were randomly assigned to either a strategy of platelet function monitoring and drug adjustment or to a conventional strategy without platelet function monitoring according to the clinicians' preference (13). The 1-year primary composite endpoint of death, MI, ST, stroke, or urgent revascularization was similar in both arms (34.6% vs. 31.1%; HR: 1.13, 95% CI: 0.98 to 1.29; p = 0.10), mostly driven by periprocedural MI that was assessed by nonstandard methodology (single troponin assessment 6 h after the procedure). However, protocol implementation was incomplete: 73% of patients with HPR received an additional clopidogrel loading dose, whereas only 4% received a prasugrel loading dose. Similar to the GRAVITAS trial, the primary intervention in the maintenance phase among patients with HPR was clopidogrel 150 mg, 15.6% of the patients in the monitoring group had HPR at 2- to 4-week follow-up despite monitoring, and the study population was at low absolute risk for cardiovascular events. Importantly, twice as many patients were lost to follow-up in the conventional than in the monitoring arm (3.8% vs. 1.9%). Finally, the composite endpoint in this study also included other events, such as death from any cause, that may not be related to platelet function (13).

The TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study is the only trial using a potentially effective strategy to overcome HPR. Stable angina patients with >208 PRU were randomized after successful drug-eluting stent PCI

to prasugrel or standard-dose clopidogrel. However, the study was terminated prematurely after a non–pre-specified interim analysis due to a largely lower rate of ischemic events than anticipated that precluded the establishment of meaningful results. Approximately 30% of the enrolled patients declined randomization after being identified as having HPR, which is suggestive of selection bias. The very low event rates in patients with stable CAD successfully treated with current drug-eluting stent, even among those hyporesponsive to clopidogrel, suggest that this patient population will be challenging for future studies to demonstrate the benefits of PFT-directed therapies (12).

Although the results of the latter 3 randomized trials were negative, smaller studies have suggested that the PFT-directed approach may be effective depending on the method of implementation. Two small multicenter trials employed the VASP-P assay to tailor incremental loading doses of clopidogrel to reduce on-treatment PR below the HPR cutoff. This strategy was associated with significantly reduced subsequent adverse event occurrence, including early ST without increasing bleeding (38,39). Similarly, 2 other studies have suggested that the selective administration of a glycoprotein IIb/IIIa receptor inhibitor to patients undergoing elective PCI who were identified as poor responders to aspirin or clopidogrel was effective in reducing both 30-day and 1-year ischemic events without increased bleeding rates (40,41). In addition, the non-randomized MADONNA (Multiple Electrode Aggregometry in Patients Receiving Dual Antiplatelet Therapy to Guide Treatment With Novel Platelet Antagonists) study (n = 798) (42) and a randomized study by Hazarbasanov et al. (43) suggested that an individualized antiplatelet regimen based on PFT measured by a Multiplate analyzer can reduce post-PCI ischemic event occurrences without an increase in bleeding risk. Of importance, all of these studies aimed to decrease PR below the threshold of HPR, which is associated with post-PCI ischemic events.

Finally, a meta-analysis of 9 randomized trials compared intensified antiplatelet therapy with standard therapy in patients with HPR (20). Although the analysis included some small-sized trials, and the strategy to intensify platelet inhibition was heterogeneous, the results showed a significant reduction in cardiovascular mortality and ST in HPR patients when intensified antiplatelet therapy was used. Of interest, the benefit was mostly observed in high-risk patients, suggesting that other factors, including demographic, clinical, and angiographic factors, must be also taken into consideration to optimally identify the patients at greatest risk. Along this line, recent studies have suggested that adding clinical variables and genotype to PFT may improve risk prediction (31,32).

