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JACC White Paper

Consensus and Future Directions on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate

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The addition of clopidogrel to aspirin treatment reduces ischemic events in a wide range of patients with cardiovascular disease. However, recurrent ischemic event occurrence during dual antiplatelet therapy, including stent thrombosis, remains a major concern. Platelet function measurements during clopidogrel treatment demonstrated a variable and overall modest level of $P2Y_{12}$ inhibition. High on-treatment platelet reactivity to adenosine diphosphate (ADP) was observed in selected patients. Multiple studies have now demonstrated a clear association between high on-treatment platelet reactivity to ADP measured by multiple methods and adverse clinical event occurrence. However, the routine measurement of platelet reactivity has not been widely implemented and recommended in the guidelines. Reasons for the latter include: 1) a lack of consensus on the optimal method to quantify high on-treatment platelet reactivity and the cutoff value associated with clinical risk; and 2) limited data to support that alteration of therapy based on platelet function measurements actually improves outcomes. This review provides a consensus opinion on the definition of high on-treatment platelet reactivity to ADP based on various methods reported in the literature and proposes how this measurement may be used in the future care of patients.

Platelet activation and aggregation play pivotal pathophysiological roles in the development of ischemic events during and after acute coronary syndromes (ACS) and percutaneous coronary interventions (PCIs) (1). Adenosine diphosphate (ADP) is a major secondary agonist released from the dense granules of platelets activated by primary agonists (Fig. 1). The ADP-$P2Y_{12}$ receptor interaction plays a central role in the sustained activation of glycoprotein (GP) IIb/IIIa receptors leading to stable platelet-rich thrombus generation at the site of vessel wall injury (2). Therefore, clopidogrel, whose active metabolite irreversibly inhibits the $P2Y_{12}$ receptor, is a cornerstone of oral antiplatelet therapy in the secondary prevention of coronary artery disease and in the immediate treatment of ACS and PCI (3).

A significant reduction in ischemic complications in a wide range of coronary artery disease patients has been demonstrated in major randomized controlled trials by adding clopidogrel to aspirin treatment (4,5). The fixed dose, "one size fits all" treatment strategy with clopidogrel therapy, which has been used in clinical trials and recommended by current guidelines, does not take into account the interindividual pharmacodynamic variability of clopidogrel therapy (4–6). Moreover, despite the relatively potent antiplatelet effect of clopidogrel in some patients, others will suffer therapeutic failure manifested by ischemic events, including stent thrombosis, that have been associated with high on-treatment platelet reactivity (7).

These observations have stimulated intensive research of the pharmacodynamic and pharmacokinetic properties of clopidogrel. Studies measuring platelet function in patients administered clopidogrel revealed that, unlike aspirin and GP IIb/IIIa receptor blocker therapies that are associated with a uniform and high level of inhibition (~95%) of their targets (COX-1 enzyme and GP IIb/IIIa receptor, respectively) with appropriate dosing in particular for GP IIb/IIIa inhibitors, clopidogrel treatment is associated with an overall variable and modest level of $P2Y_{12}$ inhibition even when high loading doses are used (4,6,8–10). In addition to distinct response variability, a substantial percentage of patients will also exhibit complete nonresponsiveness (resistance) to clopidogrel (10).

Multiple studies now have demonstrated a relationship between clopidogrel nonresponsiveness and/or high on-treatment platelet reactivity measured by multiple platelet assays and adverse clinical ischemic events (7). However, due to a lack of consensus on the optimal methods to quantify high platelet reactivity and the cutoff values associated with clinical risk, the routine measurement of platelet reactivity has not been widely implemented in clinical practice nor recommended in the guidelines (11). In addition, there are only limited data to support the concept that alterations of therapy based on platelet function measurements improve clinical outcome (7).

Herein, we provide a comprehensive overview of the available data that have identified high on-treatment platelet reactivity to ADP as a risk factor for post-PCI ischemic/thrombotic events as well as a consensus opinion on the definition of high on-treatment platelet reactivity to ADP based on the primary methods reported in the literature.

Clopidogrel Metabolism

Clopidogrel is a prodrug that requires hepatic conversion into an active metabolite to exert its antiplatelet response. Most of absorbed clopidogrel (~85% to 90%) is hydrolyzed by carboxylase to an inactive carboxylic acid metabolite, SR26334, whereas the remaining ~10% to 15% is rapidly metabolized by hepatic cytochrome (CYP) P450 isoenzymes in a 2-step process. In the first step, the thiophene ring of clopidogrel is oxidized to 2-oxo-clopidogrel, which is then hydrolyzed to a highly labile active metabolite, R-130964, that has both carboxylic acid and thiol groups (12–14). Recent studies indicate that CYP2C19, CYP1A2, and CYP2B6 participate in the first metabolic step, whereas CYP2C19, CYP2C9, CYP2B6, and CYP3A are responsible for the second step (12,13) (Fig. 2). The highly unstable active metabolite, R-130964, covalently binds to platelet $P2Y_{12}$ receptor specifically and irreversibly during passage through the hepatic circulation resulting in inhibition of ADP-induced platelet activation-aggregation for the life span of the platelet (15). This metabolic activation scheme

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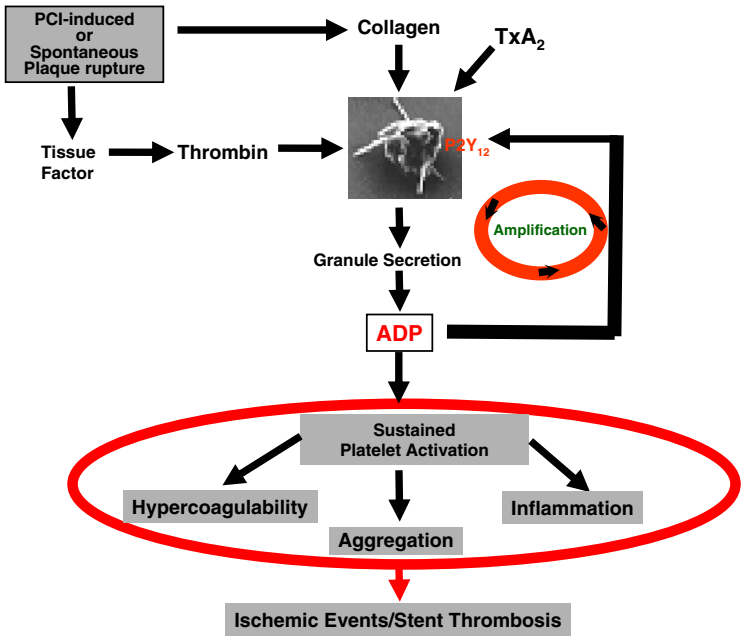
Figure 1

