

Peri-Procedural Platelet Reactivity in Percutaneous Coronary Intervention

Dimitrios Alexopoulos¹ Iosif Xenogiannis¹ Panagiotis Vlachakis¹ Udaya Tantry² Paul A. Gurbel²

¹2nd Department of Cardiology, Attikon University Hospital, National and Capodistrian University of Athens Medical School, Athens, Greece

²Inova Center for Thrombosis Research and Drug Development, Inova Heart and Vascular Institute, Fairfax, Virginia, United States

Address for correspondence Dimitrios Alexopoulos, MD, 2nd Department of Cardiology, Attikon University Hospital, Rimini 1, Chaidari 12462, Athens, Greece (e-mail: dalex@med.uoa.gr).

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Abstract

Platelet activation and aggregation play a pivotal role in thrombotic complications occurring during percutaneous coronary intervention (PCI), and peri-PCI anti-platelet therapy represents a standard of care. High platelet reactivity prior to PCI has been correlated with an increased incidence of peri-procedural myonecrosis. Pre-PCI platelet reactivity predicts post-PCI platelet reactivity and has a prognostic impact on subsequent ischaemic and bleeding events, so as the platelet inhibition measured post-PCI. Many anti-platelet treatment strategies, including aspirin, glycoprotein IIb/IIIa inhibitors, P2Y₁₂ receptor blockers and vorapaxar, are being used in the routine clinical practice to modify platelet reactivity at each stage, e.g. pre-, during and post-PCI. Anti-platelet strategies with a ‘stronger and faster’ pharmacodynamic effect than clopidogrel have been mostly adopted in patients with acute coronary syndromes. However, several issues regarding the anti-platelet treatment such as benefits/risks of anti-platelet therapy pre-treatment and duration, and definite association between speed and potency of various anti-platelet agents and clinical outcomes remain controversial. We believe that a better understanding of peri-PCI platelet reactivity and its relations to outcomes may lead to the development of more effective and safe treatment strategies.

Keywords

- ▶ coronary angioplasty
- ▶ anti-platelet treatment
- ▶ platelet reactivity

Introduction

Percutaneous coronary intervention (PCI) is the major revascularization strategy in patients with high-risk coronary artery disease (CAD). However, by inducing vascular injury, PCI further exacerbates the risk of thrombosis in the presence of dysfunctional endothelium, vulnerable plaques and systemic prothrombotic propensity. Vascular injury results in the exposure of the sub-endothelial matrix that facilitates platelet adhesion and activation. Following platelet activation, secondary agonists, thromboxane (Tx) A₂ and adenosine diphosphate (ADP) are released from platelets. These agonists act synergistically to produce sustained activation of glycoprotein (GP) IIb/IIIa receptors and stable platelet-rich thrombus by amplify-

ing the response to multiple agonists. Tissue factor exposed at the site of vascular injury facilitates the initial generation of picomolar amounts of thrombin. A vicious cycle occurs in which activated coagulation factors are formed on the activated platelet surface, generating more thrombin, and further enhancing platelet activation and coagulation processes. Platelet-rich thrombus is further stabilized by fibrin mesh formation that is simultaneously generated by thrombin through the coagulation cascade. Occlusive thrombus formation at the site of vascular injury results in type IV myocardial infarction (MI) and stent thrombosis (ST). In addition, iatrogenic embolization that occurs during PCI causes downstream micro-vascular obstruction and myocardial ischaemia/infarction despite a re-analyzed infarct-related epicardial coronary artery. These

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observations position the platelet as a 'nidus of evil', support the concept of the 'platelet hypothesis' that describes the platelet as the central component in acute thrombotic cardiovascular disease and provide the rationale for anti-platelet therapy prior, during and following PCI. Since coagulation also plays a pivotal role in the generation of a platelet-fibrin clot and in subsequent ischaemic event occurrences, a combination of anti-platelets and anticoagulants is the cornerstone of treatment for patients with CAD/acute coronary syndrome (ACS) undergoing PCI. However, the choice, intensity and duration of treatment depend on the severity of the disease, comorbid disease and the clinical setting of intervention (elective, acute or primary intervention). The goal of optimal antithrombotic strategy is to achieve a maximal antithrombotic effect associated with an acceptable bleeding risk.