PR and Bleeding

During the era of dual antiplatelet therapy with aspirin and ticlopidine/clopidogrel, the evaluation of antiplatelet therapies has been largely focused on reducing ischemic event occurrence (efficacy). Bleeding (safety) was often considered as an inevitable and acceptable complication. However, in the era of more potent $P2Y_{12}$ receptor inhibitors, there is a heightened risk for bleeding. The balance between the absolute risk reduction in ischemic events and the absolute risk increase in bleeding events (particularly assessed by more sensitive bleeding scales) with more potent agents remains delicate. A therapeutic counterpoise may occur, with the absolute risk reduction in ischemic event occurrence and the absolute risk increase in bleedings approaching to the same magnitude (44). Current knowledge suggests that there may be a "ceiling effect" in reducing ischemic event occurrence even with new $P2Y_{12}$ receptor inhibitors (i.e., 10% residual ischemic event occurrence). Furthermore, in the contemporary registries and trials of PCI, the absolute rate of ischemic events at 1-year follow-up is low (16,32). Given this scenario, the focus is now shifting toward finding strategies that could avoid excessive bleeding while maintaining the benefit of reduced ischemic/thrombotic events (45). This paradigm evolution also led to the introduction of novel clinical endpoints such as the "net adverse clinical events" in ongoing and future trials. It could be argued that more potent antiplatelet therapies may be optimal when the benefit of reducing ischemic events outweighs the risk of bleeding. Accordingly, the greater net clinical benefit of the more potent $P2Y_{12}$ blockade may be observed early after stenting when thrombotic risk is the highest (46).

Bleeding events have been associated with an increased risk of short- and long-term morbidity and mortality in CAD patients during long-term antiplatelet therapy and anticoagulant therapy (47). In addition, the results of randomized trials of anticoagulants suggest that a survival benefit might be attributable to reduction in bleeding alone (48,49). Several potential reasons for the higher risk of mortality associated with bleeding include: 1) premature termination of obligatory therapies including antiplatelet agents; 2) immunosuppression and platelet activation by blood transfusion; and 3) hemodynamic compromise associated with bleeding and greater prevalence of comorbidities in patients who suffer from bleeding events (50). In addition, inflammatory, procoagulant, and other mechanisms have been suggested as mediating factors for risk associated with bleeding and transfusion (51). Finally, even superficial or "nuisance" bleeding may be clinically important as these events are associated with premature drug discontinuation, which may have an impact on clinical outcomes (52).

Challenges in Studying Bleeding Complications

A consensus has been reached regarding the definition of ischemic events such as MI and ST (53,54). Although these ischemic events are highly platelet-dependent, the underlying mechanisms of bleeding are more complex and heterogeneous in origin. For example, the etiologies of

gastrointestinal, intracranial, surgical, and nuisance bleedings are distinct. The role that platelet function plays in these different types of bleeding might vary, and it might be related to the extent of impaired hemostatic potential and possibly a higher degree of platelet inhibition. Moreover, variable transfusion triggers and perioperatively relevant covariates have to be considered in surgery-related bleeding (55). Compared with the composite endpoint of cardiovascular death, MI, or stroke, the prevalence of "major" or "severe" bleeding is generally low; therefore, it is more difficult to study mechanisms of major bleeding as compared to ischemic event outcomes due to the large number of patients required. Moreover, characteristics such as older age, chronic kidney disease, female sex, and diabetes share heightened risk for both bleeding and ischemic events (56). Previous randomized clinical trials used various bleeding definitions, and this has produced a library of heterogeneous classifications for incidence and severity. These diverse definitions have limited comparisons of bleeding across trials (57). The Bleeding Academic Research Consortium proposed a standardized definition to better quantify bleeding events and to evaluate new strategies to reduce the risk of bleeding in future trials (48).

Relation of Platelet Function to Bleeding in PCI-Treated Patients

Although the link between HPR and ischemic event occurrence is well established, the association between on-treatment PR and bleeding events is less clear. Observational studies involving patients undergoing PCI have suggested a possible link between LPR and bleeding (Table 1) (8,9,11,13,18,58–63). A first report suggested an association between clopidogrel hyper-responsiveness (or LPR) and post-discharge TIMI minor or major bleeding events in a cohort of patients undergoing PCI for non–ST-segment elevation MI (n = 597). In this study, patients in the first quartile of 10 μmol/l ADP-induced platelet aggregation (<40% aggregation) had more bleeding events than patients in the other quartiles did (58). Following this preliminary finding, further confirmation came from a large prospective cohort (n = 2,533) in which a relationship between post-PCI major non–coronary artery bypass graft (CABG)–related bleeding and PR was observed (8).