Central Role of ADP-P2Y$_{12}$ Receptor Interaction in Platelet Activation and Aggregation



Central role of adenosine diphosphate P2Y$_{12}$ receptor interaction in platelet activation and aggregation during occurrence of ischemic events and stent thrombosis. After plaque rupture, tissue factor and collagen are exposed leading to platelet activation. Three important pathways (thrombin-PAR-1 receptor, thromboxane A$_2$-TP receptor, and adenosine diphosphate P2Y$_{12}$ receptor) amplify the response. The adenosine diphosphate P2Y$_{12}$ interaction plays a central role. ADP = adenosine diphosphate; PCI = percutaneous coronary intervention; TxA$_2$ = thromboxane A$_2$.

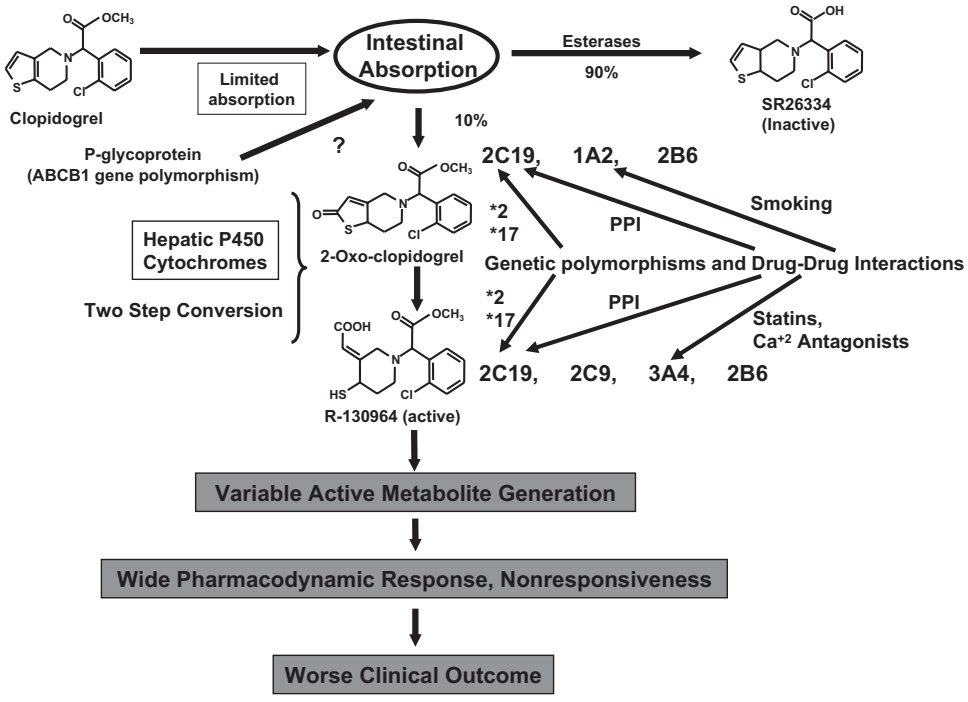
is consistent with the time-dependent cumulative inhibition of ADP-induced platelet aggregation as observed with repeated daily dosing of clopidogrel and is further highlighted by slow recovery of platelet function following drug withdrawal (4,16,17).

Multiple lines of evidence strongly suggest that variable and insufficient active metabolite generation are the primary explanations for clopidogrel response variability and nonresponsiveness, respectively (9). Variable levels of active metabolite generation following clopidogrel administration could be explained by: 1) variable or limited intestinal absorption, which may be affected by an *ABCB1* gene polymorphism (18–20); 2) functional variability in P450 isoenzyme activity influenced by drug-drug interactions as well as other factors; and 3) single nucleotide polymorphisms of specific genes encoding CYP450 isoenzymes (21,22). Stimulation of CYP3A4 activity by rifampin and St. John's wort and CYP1A2 activity by tobacco smoking have both been shown to enhance platelet inhibition induced by clopidogrel (23–25). The effect of smoking on the antiplatelet effect of clopidogrel has been associated with clinical outcomes and may, in part, explain the "smoker's paradox" (26,27). Conversely, agents that compete with clopidogrel for CYP and/or inhibit CYP attenuate the antiplatelet effect of clopidogrel. A diminished pharmacodynamic response to clopidogrel has been observed with coadministration of proton pump inhibitors, lipophilic statins, and calcium-channel blockers that are metabolized by the CYP2C19 and CYP3A4 isoenzymes (21,28–31). Although a diminished level of platelet inhibition induced by clopidogrel has been demonstrated in some ex vivo studies following coadministration of these agents, the consequence of these interactions with respect to ischemic events remains controversial.

Recent studies have evaluated the influence of the single nucleotide polymorphisms of genes encoding CY2C19 isoenzymes with different activities, as well as single nucleotide polymorphisms of the p-glycoprotein transporter gene on clopidogrel response variability and clinical outcomes (22,32). Multiple independent studies have demonstrated a link between the presence of genetic polymorphisms associated with suboptimal clopidogrel active metabolite generation (pharmacokinetic measurement), decreased clopidogrel responsiveness as measured by platelet function assays (pharmacodynamic measurement), and adverse clin-

Figure 2

Clopidogrel Response Variability



Clopidogrel response variability is a pharmacokinetic problem primarily influenced by the activity of cytochrome P450 isoenzymes in the generation of the active metabolite. Absorption may be affected by polymorphism of the *ABCB1* gene. The activity of hepatic cytochrome isoenzymes are influenced by drug-drug interactions, single nucleotide polymorphisms, and environmental influences (smoking).

ical outcomes. No single study has conclusively associated all of these parameters in the same patient population. Moreover it was observed that other genetic determinants may be involved and that overall, ~12% of the variation in the response to clopidogrel can be attributed to the *CYP2C19*2* loss-of-function allele (33). At this time, it is uncertain whether the factors associated with a poor response to clopidogrel are additive in diminishing the antiplatelet effect of clopidogrel and worsening patient outcomes.