Inhibition of peri-PCI platelet activation with simultaneous blockade of TxA_2 and ADP pathway represents therefore a major therapeutic target in patients undergoing PCI.¹ Earlier, GP IIb/IIIa inhibitors (GPIs) were widely used to achieve rapid and profound platelet inhibition, particularly during high-risk PCI. Older studies showed an improvement in clinical outcomes, although with an increased bleeding potential.² Following the development of fast acting, potent oral P2Y₁₂ receptor blockers, such as prasugrel and ticagrelor, the use of GPIs in high-risk patients waned and is now more limited in the current interventional practice as compared with that of two decades ago.³ In this context, cangrelor, an intravenous P2Y₁₂ receptor antagonist with a very fast onset and offset of action, represents new strategy of modulating peri-PCI platelet reactivity.

This review focuses on the significance of platelet reactivity assessed pre-, during and post-PCI and on therapeutic approaches targeting peri-PCI platelet reactivity in light of contemporary anti-platelet treatment.

Pre-Procedural Platelet Reactivity

Platelet reactivity prior to PCI varies according to the clinical setting. Platelet aggregation has been reported to be higher in ST segment elevation MI (STEMI) versus stable angina patients and is considered as a hallmark of acuity of the disease.⁴ Of note, high platelet reactivity (HPR) is not an invariable phenomenon even in STEMI cases as approximately 30% of patients present with levels of platelet reactivity below the threshold associated with ischaemic events.⁵ Whether these patients had an increase in their platelet reactivity is not clear, as platelet reactivity assessment prior to the acute event was not available.

In STEMI patients, collagen/ADP closure time before treatment has been inversely correlated with creatine kinase-muscle/brain (CK-MB) and troponin levels.⁴ In patients undergoing primary PCI, platelet reactivity measured before P2Y₁₂ blockade has been also linked to the degree of angiographic success, extent of ST-segment resolution, thrombus burden, early and late left ventricular functional recovery and short- and mid-term clinical outcomes.⁴⁻⁶ In addition, among non-ST elevation (NSTEMI) ACS patients, cases with pre-PCI HPR had more frequent peri-procedural MI after stenting.⁷

In stable patients undergoing PCI HPR during clopidogrel therapy was described as independent predictor of peri-procedural MI.⁸ However, in the Stent Thrombosis In Belgium (STIB) trial including 891 patients undergoing PCI for stable angina pectoris who had been loaded with 600 mg of clopidogrel 12 to 24 hours before, platelet reactivity before PCI was not associated with peri-procedural myonecrosis.⁹ The later findings raise the issue of acuity of disease-dependent impact of pre-PCI platelet reactivity on subsequent myonecrosis.

In patients treated with a thienopyridine–clopidogrel or prasugrel—and undergoing elective PCI, platelet reactivity prior to PCI is associated with post-PCI platelet reactivity.^{10,11} Association of pre-treatment platelet reactivity to on-treatment one has been reported in STEMI patients treated with prasugrel, but not in ticagrelor-treated patients.¹² The response to anti-platelet agents (aspirin, GPI or P2Y₁₂ receptor antagonist) as determined prior to PCI has been extensively analysed and in most studies appears to carry a prognostic impact on both post-procedural ischaemic and bleeding events (► **Table 1**).