The link between post-PCI non-CABG-related major bleedings and LPR was also suggested by a retrospective analysis of 346 patients using the VASP–platelet reactivity index (PRI). In this study, lower PR measured by VASP-PRI was observed in patients with non-CABG-related TIMI major bleeding events, compared with patients without major bleeding (32.5 ± 22.4% vs. 51.2 ± 21.9%; p = 0.006) (60). These findings regarding major bleedings were reproduced in a prospective cohort of 310 patients treated with clopidogrel, demonstrating a 4.5-fold increased risk for TIMI major bleeding in patients in the lowest quartile of VerifyNow PRU levels measured before PCI. Receiver-operating characteristic (ROC) curve analysis identified the LPR cut point of PRU ≤189 to be the best predictor of bleeding (61).

A link between PR and bleeding was further observed in prasugrel-treated patients. Parodi et al. (63) reported that patients undergoing PCI with LPR on prasugrel therapy had more frequent access site bleeding. Accordingly, a strong independent relationship between platelet inhibition assessed by VASP-PRI and bleeding (including non-CABG-related TIMI major or minor bleeding) during 1-year follow-up was reported in ACS patients treated with prasugrel after successful PCI. Specifically, VASP-PRI ≤16% was associated with a higher rate of bleeding events. In multivariate analysis, VASP-PRI predicted both thrombotic and bleeding events (odds ratio [OR]: 1.44, 95% CI: 1.22 to 1.72; $p < 0.001$; and OR: 0.75, 95% CI: 0.59 to 0.96; $p = 0.024$, respectively [per 10% increase]). The frequency of thrombotic (excluding repeat revascularization) and bleeding events at 1-year follow-up were similar in this study (9). The observation of a link between non-CABG-related major bleeding and LPR during prasugrel therapy further supports the potential role of PFT, particularly as these findings do not appear to be specific for any $P2Y_{12}$ inhibitor. The consistent potent platelet inhibition achieved in ticagrelor-treated patients with PR values presenting within a small range have limited the ability to determine a bleeding threshold in such patients, at least by using the VerifyNow assay (64,65).

However, meaningful relationships between PR and bleeding events were not observed in large-scale platelet function studies such as the POPULAR (Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective PCI), GRAVITAS, and ARCTIC studies (11,13,18). A potential reason for the discrepancy between the results of the latter trials and those of smaller studies may be related to overall lower major bleeding event rates, different bleeding definitions, and the inclusion of procedural-related bleeding into the primary endpoints. However, in the largest study of all, ADAPT-DES (n = 8,583), HPR (>208 PRU) was inversely related to major bleeding (HR: 0.73, 95% CI: 0.61 to 0.89; p = 0.002) in a propensity-adjusted analysis accounting for 84 baseline and treatment-related variables (16).

Relation of PR to Surgery-Related Bleeding

Some observational studies demonstrated a relation of platelet function and bleeding in patients undergoing cardiac surgery (Table 2) (66–69). The major rationale for 5-day clopidogrel discontinuation recommended by the guidelines is the avoidance of excessive perioperative bleeding by allowing recovery of platelet function (70). However, demonstration of response variability, an ~30% non-responsiveness rate to clopidogrel therapy, and also variability in platelet function recovery following clopidogrel therapy cessation indicate that an objective measurement of

Table 1 Relation Between Platelet-Function Measurement and Bleeding in Patients Treated With PCI