The controversy surrounding the diminished effectiveness of clopidogrel in poor metabolizers (those having 2 loss-of-function *CYP2C19* alleles) and the utility of genetic tests to identify differences in CYP2C19 function has been recently highlighted by the "boxed warning" issued by the Food and Drug Administration advising health care professionals to consider use of other antiplatelet medications or alternative dosing strategies for clopidogrel in these patients (34). The preceding statement was based on observations from a study of 40 healthy subjects that poor metabolizers had diminished active metabolite exposure and higher platelet aggregation. Although it is believed that the loss-of-function allele confers its clinical risk by affecting the pharmacodynamic response to clopidogrel, no single study thus far has demonstrated a conclusive link between the presence of a loss-of-function genetic polymorphism, suboptimal clopidogrel active metabolite generation (pharmacokinetic measurement), decreased clopidogrel responsiveness (pharmacodynamic measurement), and adverse clinical outcomes. The warning only addresses patients with 2 loss-of-function alleles. No information is provided for heterozygotes. Earlier Simon et al. (18) suggested that increased ischemic risk is confined to homozygotes. Other studies involving patients treated with stenting found a significant relation between ischemic risk and loss-of-function allele carriers (homozygotes and heterozygotes) (33,35–38). The picture is even more confusing with the recently presented CHARISMA (Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance) Genomics substudy (39) results that showed an increase in the combined end point of cardiovascular death, myocardial infarction, and stroke in poor metabolizers (*2/*2) compared with wild-type carriers (wt/wt) treated with clopidogrel. Unlike the latter studies,

CHARISMA investigated a lower-risk population and was not a study of stented patients. The CHARISMA Genomics study investigators pointed out 2 important caveats: 1) poor metabolizers in the placebo arm also had an increased risk; but 2) only a small number of primary events occurred in poor metabolizers (placebo arm, n = 5 [8.77%] and clopidogrel arm, n = 8 [13.79%]). The CHARISMA Genomics study (39) is the only investigation in which the influence of genotyping on clinical outcome was studied in both the clopidogrel arm and the placebo arm.

Moreover, the safety and efficacy of altering therapy in response to genotype is entirely unknown. Whereas neither genotyping nor platelet function tests alone adequately describe the global risk profile of an individual patient treated with clopidogrel, point-of-care platelet function testing to identify high-risk patients combined with CYP2C19 genetic testing may be more effective in identifying high-risk individuals for alternative antiplatelet therapies. Ultimately, prospective randomized clinical trials will be needed to test specific personalized antiplatelet algorithms to provide the evidence base necessary for widespread adoption into clinical practice.

In addition to the preceding mechanisms for clopidogrel pharmacodynamic variability, increased body mass index, diabetes mellitus, and acute coronary syndromes have also been associated with a diminished antiplatelet response to clopidogrel (40–42). Several studies have demonstrated the coexistence of clopidogrel and aspirin resistance in the same patient population (43,44). It has also been demonstrated that patients with low responsiveness to a 600-mg loading dose, in addition to exhibiting a low level of inhibition of ADP-induced aggregation, also exhibit lower inhibition of aggregation induced by collagen and thrombin receptor agonist peptide as compared to moderate and high clopidogrel responders (45). Taken together, these data support the existence of a "hypo-responsive" or global high platelet-reactivity phenotype. Patients with the latter phenotype will have platelets that react robustly to multiple agonists. Finally, noncompliance is an obvious factor that must be excluded in the diagnosis of clopidogrel nonresponsiveness. When attempting to define causality for high platelet reactivity related to the occurrence of clinical events in patients receiving clopidogrel, all of the aforementioned mechanisms should be considered.

Concept of Clopidogrel Nonresponsiveness, Resistance, and High On-Treatment Platelet Reactivity

A single treatment strategy directed against a specific receptor cannot be expected to overcome all thrombotic events, and clinical treatment failure (occurrence of an ischemic event) during clopidogrel treatment is not synonymous with clopidogrel resistance. The optimal definition of resistance or nonresponsiveness to any antiplatelet agent should be the failure of the antiplatelet agent to inhibit the target of its action (7). The identification of resistance should therefore utilize a laboratory technique that detects the activity of the target receptor before and after administration of the specific antiplatelet agent. For example, the absence of a change in platelet response (reactivity) to ADP from baseline after clopidogrel intake is an indicator of clopidogrel resistance. Earlier studies that measured light transmission platelet aggregation used an absolute difference of ≤10% aggregation as the definition of clopidogrel resistance (baseline vs. on-treatment) (6,7). Patients were also categorized as "nonresponsive," "semiresponsive," and "responsive" using absolute platelet inhibition cut points of <10%, 10% to 30%, and >30%, respectively (6,46).

Even though a measurement of responsiveness (absolute or relative changes in platelet aggregation from baseline) appears as the most reliable indicator of a treatment effect, it may not be the optimal method to identify patients at high risk. Given the interindividual variability in baseline ADP-induced platelet aggregation, the measurement of clopidogrel responsiveness (inhibition) may overestimate ischemic risk in nonresponders with low pre-treatment reactivity as well as underestimate risk in responders who remain with high platelet reactivity after treatment (47,48). Therefore, the absolute level of platelet reactivity during treatment (i.e., on-treatment platelet reactivity) has been proposed as a better measure of thrombotic risk than responsiveness to clopidogrel.

The relationship of on-treatment platelet reactivity to both periprocedural and long-term ischemic risk has been most widely investigated. However, the optimal method to quantify platelet reactivity as well as the threshold definition for high on-treatment platelet reactivity to ADP have been subjects of controversy. Another concern surrounds the timing of platelet reactivity measurement that is optimally associated with short- and long-term risk. Any definition of high on-treatment platelet reactivity will only be meaningful when a cutoff or target value is identified by an accepted statistical test. Most commonly, the receiver-operator characteristic (ROC) curve analysis has been used to define the optimal cut point definition of high on-treatment platelet reactivity associated with ischemic risk. This method allows us to determine the cutoff value of platelet reactivity that would be associated with the lowest false negative and false positive rates and thus provides the greatest sum of sensitivity and specificity. The ROC curve analysis has been used to define cut points currently employed in prospective studies of individualized antiplatelet therapy in PCI patients (49).