Platelet Reactivity during PCI

Since platelet function is, in part, regulated by an intact functioning endothelium, platelet function could be expected to change during ischaemia reperfusion due to endothelial dysfunction. In early studies, a brief period of myocardial ischaemia followed by reperfusion on regional and systemic platelet function was evaluated in a swine model.²⁰ Platelet function was observed not to be static during ischaemia reperfusion. Instead, during ischaemia, regional platelet function increased and both regional and systemic and platelet function increased during myocardial reperfusion. The mechanism(s) of these responses remain unknown but may be related to regional endothelial dysfunction created by ischaemia and the release of pro-aggregatory mediators in the coronary and/or systemic circulation during ischaemia reperfusion. During PCI, platelets are activated due to iatrogenic reasons. On the activated platelet surface, thrombin is generated through coagulation pathway activation that further activates platelets and augments the generation of thrombus on the damaged wall of coronary arteries. Most studies have demonstrated platelet activation before PCI and also immediately after PCI.²¹⁻²³ In the Plavix Reduction Of New Thrombus Occurrence (PRONTO) trial, platelet reactivity was increased immediately (2 hours) after PCI and returned to baseline after 5 hours post-PCI. In addition, a clopidogrel loading dose (LD) given 3 to 24 hours prior to stent implantation inhibited platelets before the onset of the procedure and reduced activation induced by stenting more than the administration of 75 mg at the time of the procedure.²⁴ It has been proposed that platelets can be activated by catheters and also by ADP that is released from red blood cells and platelets that are damaged by contact with materials such as the stent or balloons, or by generated thrombin.^{25,26} A heightened platelet reactivity was observed in patients undergoing PCI combined with more invasive rotational atherectomy as compared with patients undergoing angiography.²⁷ Moreover, underlying

Table 1 Correlation between pre-PCI platelet reactivity and post-procedural events

Study	Patients	Methods	Outcomes
Mayer et al ¹³	7,090 PCI-treated patients All patients pre-treated with aspirin (IV dose of 500 mg) and P2Y ₁₂ receptor antagonist	Blood was drawn after administration of aspirin and before PCI AA-induced platelet aggregation Multiplate Analyzer (Roche Diagnostics, Basel, Switzerland)	HAPR: > 203 AU × min (upper quintile) Death or ST at 1 year HAPR patients: 6.2% non-HAPR patients 3.7%, OR (95% CI) 1.78 (1.39–2.27), <i>p</i> < 0.0001 HAPR: independent predictor of the composite of death from any cause or ST at 1 year with adjusted HR (95% CI) 1.46 (1.12–1.89), <i>p</i> = 0.005
Gurbel et al ¹⁴	160 patients undergoing non-emergent PCI	Pre-treatment blood samples were obtained in the catheterization laboratory LTA (20 μM ADP) 6 months follow-up	No difference in aggregation in patients with (71 ± 9%) versus without (73 ± 12%) ischaemic events
Kabbani et al ¹⁵	112 symptomatic CAD patients undergoing PCI	Blood was drawn before the PCI Flow cytometric analysis and assay of activation of GP IIb/IIIa in response to a low concentration of ADP (0.2 μmol/L)	Low reactivity group: ≤24.9% GP IIb/IIIa activation High reactivity group: > 24.9% GP IIb/IIIa activation Rate of primary endpoint (MI, urgent or repeat revascularization in the 90-day follow-up: 26.8% in the high- and 7.1% in the low-reactivity group, OR = 4.8, <i>p</i> = 0.01
Hochholzer et al ¹⁶	802 patients undergoing PCI All patients pre-treated with 600 mg of clopidogrel, aspirin (≥ 100 mg per day for at least 5 days)	Blood was drawn: at the time of catheterization before administration of heparin or contrast sodium Optical aggregometry (5 μmol/L ADP)	Primary end point: 30-day cumulative incidence of death, MI or urgent target lesion revascularization Platelet aggregation above the median carried a RR (95% CI) for primary endpoint of 6.7 (1.52–29.41), <i>p</i> = 0.003
Breet et al ¹⁷	951 patients undergoing PCI All patients on aspirin 80–100 mg od for ≥ 10 days Received optimal clopidogrel treatment	Blood was drawn before heparinization (before PCI) LTA (AA-induced and ADP-induced) and VerifyNow	Primary endpoint (composite of death, non-fatal MI, ST and ischaemic stroke) rate By LTA, in patients with isolated HCPR: 11.7% In patients with isolated HAPR: 9.6% In patients with DAPR: 10.7% versus patients without HPR: 4.2%, all <i>p</i> < 0.01 By VerifyNow, patients with DAPR had the highest risk for the primary endpoint: 17.7% versus 4.1% in patients without, <i>p</i> = 0.001
Patti et al ¹⁸	310 clopidogrel-treated patients who underwent PCI	Blood was drawn immediately before PCI VerifyNow P2Y ₁₂ assay	Major bleeding rate at 1 month Patients in the lowest PRU quartile: 10.1% Patients in the highest PRU quartile: 1.3%, <i>p</i> = 0.043 Patients in the third quartile: 1.4%, <i>p</i> = 0.05 Baseline PRU in patients with bleeding at 30 days: 171 ± 49 Baseline PRU in patients without bleeding at 30 days: 227 ± 68, <i>p</i> = 0.002