First Author/Study (Ref. #)	Patients (n); $P2Y_{12}$ Treatment	Platelet Function Test(s)	Bleeding Criteria	Outcome
Sibbing et al. (8)	PCI (n = 2,533); clopidogrel	Multiplate analyzer, ADP-induced aggregation	Procedure-related TIMI major bleeding	<188 AU associated with 3.5× bleeding
Bonello et al. (9)	ACS patients undergoing PCI (n = 301); prasugrel	VASP assay	Major and minor TIMI bleeding	VASP-PRI ≤16% associated with major bleedings
GRAVITAS (11)	PCI with DES implantation; clopidogrel	VerifyNow $P2Y_{12}$ assay	GUSTO bleeding	No association between bleeding and platelet reactivity
ARCTIC (13)	PCI (n = 2,440); clopidogrel, prasugrel	VerifyNow $P2Y_{12}$ assay	Major bleeding—STEEPLE trial	No association between bleeding and platelet reactivity
POPULAR (18)	PCI (n = 1,069); clopidogrel	LTA, VerifyNow$P2Y_{12}$ assay; Plateletworks; IMPACT-R; PFA-100 with collagen-ADP; Innovance PFA P2Y	TIMI bleeding	No relation between bleeding and platelet reactivity measured by any assay
Cuisset et al. (58)	NSTE-ACS (n = 597); clopidogrel	LTA pre-heparin ADP-induced aggregation and VASP-PRI	Non-CABG TIMI major and minor	<40% aggregation associated with higher risk of 30 days post-discharge bleeding
Gurbel et al. (59)	PCI (n = 225); clopidogrel	MA-ADP TEG platelet mapping assay		≤31 MA-ADP associated with post-PCI bleeding
Mokhtar et al. (60)	PCI (n = 346); clopidogrel	VASP assay	Non-CABG TIMI minor and major	Low on-treatment PRI independent predictor of bleedings
Patti et al. (61)	PCI (n = 310); clopidogrel	VerifyNow $P2Y_{12}$ assay	TIMI major bleeding	ROC analysis; ≤189 PRU associated with bleeding
Tsukahara et al. (62)	PCI (n = 184); clopidogrel	LTA	REPLACE 2 bleeding	First quartile of ADP-induced aggregation associated with bleeding
Parodi et al. (63)	PCI (n = 298); prasugrel	LTA	Entry site bleeding	LPR associated with bleeding

ACS = acute coronary syndromes; ADP = adenosine diphosphate; ARCTIC = Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting study; AU = arbitrary aggregation unit(s); CABG = coronary artery bypass graft; DES = drug-eluting stent(s); GRAVITAS = Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety; GUSTO = Global Use of Strategies to Open Occluded Arteries; IMPACT-R = cone and platelet analyzer (IMPACT-R, Beersels, Belgium); LPR = low platelet reactivity to adenosine diphosphate; LTA = light transmittance aggregometry; MA = maximum amplitude; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PFA = platelet function analyzer; POPULAR = Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective PCI study; PRI = platelet reactivity index; PRU = $P2Y_{12}$ reaction units; REPLACE 2 = Randomized Evaluations of PCI Linking Angiomax to Reduced Clinical Events trial; ROC = receiver-operating characteristic; STEEPLE = Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation trial; TEG = thrombelastography; TIMI = Thrombolysis In Myocardial Infarction; VASP = vasodilator stimulated phosphoprotein-phosphorylation.

the antiplatelet effect of clopidogrel before surgery may obviate the need for the recommended standardized waiting period in a substantial percentage of patients (71–73).

Chen et al. (66) demonstrated that <40% pre-heparin ADP-induced aggregation predicted 92% of severe bleeding needing multiple transfusions in patients on clopidogrel undergoing first-time on-pump CABG. Recently, the prospective TARGET-CABG (Time Based Strategy to Reduce Clopidogrel Associated Bleeding During CABG) study demonstrated that stratifying clopidogrel-treated patients on background aspirin therapy to specific waiting periods based on a pre-operative assessment of clopidogrel response resulted in similar perioperative bleeding, as determined by chest tube output and transfusion of red

Table 2 Relation Between Platelet Function Measurement and Bleeding in Patients Undergoing Cardiac Surgery