Methods to Assess Platelet Responsiveness to ADP and $P2Y_{12}$ Receptor Reactivity

Because clopidogrel specifically inhibits the $P2Y_{12}$ receptor, ex vivo measurement of ADP-induced platelet aggregation in platelet-rich plasma by light transmittance aggregometry has been the most commonly used laboratory method to evaluate platelet inhibition by clopidogrel and its relation to ischemic risk. In the strictest sense, aggregometry evaluates an integrated response of the platelet to ADP through the function of both $P2Y_1$ and $P2Y_{12}$ receptors. In most studies, the maximal amplitude of measured platelet aggregation in response to 5-, 10-, or 20-μmol/l ADP has been recorded. Citrate remains the most widely used anticoagulant during platelet function testing, although it affects intracellular calcium ion concentrations, which may influence platelet function. Alternatively, D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone or hirudin may be used to reduce changes in calcium ion concentrations. In addition to maximum platelet aggregation, late (final or residual) aggregation measured 5 to 6 min after the addition of agonist, a time when platelet disaggregation normally appears, has been proposed as a better indicator of clopidogrel responsiveness. Although Collet et al. (20) and Labarthe et al. (50) have correlated late aggregation with the antiplatelet response to clopidogrel, Gurbel et al. (51) suggested that clopidogrel nonresponders may be similarly identified by both maximal and late aggregation. Although some investigators have advocated the adjustment of platelet concentration in plasma to ~250,000/mm^3 before measuring, others have suggested that such an adjustment may introduce artifacts and contribute to assay variability (52). Unfortunately, because many other procedures involved in the performance of light transmittance aggregometry are not standardized between institutions, light transmittance aggregometry may not be the ideal test to monitor the effects of antiplatelet therapy outside of clinical trials (53).

Flow cytometric measurements of platelet expression of both activated GP IIb/IIIa receptor and P-selectin (CD62) following ADP stimulation in addition to ADP-induced platelet-fibrin clot strength as measured by whole blood thrombelastography have also been used to identify clopidogrel nonresponsiveness. Thrombelastography measurements correlated platelet function with ischemic risk in the PCI population (54,55). In addition, 2 point-of-care whole blood assays, the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) and the Multiplate analyzer (Dynabyte Informationssysteme, Munich, Germany) (both employing ADP as the agonist) have been used to measure platelet reactivity during clopidogrel therapy. The VerifyNow P2Y12 assay is a turbidimetric assay that measures aggregation of platelets to fibrinogen-coated beads in whole blood. The Multiplate analyzer is an impedance aggregometer that assesses platelet function in whole blood. The platelet function analyzer PFA-100 (Dade Behring, Deerfield, Illinois) method, which utilizes collagen/ADP-based cartridges and measures shear-induced platelet aggregation, has been associated with inconsistent estimates of platelet reactivity to ADP. Finally, the phosphorylation state of vasodilator-stimulated phosphoprotein (VASP) is a specific intracellular marker of residual $P2Y_{12}$ receptor reactivity in patients treated with $P2Y_{12}$ blockers, which is currently measured by flow cytometry and has also been correlated with ischemic risk (7). In addition, this is the only test that specifically assesses $P2Y_{12}$ receptor activity. Unlike methods employing the aggregation induced by ADP, in VASP, phosphorylation assay measurement does not include the contribution of the $P2Y_1$ receptor to the overall response (56).

Clopidogrel Nonresponsiveness and On-Treatment Platelet Reactivity: Early Studies

Järemo et al. (57) first reported interindividual variability in response to clopidogrel in patients with coronary artery disease by using flow cytometry to detect ADP-induced fibrinogen binding to platelets. Gurbel et al. (6) first demonstrated clopidogrel response variability and resistance using conventional platelet aggregometry and flow cytometry studies in patients undergoing PCI who had received a 300-mg loading dose followed by 75-mg daily maintenance dose of clopidogrel. The level of platelet inhibition induced by clopidogrel was dependent on the time after clopidogrel treatment when platelet function was measured and the prevalence of resistance fell from 31% (days 1 and 5) to 15% (day 30). Importantly, although a 600-mg clopidogrel loading dose is associated with more potent platelet inhibitory effects than a 300-mg dose, this higher-dose regimen was not able to completely overcome resistance, and a broad variability in response profiles continued to persist (8,9). In the Gurbel et al. studies (6,8), pharmacologic resistance to clopidogrel was defined as an absolute ≤10% decrease in platelet aggregation in response to agonist from baseline (pre-treatment measurement). Based on these studies, it became similarly apparent that the level of post-treatment platelet reactivity during clopidogrel therapy was largely unpredictable. Only early platelet reactivity (24 h after PCI) correlated with pre-treatment platelet reactivity (6).

Link Between High Platelet Reactivity and Post-PCI Ischemic/Thrombotic Events

Numerous studies have reported pharmacological "resistance" to clopidogrel as a potential etiology for thrombotic events after PCI (Table 1) (43,54–83). Barragan et al. (58)

were the first to demonstrate an association between post-treatment platelet reactivity and the occurrence of thrombotic events (clinical treatment failure) in a case-control study of PCI patients. In the study by Barragan et al. (58), a platelet reactivity index (PRI) >50% measured by VASP-phosphorylation assay was associated with thrombotic risk. Of note, in this study, turbidimetric aggregation was not associated with ischemic risk. However, at the same time, Matetzky et al. (59), using aggregometry, observed that patients undergoing primary PCI for ST-segment elevation myocardial infarction who were in the lowest quartile of clopidogrel responsiveness had the highest rates of ischemic events during follow-up.

Subsequently, it was suggested that the level of on-treatment platelet reactivity might be a superior risk predictor compared with the difference between baseline and post-treatment platelet reactivity, because platelet reactivity to ADP was variable before clopidogrel treatment in patients on aspirin therapy (47,48). The important relationship between high on-treatment platelet reactivity to ADP as measured by turbidimetric aggregometry and the occurrence of ischemic events in patients treated with stents was first prospectively demonstrated in the PREPARE POST-STENTING (Platelet Reactivity in Patients and Recurrent Events Post-Stenting) study (upper quartile, odds ratio: 2.6) (55). Multiple subsequent studies have confirmed the direct relationship between the level of platelet reactivity and post-PCI ischemic event occurrence using aggregation. Most recently, there have been further studies employing the VASP-phosphorylation assay, the VerifyNow P2Y12 assay, and the Multiplate analyzer. These studies have consistently demonstrated that high on-treatment platelet reactivity is an important independent risk factor for the occurrence of thrombotic/ischemic events after PCI (56–84).