(Continued)

Table 1 (Continued)

Study	Patients	Methods	Outcomes
Mangiarcapa et al ¹⁹	800 patients undergoing elective PCI clopidogrel 600 mg LD at least 6 hour prior to PCI or 75 mg/d for at least 5 days aspirin (80–100 mg)	Blood was drawn immediately before PCI PR (VerifyNow P2Y12 assay)	Both BRS ^a and PR showed high discriminatory power for bleeding (AUC > 0.7 for all definitions) Discriminatory power of BRS-PR (AUC = 0.809 for TIMI bleeding; AUC = 0.814 for BARC class ≥ 2 bleeding; and AUC = 0.813 for REPLACE-2 bleeding); higher than that of BRS alone ($p < 0.001$ for all definitions)

Abbreviations: AA, arachidonic acid; ADP, adenosine diphosphate; AU, aggregation units; BARC, Bleeding Academic Research Consortium; BRS, bleeding risk score; CAD, coronary artery disease; CI, confidence interval; DAPR, dual high on treatment platelet reactivity; GP, glycoprotein; HAPR, high on aspirin platelet reactivity; HCPR, high on clopidogrel platelet reactivity; HR, hazard ratio; HPR, high on treatment platelet reactivity; LTA, light transmittance aggregometry; MI, myocardial infarction; OR, odds ratio; PR, platelet reactivity; PRU, P2Y12 reaction units; REPLACE-2, randomized evaluation in PCI linking angiomax to reduced clinical events-2; PCI, percutaneous coronary intervention; ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction.

^aCalculation of BRS included: age, sex, intra-aortic balloon pump, glycoprotein IIb/IIIa inhibitors, chronic kidney disease, anaemia and low-molecular-weight heparin within 48-hour pre-PCI.

mechanisms have been attributed to damaged vascular wall and endothelium activation.

Intravenous anticoagulant therapy, administered before PCI to prevent ischaemic complications appears to affect platelet activation.²⁸ The impact of bivalirudin on platelet activation during PCI, either alone or compared with unfractionated heparin (with or without GPIs), has been extensively analysed. Overall, bivalirudin appears not to increase and even to decrease various indices of platelet activation (→ **Supplementary Table S1**, available in the online version). An excess in acute ST rate has been described in clinical studies in patients treated with bivalirudin compared with heparin.^{29,30} In an effort to explain this increase, investigators have described in ACS patients loaded with ticagrelor similar thrombin generation during PCI between heparin-versus bivalirudin-anticoagulated patients. However, 4 hours after the end of bivalirudin infusion a quick restoration of thrombin activity was seen, whereas in heparin-treated patients this remained significantly inhibited.³¹ Same investigators recently described in the bivalirudin group compared with the heparin group a significantly lower level of antithrombotic activity during PCI, as assessed by activated partial thromboplastin time.³² Of note, in both studies no difference in the course of platelet reactivity following ticagrelor loading over time was seen.