First Author (Ref. #)	Treatment	Platelet Function Test (Criteria for Bleeding)	Outcome
Chen et al. (66)	Clopidogrel (n = 45); on-pump CABG	LTA (<40% pre-heparin ADP-induced PA)	Low PA correlated with 92% of severe coagulopathies that required multiple transfusions
Mahla et al. (67)	Clopidogrel or clopidogrel-naïve on background aspirin (n = 180); on-pump CABG	MA-ADP TEG platelet mapping assay	Individualized pre-operative waiting in clopidogrel-treated patients, as compared to clopidogrel-naïve patients, resulted in similar bleeding and ~50% reduction of pre-operative waiting as compared to that recommended in the guidelines
Kwak et al. (68)	Clopidogrel and aspirin (n = 100); off-pump CABG	MA-ADP TEG platelet mapping assay (70% inhibition of PA)	Platelet inhibition >76% was the only independent predictor of post-operative transfusion requirements (OR: 11.44, 95% CI: 2.77–47.30; p = 0.001)
Ranucci et al. (69)	Clopidogrel or ticlopidine (n = 87); CABG and/or valves	Multiplate analyzer	ADP-induced platelet aggregation independently predicted bleeding (cutoff: 31 U; AUC: 0.71; p = 0.013)

AUC = area under the curve; CI = confidence interval; OR = odds ratio; PA = platelet aggregation; other abbreviations as in Table 1.

blood cells, as compared to clopidogrel-naïve patients undergoing elective first-time on-pump CABG after adjustment for potential confounders (67). In TARGET-CABG, pre-operative clopidogrel response was measured by thrombelastography with Platelet Mapping assay (Haemonetics Corporation, Braintree, Massachusetts). Surgery was scheduled with no delay in those patients with an ADP-induced platelet-fibrin clot strength (MA_{ADP}) >50 mm, within 3 to 5 days in those with an MA_{ADP} = 35 to 50 mm, and after 5 days in those with an MA_{ADP} <35 mm (59). Compared with the guidelines, this individualized approach reduced the pre-operative waiting period by about 50% (68). Considering the preliminary evidence from observational studies, the Society of Thoracic Surgeons has given a Class IIa recommendation regarding the use of PFT to assist in the timing of surgery (Online Appendix, Box-2) (70).

Therapeutic Window for $P2Y_{12}$ Receptor Blockade

Early small turbidimetric aggregometry-based studies demonstrated that ischemic event occurrences, including periprocedural MI and ST, were not linearly related to on-treatment PR but instead occurred above a moderate level of on-treatment PR (74). Based on this preliminary evidence, it was first hypothesized that a "therapeutic window of PR" exists, similar to the international normalized ratio range used for warfarin therapy (74).

In the first observational study of 2,533 patients undergoing PCI, patients with >46 AU (arbitrary aggregation units) were defined as "clopidogrel low responders" based on ROC curve analysis. This cut point was associated with the primary efficacy endpoint of 30-day incidence of definite or probable ST. In contrast, patients with <19 AU were defined as "enhanced responders," and this cut point was associated with the primary safety endpoint of in-hospital TIMI major bleeding (8). Subsequently, a MA_{ADP} >47 mm was shown to have a high predictive value for 3-year post-PCI ischemic events during dual antiplatelet therapy. Moreover, ROC curve and quartile analysis suggested MA_{ADP} ≤31 mm as a predictive value for post-PCI bleeding events (59). Similarly, a therapeutic window of 86 to 238 PRU was demonstrated by the VerifyNow testing in another study of 300 patients undergoing PCI (73). In a recent prospective study of 732 patients on dual antiplatelet therapy, PR was measured before PCI using the VerifyNow $P2Y_{12}$ assay. Based on ROC curve analysis, an LPR cutoff of ≤178 PRU was associated with 30-day bleeding (area under the curve: 0.72; $p < 0.0001$) and an HPR cutoff of ≥239 PRU was associated with ischemic events (area under the curve: 0.68; $p < 0.0001$) (75).