High Platelet Reactivity Defined by ROC Analysis

Importantly, studies have emerged that have used ROC curve analysis to define a threshold or cut point of on-treatment platelet reactivity associated with the optimal combination of sensitivity and specificity to identify thrombotic risk (Table 2). Thrombotic events may be prevented by achieving platelet reactivity below this threshold. It should be noted that such cut points might depend on the subset of patients studied. In fact, to date, cutoff values have been mainly investigated in patients undergoing PCI and different targets may be obtained in other settings depending on patient management or baseline risk profile (77,78).

Recent studies (62,64,72,76,77) have observed the prognostic value of the VASP phosphorylation analysis, with an optimal cutoff value for VASP-PRI between 48% and 53%, which is similar to the threshold defined by Barragan et al. (58) in their earlier study of early stent thrombosis. Although these studies used different ischemic end points such as stent thrombosis or major adverse cardiac events (e.g., cardiovascular death, myocardial infarction, and urgent revascularization with or without stroke), they nevertheless found similar cutoff values for the VASP-PRI that were associated with post-PCI thrombotic event occurrence. Similarly, using the VerifyNow P2Y12 assay, a cutoff value of ~240 $P2Y_{12}$ reaction units appears to be prognostic for subsequent thrombotic events (including cardiovascular death and stent thrombosis or cardiovascular death, nonfatal myocardial infarction, and stent thrombosis) (68,78,79,82). In a recent study, maximal platelet aggregation >46% in response to 5-μmol/l ADP following PCI was associated with major adverse cardiac events (69). Using the Multiplate analyzer, Sibbing et al. (80) demonstrated that high on-treatment ADP-induced platelet reactivity measured before PCI was associated with the occurrence of 30-day stent thrombosis in 1,608 patients who had received a 600-mg clopidogrel loading dose before PCI. Moreover, based on ROC analysis, a cut point of 468 arbitrary aggregation units/min (approximately corresponding to the highest quintile) was associated with the occurrence of stent thrombosis (80). Recently, Breet et al. (82) evaluated the utility of multiple platelet function assays in predicting 1-year outcome of death, myocardial infarction, stent thrombosis, and stroke in 1,069 consecutive patients treated with clopidogrel following elective coronary stent implantation. In this large, prospective, observational study, high on-treatment platelet reactivity cut points of 42.9% maximal aggregation induced by 5-μmol/l ADP and 64.5% by 20-μmol/l ADP light transmittance aggregometry; 236 $P2Y_{12}$ reaction units measured by VerifyNow P2Y12 assay; and 80.5% aggregation by Plateletworks (Helena Laboratories, Beaumont, Texas) all correlated with the occurrence of the composite primary end point, with an area under the curve of ~0.62 for each assay. The addition of high on-treatment platelet reactivity as measured by the noted platelet assays to more classical clinical and procedural risk factors improved the area under the curve to ~0.73 (82).

Each of these studies may thus provide a target level of platelet reactivity for future investigations, similar to the international normalized ratio used for warfarin therapy. The consistent findings across multiple investigations support the crucial role of high on-treatment reactivity in the etiology of ischemic events after PCI, including stent thrombosis, and suggest the existence of a threshold level of platelet reactivity below which ischemic events may be prevented

Table 1

Studies Linking High On-Treatment Platelet Reactivity to ADP and Clopidogrel Nonresponsiveness to Post-PCI Adverse Clinical Event Occurrence

Study (Ref. #)	Patients (n)	Treatment	Methods	Definition	Clinical Relevance
Barragan et al. (58)	PCI (46)	250 mg qd TLP or CLP 75 mg qd	VASP-PRI	>50% VASP-PRI	↑ ST
Gurbel et al. (55)	Elective PCI (192)	300-mg LD + 75 mg qd CLP +/– EPT	5-μmol/l ADP-LTA	HPR = 75th percentile post-PCI aggregation	↑ 6-month post-PCI events, OR: 2.7
Matetzky et al. (59)	PCI/STEMI (60)	300-mg LD + 75 mg qd CLP +/– EPT	5-μmol/l ADP-LTA	Reduction in platelet aggregation Upper quartile	↑ 6-month cardiac events
Gurbel et al. (60)	Elective PCI (120)	300-mg LD CLP +/– EPT	5-μmol/l ADP-LTA	Mean periprocedural platelet aggregation >50%	↑ Periprocedural myonecrosis
Gurbel et al. (61)	Elective PCI (200)	300-/600-mg LD CLP +/– EPT	5-μmol/l ADP-LTA	Mean periprocedural platelet aggregation >40%	↑ Periprocedural myonecrosis
Bliden et al. (54)	Elective PCI (100)	75 mg qd CLP	5-μmol/l ADP-LTA	>50% platelet aggregation	↑ 1-yr post-PCI events
Lev et al. (43)	Elective PCI (150)	300-mg CLP LD	5- and 20-μmol/l ADP-LTA	Baseline—post-treatment aggregation ≤10%	↑ Periprocedural myonecrosis
Blindt et al. (62)	High risk for ST/PCI (99)	75 mg qd for 6 months	VASP-PRI (72–96 h after stenting)	>48% PRI (ROC)	↑ 6-month ST
Cuisset et al. (63)	NSTEMI/ACS/PCI (190)	600-mg CLP LD >6 h before PCI	10-μmol/l ADP-LTA VASP-PRI	HPR >70% post-treatment LTA	↑ Periprocedural myonecrosis
Frere et al. (64)	NSTEMI/ACS/PCI (195)	600-mg CLP LD >6 h before PCI	10-μmol/l ADP-LTA	HPR (ROC) >70% post-treatment LTA >53% VASP-PRI	↑ 30-day post-PCI events MACE + stroke
Geisler et al. (65)	CAD/PCI (379)	600-mg CLP LD >6 h before PCI	20-μmol/l ADP-LTA	Clopidogrel low responders = <30% platelet inhibition	↑ 3-month MACE and death OR: 4.9
Geisler et al. (66)	CAD/PCI (1,092)	600-mg CLP LD >6 h before PCI + 75 mg qd	20-μmol/l ADP-LTA Residual aggregation measured after 5 min	Upper quartile	↑ 30-day MACE
Hochholzer et al. (67)	Elective PCI (802)	600-mg CLP LD >2 h before PCI + 75 mg qd	5-μmol/l ADP-LTA Residual aggregation measured after 5 min	Platelet aggregation above median	↑ 30-day MACE OR: 6.7
Price et al. (68)	PCI (380)	600-mg CLP LD >12 h before PCI or 75 mg qd >5 days	VerifyNow P2Y12 assay	HPR = post-treatment ≥235 PRU (ROC)	↑ 6-month post-PCI events including ST
Gurbel et al. (69)	Elective PCI (297)	300-/600-mg LD/ 75 mg qd CLP +/– EPT	5- and 20-μmol/l ADP-LTA	HPR = post-procedural (ROC) >46% 5-μmol/l ADP >59% 20-μmol/l ADP	↑ 2-yr ischemic events 5-μmol/l ADP OR: 3.9 20-μmol/l ADP OR: 3.8
Gurbel et al. (70)	Stenting (120)	75-mg qd CLP >5 days	5- and 20-μmol/l ADP-LTA	HPR >75th percentile of platelet reactivity 5-μmol/l ADP = 50% 20-μmol/l ADP = 65%	↑ ST
Buonamici et al. (71)	PCI/DES (804)	600-mg LD + 75 mg qd for 6 months	10-μmol/l ADP-LTA	HPR ≥70% aggregation	↑ ST HR: 3.08
Bonello et al. (72)	PCI/stenting (144)	300-mg LD >24 h	VASP-PRI	>50% PRI (ROC)	↑ 6-month post-PCI MACE
Cuisset et al. (73)	PCI/SA (120)	600-mg LD ≥12 h before PCI	VerifyNow P2Y12 assay	↑ Platelet reactivity	↑ Post-PCI myonecrosis