Post-Procedural Platelet Reactivity

An increase in platelet reactivity occurs immediately or 2 hours after PCI.^{33,34} Beyond the duration of the PCI procedure itself, platelet inhibition is desirable for the post-procedure period. Data regarding how strong platelet inhibition is needed and for how long is mandatory following the procedure, e.g. for hours, days or months, are scarce. Among 5,842 patients participating in the Dutch ST registry, 1.7% suffered acute ST at a mean time of 3.4 ± 5.3 hours post-

PCI signifying the most vulnerable period post-PCI and delineating the necessity for strong platelet inhibition during this period.³⁵ In non-STEMI patients presenting with HPR while on clopidogrel, Sibbing et al described a vulnerable phase, directly surrounding the invasive procedure, for which intensive platelet inhibition achieved by GPI offered better protection. It is not clear whether stable patients are similarly “vulnerable” and for how long post-PCI.³⁶ Several studies of a ‘tailored’ intensification of anti-platelet treatment, which led to neutral/negative results, argue in favour of a ‘more quiet’ phase post-PCI in such patients, having less chances for ischaemic events and being less dependent on platelet inhibition.^{37–40}

Several lines of evidence support the short- and long-term prognostic value of post-procedural platelet reactivity.^{14,41,42} High on-clopidogrel platelet reactivity 1 day post-PCI is associated with an increased risk of death or MI after the planned discontinuation of clopidogrel and for 1 year thereafter.⁴³ In STEMI patients on aspirin and clopidogrel, high on-treatment platelet reactivity also predicts the risk of adverse left ventricular remodelling, with synergism between platelets and inflammation being implicated for this effect.⁴⁴

It is emphasized that platelet reactivity should be taken into account in conjunction with other clinical factors that influence the incidence of post-PCI ischaemic events, such as the presence of diabetes and chronic kidney disease, age, ACS versus non-ACS and post-PCI time (early vs. late).¹ Beyond platelet reactivity and during the last decade, other factors, like technology evolution and introduction of second (vs. first) generation drug-eluting stents, may also be implicated for the reduction in ST rates observed post-PCI.⁴⁵

On the other hand, low platelet reactivity—below a certain threshold—has been linked to increased bleeding potential and the concept of a therapeutic window has been introduced.^{1,46,47} Notably, in a recent study involving patients after PCI on aspirin and clopidogrel, reticulated platelet

fraction—an index of increased platelet turnover—but not platelet function, was predictive of 6-month major adverse cardiovascular event (MACE).⁴⁸

Due to the aforementioned heightened platelet reactivity immediately after PCI as compared with before PCI, the most appropriate time for blood sampling for platelet function assessment remains debatable. The timing of clopidogrel administration also should be taken into account. It is common practice in the United States to treat patients during PCI, whereas in most of the European countries, clopidogrel is administered before PCI. It has been shown that clopidogrel responsiveness is dependent on the time of platelet function measurement.¹⁰ In a recent systematic search and analysis of studies involving clopidogrel pre-treated patients in which platelet function measurements were performed on multiple time points, authors postulated that blood sample taken shortly after a PCI procedure could lead to misinterpretation of the patient's response to anti-platelet therapy and an over-estimation of the patient's ischaemic risk.²⁶

Modifying PERI-PCI Platelet Reactivity

Pre-PCI (Pre-Treatment)

Aspirin is routinely used prior to PCI and its value has been indirectly demonstrated in a study where the absence of aspirin treatment before PCI has been associated with a higher risk of death and stroke.⁴⁹ In patients on chronic low dose aspirin undergoing elective PCI, 325 mg LD of aspirin prior to PCI attenuated the increase in serum thromboxane B₂ and improved reperfusion and myocardial injury indices.⁵⁰ On the other hand, platelet or COX-1 functional testing was not predictive of clinical outcomes in stable patients on aspirin monotherapy.⁵¹

Probably, the most potent platelet inhibition prior to PCI has been applied in the very early hours of STEMI, in the form of 'upstream' (vs. catheterization laboratory) administration of GPIs. However, in two randomized trials of very early versus during PCI potent platelet blockade, no differences in death or re-infarction rates and borderline results in ST-segment resolution or thrombolysis in myocardial infarction (TIMI)-3 flow in the infarct-related artery were observed.^{52,53}