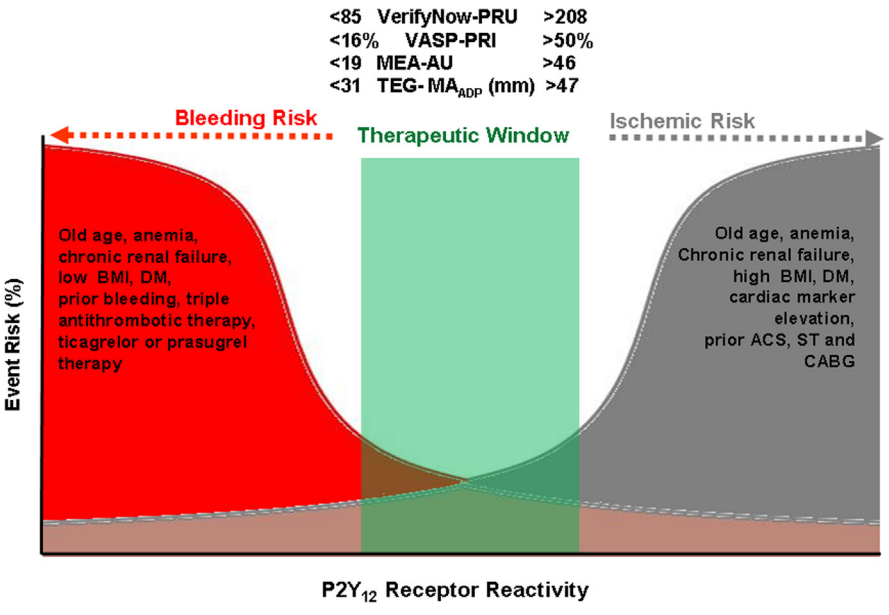

Figure 1 Evidence for $P2Y_{12}$ Receptor Reactivity Associated With Post-PCI Ischemic and Bleeding Events

Similar to previously proposed high on-treatment platelet reactivity to ADP associated with post-PCI ischemic events, recent data suggest that low on-treatment platelet reactivity to ADP is associated with a higher risk of bleeding. Cutoff values for both ischemic and bleeding events based on various platelet function assays have been shown. In addition, both ischemic and bleeding events are influenced by various demographic variables. Adapted with permission from Sibbing et al. (8), Bonello et al. (9), Stone et al. (16), Alexander and Peterson (56), Gurbel et al. (59), and Campo et al. (76). ACS = acute coronary syndromes; BMI = body mass index; CABG = coronary artery bypass graft; DM = diabetes mellitus; MA = maximum amplitude; MEA = multiplate analyzer; PRI = platelet reactivity index; PRU = $P2Y_{12}$ reaction units; ST = stent thrombosis; TEG = thrombelastography; VASP = vasodilator stimulated phosphoprotein-phosphorylation.