continued on next page

Table 1

Continued

Study (Ref. #)	Patients (n)	Treatment	Methods	Definition	Clinical Relevance
Migliorini et al. (74)	PCI/DES/ULMD (215)	600-mg LD + 75 mg qd for 12 months	10-μmol/l ADP-LTA	HPR ≥70% aggregation	↑ 3-yr cardiac death and ST HR CV death: 3.82 HR ST: 3.69
Marcucci et al. (75)	PCI/ACS (683)	600-mg LD + 75 mg qd	VerifyNow P2Y12 assay	HPR ≥240 PRU	12-month ischemic event HR CV death: 2.55 HR nonfatal MI: 3.36
Bonello et al. (76)	PCI/stenting (162)	600 mg repeated dose until PRI <50%	VASP-PRI	<50% VASP-PRI	↓ 1-month ischemic event
Bonello et al (77)	PCI/stenting (214)	600-mg repeated dose until PRI <50%	VASP-PRI	<50% VASP-PRI	↓ Early ST and MACE (OR: 9.4)
Valgimigli et al. (78)	Elective PCI (1,277)	600-mg LD before PCI	VerifyNow aspirin and P2Y12 assay	>235 PRU >550 ARU	↑ Post-PCI myonecrosis
Patti et al. (79)	PCI (160)	600-mg LD or 75 mg qd >5 days	VerifyNow P2Y12 assay	HPR ≥240 PRU (Pre-PCI)	↑ 1-month major cardiovascular event occurrence
Sibbing et al. (80)	PCI/DES (1,608)	600-mg LD before PCI	6.4-μmol/l ADP Multiplate analyzer	Upper quintile (>416 AU/min) (ROC)	↑ 1-month definite ST (OR: 9.4)
Cuisset et al. (81)	NSTEMI/stenting (598)	600-mg LD ≥12 h before PCI	10-μmol/l ADP-LTA VASP-PRI	>67% aggregation (ROC)	↑ ST
Breet et al. (82)	Elective PCI (1,069)	75-mg qd >5 days 300-mg LD >1 day 600-mg LD	20-μmol/l ADP-LTA VerifyNow P2Y12 20-μmol/l ADP Plateletworks Before PCI	>42.9% 5-μmol/l ADP (ROC) >64.5% 20-μmol/l ADP >236 PRU 80.5% Plateletworks	OR for 1-yr death, MI, ST, and stroke 5-μmol/l ADP: 2.09 20-μmol/l ADP: 2.05 VerifyNow: 2.53 Plateletworks: 2.22

ACS = acute coronary syndromes; ADP = adenosine diphosphate; ARU = aspirin resistance units; AU = arbitrary aggregation units; CAD = coronary artery disease; CLP = clopidogrel; CV = cardiovascular; DES = drug-eluting stent; EPT = eptifibatide; HPR = high on-treatment platelet reactivity; HR = hazard ratio; LD = loading dose; LTA = light transmittance aggregometry; MACE = major adverse cardiac events; MI = myocardial infarction; NSTEMI = non–ST-segment elevated myocardial infarction; OR = odds ratio; PCI = percutaneous intervention; PRU = $P2Y_{12}$ reaction units; qd = once daily; ROC = receiver-operator characteristic curve; SA = stable angina; ST = stent thrombosis; STEMI = ST-segment elevated myocardial infarction; TLP = ticlopidine; ULMD =unprotected left main disease; VASP-PRI = vasodilator stimulated phosphoprotein—platelet reactivity index.

(62,64,68,69,72,75,80–82). Most importantly, the observed cut-off values for platelet reactivity noted previously had a very high negative predictive value for thrombotic/ischemic event occurrence, an observation of potential great clinical importance. However, the positive predictive value is fairly low for all assays. This is consistent with the fact that although it is a major determinant of thrombotic events, high on-treatment platelet reactivity is not the sole factor responsible for these events.

Personalized Antiplatelet Therapy: Preliminary Prospective Studies

Following the demonstration of a link between high on-treatment platelet reactivity in patients undergoing PCI together and thrombotic/ischemic events, several studies have aimed to lower the level of platelet reactivity by modifying therapy. These studies have demonstrated that platelet reactivity to ADP on standard clopidogrel therapy can be lowered by using higher loading or maintenance doses of clopidogrel, the addition of cilostazol, switching to more potent alternative $P2Y_{12}$ receptor blockers such as prasugrel or ticagrelor (AstraZeneca, Wilmington, Delaware), and by adding elinogrel or GP IIb/IIIa inhibitors (76–78,85–93). An improved outcome with altered therapy was observed in some of these studies (76–78,93).