In a meta-analysis including 8,608 patients from 7 randomized studies, clopidogrel pre-treatment was not associated with a reduction in mortality or an increase in major bleeding, but was associated with a lower risk of major cardiac events.⁵⁴ In the STEMI sub-group, clopidogrel pre-treatment versus no pre-treatment was associated with reduced mortality (1.28% vs. 2.54%, odds ratio [OR] = 0.50, 95% confidence interval [CI] = 0.26–0.96). Lack of benefit for a pre-treatment strategy and even an increase in bleeding was reported in the ACCOAST (A Comparison of prasugrel at the time of percutaneous Coronary intervention Or as pre-treatment At the time of diagnosis in patients with non-ST-segment elevation myocardial infarction) trial, where 2,770 non-STEMI patients undergoing PCI were randomized to pre-treatment with 30 mg prasugrel plus another 30 mg at the time of PCI versus placebo plus 60 mg of prasugrel at the time of PCI.⁵⁵

Pre-hospital treatment with ticagrelor was tested in the Administration of Ticagrelor in the Cath Laboratory or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) study.⁵⁶ Among 1,862 randomized patients, the co-primary endpoints of proportion of patients without > 70% resolution of ST-segment elevation before PCI and the proportion of patients without TIMI flow grade 3 in the infarct-related artery at initial angiography did not differ between the two strategies and also no differences in MACEs or bleeding events were observed. In a pre-specified platelet sub-study, maximum difference in platelet inhibition was detected 1 hour after PCI, largely explaining the lack of difference in the primary endpoints between groups.⁵⁷ A higher value of pre-hospital administration of ticagrelor has been postulated in real-life cases with longer treatment delays.⁵⁸ Overall, the absence of a clear benefit with pre-treatment therapy is likely responsible for the low (23% of PCI cases) adoption by clinicians of such strategy in contemporary U.S. practice.⁵⁹ The timing of initiation of a P2Y₁₂ inhibitor is both drug- (i.e. ticagrelor or clopidogrel vs. prasugrel) and clinical setting-specific (i.e. ACS NSTEMI vs. STEMI). In STEMI patients, early administration of oral P2Y₁₂ receptor blockers (prasugrel, ticagrelor) outweighs any potential risks: In NSTEMI patients, ticagrelor (or clopidogrel) as soon as the diagnosis is established seem to be a reasonable therapeutic strategy. Current practice guidelines regarding anti-platelet pre-treatment are shown in **Supplementary Table S2** (available in the online version).

During PCI

A superior and faster platelet inhibition in most cases can be achieved with GPI administration.⁶⁰ Of importance, the benefit offered by GPIs seems to depend on the clinical setting. In the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) study involving 2,022 NSTEMI ACS patients undergoing PCI who were pre-treated with 600 mg of clopidogrel and randomized to either abciximab or placebo, the composite of death, MI or urgent target vessel revascularization at 30 days was reduced with abciximab versus placebo (8.9% vs. 11.9%, relative risk [RR] = 0.75, 95% CI = 0.58–0.9). Maximum benefit was observed in patients with elevated troponin levels.⁶¹

Oral P2Y₁₂ receptor antagonists, particularly faster acting prasugrel and ticagrelor, administered at the beginning of PCI appear to start exhibiting their anti-platelet effect shortly thereafter and during the procedure. In elective PCI patients, prasugrel 60 mg LD immediately before the procedure was associated with faster and higher platelet inhibition than clopidogrel 600 mg LD, as indicated by a lower HPR rate at 60 minutes post-LD.⁶² Similarly, among troponin-negative ACS patients undergoing ad hoc PCI who were randomized to either ticagrelor 180 mg LD or clopidogrel 600 mg LD, platelet reactivity levels diverged as early as 30 minutes post-LD.⁶³ Nevertheless, adequate platelet inhibition with either prasugrel or ticagrelor LD immediately prior to the procedure is not expected during PCI, unless if this becomes a lengthy (> 30–60 minutes) procedure. This phenomenon is further exacerbated in STEMI patients where a significant delay in

the onset of anti-platelet action even with prasugrel and ticagrelor, is well appreciated.⁶⁴ Therefore, and following oral agents loading, in most cases primary PCI is performed without adequate P2Y₁₂ inhibition.