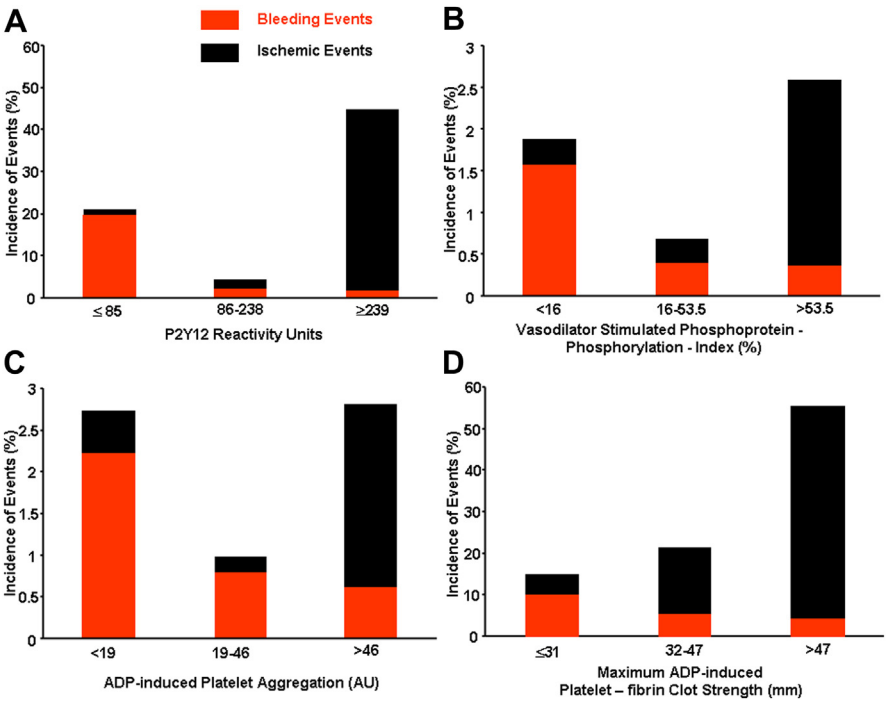

Figure 2 **Therapeutic Window Concept for $P2Y_{12}$ Receptor Reactivity**

Evidence for high and low on-treatment platelet reactivity to adenosine diphosphate (ADP) associated with post–percutaneous coronary intervention (PCI) ischemic and bleeding events based on **(A)** VerifyNow $P2Y_{12}$ assay, **(B)** vasodilator stimulated phosphoprotein-phosphorylation assay, **(C)** Multiplate analyzer, and **(D)** thrombelastography platelet mapping assay following $P2Y_{12}$ receptor blocker therapy. Adapted with permission from Sibbing et al. (8), Bonello et al. (9), Gurbel et al. (59), and Campo et al. (76). AU = arbitrary aggregation units; other abbreviations as in Figure 1.

Finally, in the ADAPT-DES trial, HPR defined by >208 PRU was also inversely related to TIMI major bleeding (adjusted HR: 0.73, 95% CI: 0.61 to 0.89; p = 0.002) (16). This observation is consistent with the post-hoc analysis of the GRAVITAS trial, which found that the achievement of a PRU <208 was associated with significantly improved clinical outcomes (36). Thus, evidence for a therapeutic window of optimal on-treatment PR to prevent both bleeding and ischemic events is emerging. This window would therefore inform future studies designed to optimally avoid thrombotic and bleeding events during $P2Y_{12}$ inhibitor therapy (8,9,16,56,59,76) (Table 3, Figs. 1 and 2).

Table 3 **Platelet Reactivity Cutoff Associated With Ischemic and Bleeding Events (Therapeutic Window)**

	Cutoff Associated With Ischemic Event Occurrences (References)	Cutoff Associated With Bleeding Event Occurrences (References)
VerifyNow PRU assay, PRU	>208 (16,76)	<85 (76)
Multiplate analyzer		
ADP-induced aggregation, AU	>46 (8)	<19 (8)
Thrombelastography platelet mapping assay		
ADP-induced platelet-fibrin clot strength, mm	>47 (59)	<31 (59)
VASP-PRI	≥50% (9)	<16% (9)

Abbreviations as in Table 1.

Platelet Function Measurement During New $P2Y_{12}$ Inhibitor Therapy

In the platelet substudies of the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) and PLATO (Platelet Inhibition and Patient Outcomes) trials and pharmacodynamic studies of ticagrelor and prasugrel in stable CAD patients, it was observed that although the interindividual variability in response to prasugrel and ticagrelor was reduced, it was not absent (77–80). Recent studies demonstrated that HPR is not limited to clopidogrel therapy but also observed during treatment with the new and more potent $P2Y_{12}$ inhibitors. Moreover, the prognostic utility of PFT may also be particularly important with respect to bleeding during therapy with the new and potent $P2Y_{12}$ inhibitors when LPR is more frequent than during

clopidogrel therapy. The cutoff values to define HPR during prasugrel and clopidogrel therapy were similar. This observation is consistent with the fact that both are thienopyridines; the mechanisms of action of their respective active metabolites are the same; they share same receptor binding site; and the active metabolites are pharmacodynamically equipotent. The similar threshold to identify at-risk patients treated with prasugrel or clopidogrel also indicates that on-treatment reactivity, rather than the drug itself, is the primary arbiter of outcome, further supporting the mechanistic principle underlying PFT-guided antiplatelet therapy.

In a recent prospective study of ST-segment elevation myocardial infarction patients undergoing PCI who were randomized to ticagrelor or prasugrel therapy, although PR did not differ between ticagrelor and prasugrel therapy, the rates of HPR (>208 PRU) measured at 2 h after dosing were 46.2% and 34.6%, respectively, and decreased significantly thereafter, not differing significantly between the 2 agents through 5 days of measurement (6). In another study, 50 patients with ST-segment elevation myocardial infarction undergoing primary PCI on bivalirudin monotherapy were randomly treated with 60-mg prasugrel or 180-mg ticagrelor loading doses. The investigators demonstrated that in only 50% of patients were both prasugrel and ticagrelor therapies effective in inhibiting PR as measured by VerifyNow assay, and at least 4 h were required to achieve an effective platelet inhibition in the majority of patients (10). These data suggest a delay in the pharmacodynamic efficacy of these drugs in selected ACS patients versus stable patients. Thus far, there are no data available on the relation between on-ticagrelor PR and bleeding/ischemic event occurrence.