In 2 small multicenter trials that employed the VASP-phosphorylation assay, tailored incremental loading doses of clopidogrel further reduced on-treatment platelet reactivity below the previously noted threshold and were effective in reducing subsequent major adverse cardiac events without increasing Thrombolysis In Myocardial Infarction (TIMI) major or minor bleedings. However, it must be noted that about 5% of patients remain resistant to clopidogrel even after repeated loading doses of 600 mg (76,77). Similarly, following these findings, 2 other studies (82,91) have suggested that the selective administration of platelet GP IIb/IIIa receptor blockers to patients undergoing elective PCI who were identified as

Table 2

Studies Linking High On-Treatment Platelet Reactivity to Ischemic Events Based on ROC Curve With a Specific Cutoff Value

Study (Ref. #)	Assay	Cutoff Value	End Point	AUC	Odds Ratio
Price et al. (68)	VerifyNow P2Y12 assay	>235 PRU	6-month post-PCI CVD + MI + ST	0.71	NA
Gurbel et al. (69)	LTA	>46% 5-μmol/l ADP >59% 20-μmol/l ADP	2-year post-PCI MACE	0.77 0.78	3.9 3.8
Blindt et al. (62)	VASP-PRI	>48% PRI	6-month ST	0.79	1.16
Frere et al. (64)	LTA VASP-PRI	>70% 10-μmol/l ADP >53% PRI	1-month post-PCI MACE + stroke	0.74 0.73	NA
Bonello et al. (72)	VASP-PRI	>50% PRI	6-month post-PCI MACE	0.55	NA
Marcucci et al. (75)	VerifyNow P2Y12 assay	≥240	1-yr CV death and nonfatal MI	0.66	2.38 CV death 2.76 nonfatal MI
Sibbing et al. (80)	Multiplate analyzer-ADP	>468 AU/min 6.4-μmol/l ADP	30-day ST	0.78	12.0
Cuisset et al. (81)	LTA	>67% 10-μmol/l ADP	1-month ST	0.69	5.8
Breet et al. (82)	LTA VerifyNow P2Y12 assay Plateletworks	>42.9% 5-μmol/l ADP >64.5% 20-μmol/l ADP >236 PRU >80.5% 20-μmol/l ADP	1-yr death, MI, ST, and stroke	0.63 0.62 0.62 0.61	2.09 2.05 2.53 2.22

AUC = area under the curve; CVD = cardiovascular disease; NA = not addressed; other abbreviations as in Table 1.

having high on-treatment platelet reactivity following an oral clopidogrel loading dose was effective in reducing subsequent post-PCI ischemic events without increased bleeding rates. These studies are the first to suggest that the cutoff value identifying patients at increased risk of thrombotic events could be used to tailor therapy and lead to an improved outcome.

Ongoing Studies of Personalized $P2Y_{12}$ Inhibitor Therapy

Larger clinical trials aimed at confirming the potential benefit of tailored doses of clopidogrel according to on-treatment platelet reactivity assessed by VerifyNow are currently recruit-

Table 3

Ongoing Clinical Studies Based Platelet Reactivity Measurement by VerifyNow Assay

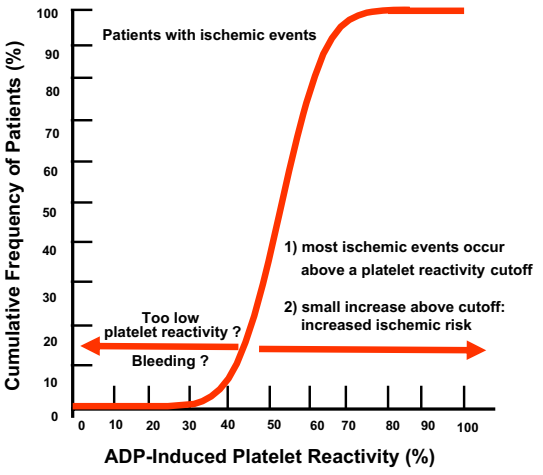
Study		ClinicalTrials.gov Identifier	Unstable or NSTEMI/PCI	Outcome	Clopidogrel Therapy
GRAVITAS	Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety	NCT00645918	Elective or ACS/PCI/DES (2,783)	6-month CV death, nonfatal MI, or ST	75 mg qd vs. 150 mg qd
ARCTIC	Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy	NCT00827411	Elective PCI/DES (2,500)	12-month composite end point of death, MI, stroke, urgent revascularization, ST	Therapy based on MD's performance
DANTE	Dual Antiplatelet Therapy Tailored on the Extent of Platelet Inhibition	NCT00774475	Unstable or NSTEMI/PCI (442)	6- and 12-month CV death, nonfatal MI, TVR by PCI or CABG	75 mg qd vs. 150 mg qd
TOPAS -1	Tailoring of Platelet Inhibition to Avoid Stent Thrombosis	NCT00914368	Previous PCI or stenting for CAD (450)	6-month ST	600-mg LD 75 mg qd for 6 months
TRIGGER-PCI	Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel	NCT00910299	PCI patients (2,150)	CV death, nonfatal MI	Prasugrel 60/10 mg vs. clopidogrel 600/75 mg

CABG = coronary artery bypass graft; MD = maintenance dose; TVR = target vessel revascularization; other abbreviations as in Table 1.