Conclusions and Recommendations

HPR can be considered a risk factor for post-PCI ST and MI. The increased hazard associated with HPR has been demonstrated with various PFT. The relation between HPR and post-PCI ischemic event occurrence must be considered in the context of the overall disease risk level (i.e., ACS vs. non-ACS, diabetes vs. nondiabetes, old age, and chronic kidney disease), post-PCI time (early [e.g., before 30 days] vs. late), and ethnicity. It appears that the relation of PR to clinical outcome occurrence in the PCI setting is stronger during the initial period (up to 30 to 60 days), when intensive $P2Y_{12}$ inhibition may be more effective. The relationship between PR and clinical outcomes in medically-managed patients recovering from ACS may be less robust.

The large randomized trials of personalized antiplatelet therapy failed to confirm the benefit of PFT to improve outcomes in patients at low absolute overall risk, resulting in low post-discharge event rates and lack of power. These randomized studies demonstrated that event rates are low in low-risk patients undergoing PCI irrespective of PR, and that high-dose clopidogrel is not an optimal strategy to overcome HPR and to improve clinical outcomes. Strategies employing agents that are more potent have largely remained untested in an adequate sample size of patients. The evidence from the ARCTIC and GRAVITAS trials have been used to support the hypothesis that HPR is a nonmodifiable risk factor. An alternative explanation is that the marker was not modified enough by high-dose clopidogrel or that the absolute risk of the patient population was not high enough, even though the patients had HPR.

At present, PFT is helpful in identifying high-risk patients, but its usefulness in influencing therapeutic management deserves further evaluation in large-scale trials. The overall low event rates observed in prospective trials would require enrollment of a large number of patients to definitively evaluate the utility of PFT for personalized therapy in those patient populations. Unlike the selected patients enrolled in prospective clinical studies, the risk of clinical events may be higher in routine practice, and personalized therapy may play a greater role.

An assessment of the utility of PFT in the individual patient requires the synthesis of multiple factors. The clinician should recognize the crucial role of platelet physiology in catastrophic event occurrence such as ST and should be cognizant of the guidelines. Furthermore, the clinician should be aware of the existing observational data demonstrating that HPR is a potent post-PCI risk factor while keeping in mind the results of the 2 major randomized trials, the populations studied, and the limitations of their designs. At present, it appears that PFT may be most appropriate in high-risk clopidogrel-treated patients with current or prior ACS or a history of ST. In addition, patients treated with clopidogrel who have poor left ventricular function, complex anatomy, high body mass index, and diabetes mellitus might be considered for PFT. PR should not be regarded as the sole prognostic marker for thrombotic event occurrence, but should rather be evaluated in relation to patient risk. A risk algorithm that includes PFT along with biomarker testing and clinical factors may improve risk prediction and facilitate personalization of antiplatelet therapy.

Emerging data suggest a relation of LPR to the risk of bleeding. Unselected therapy with the new $P2Y_{12}$ receptor blockers is associated with increased bleeding. It is also important to note that clopidogrel is pharmacodynamically effective; its use results in an adequate $P2Y_{12}$ receptor inhibition, according to the above-proposed definition, in about two-thirds of the patients undergoing PCI. Selectively treating these patients with generic clopidogrel rather than treating all patients with new and potent $P2Y_{12}$ inhibitors might provide significant cost savings. Finally, personalized antiplatelet therapy based on a concept of therapeutic window may improve the balance between better efficacy and reasonable safety. A trial to validate a therapeutic window for $P2Y_{12}$ inhibitors is warranted based on the information presented in this consensus document.

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Key Words: adenosine diphosphate ■ bleeding ■ consensus ■ ischemia ■ platelet reactivity.

APPENDIX

For supplemental information regarding guidelines, please see the online version of this article.