ing patients (Table 3) (94). The clinical benefit of achieving lower levels of on-treatment platelet reactivity was suggested by the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) (95) and the PLATO (Platelet Inhibition and Patient Outcomes) trials (96). In TRITON–TIMI 38, prasugrel, a third-generation thienopyridine associated with faster and lower on-treatment platelet reactivity than clopidogrel, was in turn associated with a lower prevalence of thrombotic events in ACS patients treated with PCI (95,97). However, prasugrel was associated with greater bleeding rates in the TRITON–TIMI 38 trial that may be related to excessively low platelet reactivity in selected patients (97). In the PLATO study, ticagrelor, the first oral nonthienopyridine reversible $P2Y_{12}$ inhibitor that provides a faster platelet inhibition and lower on-treatment platelet reactivity than clopidogrel was also associated with lower rates of ischemic events in an ACS population. Similar to the results of TRITON–TIMI 38, increased bleedings in ACS patients undergoing PCI were also noted in the ticagrelor group (95–97). These findings are consistent with the hypothesis that lower levels of platelet aggregation are associated with reduced ischemic events but increased bleeding risk. In the PLATO study, a similar bleeding event rate in patients undergoing coronary artery bypass grafting where ticagrelor therapy was discontinued within 3 days before surgery was observed (96). This was supported by the observation that ticagrelor was associated with faster offset of antiplatelet effects compared with clopidogrel therapy despite superior platelet inhibition in the ONSET/OFFSET (Randomized Double-Blind Assessment of the Onset and Offset of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Disease) study (17). Moreover, in the RESPOND (Response to Ticagrelor in Clopidogrel Nonresponders and Responders and the Effect of Switching Therapies) study (93), ticagrelor therapy was associated with uniform and superior platelet inhibition in both previously identified clopidogrel responders and nonresponders, and that inhibition, in turn, was associated with an extremely low prevalence of high on-treatment platelet reactivity. In addition, another novel reversible $P2Y_{12}$ receptor blocker, elinogrel, has been shown to be associated with enhanced platelet inhibition when administered to selected patients with high platelet reactivity during standard clopidogrel therapy. Moreover, the antiplatelet effect of elinogrel was completely reversible within 24 h (92). The previously discussed alternative therapies may provide important advances to attenuated ischemic events occurrence, particularly in selected patients with high platelet reactivity on standard clopidogrel treatment. Dose adjustments based on objective measurements of platelet reactivity may reduce the prevalence of bleeding. Reversibility may facilitate the management of patients requiring unanticipated surgery. The results of TRITON–TIMI 38 and PLATO suggest that there may be a fine balance between ischemic event occurrences and bleeding in patients treated with $P2Y_{12}$ receptor blockers. Consistently tailored $P2Y_{12}$ receptor blockade has the potential to improve outcome.

Figure 3

Post-PCI Ischemic/Thrombotic Clinical Events



The sigmoid cumulative frequency curve in patients with post–percutaneous coronary intervention ischemic/thrombotic clinical events relative to platelet reactivity to adenosine diphosphate. These data support the concept of a therapeutic window for $P2Y_{12}$ blockade. Adapted, with permission, from Gurbel et al. (7). Abbreviation as in Figure 1.

$P2Y_{12}$ Inhibitor Therapeutic Window

As platelet-mediated ischemic events appear to be clustered in the upper tertile or quartile of on-treatment platelet reactivity (i.e., above the optimal cut points previously identified), there may exist a "therapeutic window" for $P2Y_{12}$ receptor antagonist therapy that is associated with both an optimal reduction in thrombotic events as well as a low rate of major bleeding. The identification of a specific threshold for platelet reactivity that confers protection against thrombotic events and yet also limits bleeding following PCI is a crucial area of investigation, particularly in light of the increasing availability of platelet point-of-care assays as well as the widening choice of $P2Y_{12}$ receptor antagonists (7,60) (Fig. 3). At this time, there have been no definitive studies confirming a cut point of platelet reactivity to ADP associated with bleeding risk. However, recent observational data have emerged showing an association of an excessive response to clopidogrel and the occurrence of major

in-hospital bleeding events in clopidogrel-treated patients undergoing PCI (98–100). Moreover, the advent of more potent antiplatelet drugs that target the $P2Y_{12}$ receptor—such as prasugrel and ticagrelor, sets the need to study the relationship of antiplatelet treatment and risk for bleeding more thoroughly.

Future Considerations

It is unknown whether on-treatment platelet reactivity cut points associated with risk for periprocedural events are the same as those associated with long-term risk. Although similar cut points have been reported, the optimal platelet reactivity target may vary with respect to the time following the PCI procedure. For example, lower on-treatment platelet reactivity may be optimal in the early period following ACS and/or PCI, whereas the same low level may not provide the same clinical advantage 6 months later due to excessive bleeding. Also, the optimal level of platelet reactivity may differ between the settings of elective as compared to emergent PCI. Another factor that must be considered is that antiplatelet therapy responsiveness has been reported to improve over time following PCI, which may result in lower on-treatment platelet reactivity (6). Finally, the comparative utility of platelet function versus genetic testing should be investigated prospectively in order to determine whether these strategies are complementary or stand-alone methods to identify the high-risk patients.

Conclusions

The absolute level of platelet reactivity during treatment (i.e., on-treatment platelet reactivity) is proposed by the consensus of all the authors to be a better measure of thrombotic risk than responsiveness to clopidogrel. Currently available evidence supports the concept of a threshold for on-treatment platelet reactivity that may be used to stratify patient risk for ischemic/thrombotic events following PCI, including stent thrombosis. At the present time, high on-treatment platelet reactivity in the setting of PCI has been defined by ROC analyses using the following criteria: 1) PRI >50% by VASP-P analysis; 2) >235 to 240 $P2Y_{12}$ reaction units by VerifyNow P2Y12 assay; 3) >46% maximal 5-μmol/l ADP-induced aggregation; and 4) >468 arbitrary aggregation units/min in response to ADP by Multiplate analyzer (68,69,72,80) (Table 2). However, there are no large-scale clinical studies to date demonstrating that the adjustment of antiplatelet therapy based on any of these cut points improves clinical outcomes. Finally, PCI patients with diabetes and patients with ACS treated medically as compared to those treated with PCI may have different high on-treatment platelet reactivity cut points (84).

Ongoing studies with the VerifyNow P2Y12 assay are underway to determine whether individually tailoring antiplatelet therapy will improve clinical outcomes after PCI. These studies will also investigate the relationship of platelet reactivity to bleeding events. Currently, platelet function testing may be considered in determining an antiplatelet strategy in patients with a history of stent thrombosis and in patients prior to undergoing high-risk PCI. However, until the results of large-scale trials of personalized antiplatelet therapy are available, the routine use of platelet function measurements in the care of patients with cardiovascular disease cannot be recommended.

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Key Words: adenosine diphosphate ■ percutaneous coronary intervention ■ platelet reactivity ■ thrombotic events.