In the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition – CHAMPION PHOENIX, the primary endpoint of death, MI ischaemia-driven revascularization or ST assessed at 48 hour was reduced by cangrelor (bolus plus 2-hour infusion or till the end of PCI) as compared with 300 mg clopidogrel, with no difference in severe bleeding.⁶⁵ Cangrelor also effectively reduced the rate of intra-procedural ST.⁶⁶ Most importantly, cangrelor has been shown to provide rapid, strong and consistent platelet inhibition during primary PCI.^{67,68}

Apart from P2Y₁₂ receptor antagonists, vorapaxar, a protease-activated receptor-1 antagonist, administered as 40 mg LD at least 1 hour before the procedure in patients undergoing non-urgent PCI, provided 80% or more inhibition of thrombin receptor agonist peptide (TRAP)-induced platelet aggregation during the procedure in 68 to 96% of the cases.⁶⁹ Of note, in a clinical outcome trial in ACS patients vorapaxar added to standard therapy (with a LD administered prior to PCI when this was performed), did not significantly alter the ischaemic composite endpoint, while increased the risk of major bleeding.⁷⁰

Post-PCI

In a collaborative meta-analysis using patient-level data from six studies, post-PCI clopidogrel responsiveness assessed by the VerifyNow P2Y₁₂ assay was associated with long-term cardiovascular events, including death, MI and ST.⁷¹ In post-PCI patients in the Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study, a > 208 P2Y₁₂ reaction unit (PRU) (VerifyNow P2Y₁₂ assay) was associated with a higher risk for ST (1.3% vs. 0.5%) and MI (3.9% vs. 2.7%), but less risk for major bleeding (5.6% vs. 6.7%) and a neutral impact on mortality.⁴² In ACS patients loaded with prasugrel and presenting at least 6 hours and within 12 hours after loading, HPR (platelet reactivity index [PRI] > 50 by vasodilator-stimulated phosphoprotein index) was associated with a higher risk of cardiovascular death, MI and definite ST at 1 month.⁷² In contrast, patients with very low platelet reactivity (PRI < 16) had a higher risk of bleeding events during 1-year follow-up.⁷³ Significant differences in post-procedural platelet reactivity levels achieved with prasugrel or ticagrelor versus clopidogrel may be responsible for significantly short-term lower ischaemic event occurrences and higher bleeding in the two large-scale studies.^{74,75} This may be of particular importance in high-risk groups like in diabetic patients.⁷⁶

The role of platelet reactivity for risk stratification after PCI has been explored in a collaborative analysis using uniform cut-offs for standardized platelet function assays.⁷⁷ Among 20,839 patients (97% clopidogrel-treated) with platelet reactivity assessment during or < 30 days from PCI, HPR was associated with a higher risk for ST and slightly reduced bleeding risk, compared with patients with optimal platelet reactivity. On the other hand, low platelet reactivity

carried a higher risk of bleeding with no difference in ST rate. Peri-PCI platelet reactivity variations and treatment-induced modifications are shown in ►Fig. 1.

Unresolved Issues

Current observations suggest that adequate P2Y₁₂ receptor inhibition has not been achieved in most cases in real-world scenario and during ad hoc PCI; its influence on clinical outcome has been clarified. In ACS patients undergoing PCI, an intensified platelet inhibition has led to dramatic reduction in ST rate within 3 days from treatment initiation: from 0.67% in clopidogrel-treated patients to 0.33% in prasugrel-treated patients (hazard ratio [95% CI] 0.49 [0.29–0.82], *p* = 0.006).⁷⁴ The onset of anti-platelet activity provided by orally administered anti-platelet agents, appears to be variable and dependent on the clinical setting. This is particularly important in STEMI cases, where prompt and superior platelet inhibition is critical to reduce peri-PCI events. Nevertheless, adequate peri-PCI platelet inhibition can also be obtained by intravenous, fast-acting agents like GPIs or cangrelor. In the pre-hospital initiation of tirofiban in patients with ST-elevation MI undergoing primary angioplasty (On-TIME 2) study, 984 patients with STEMI undergoing PCI were randomly treated with either high-bolus dose tirofiban or placebo plus to aspirin, heparin and clopidogrel in the ambulance or referral centre. This study demonstrated that pre-hospital initiation of high-bolus dose tirofiban improved ST-segment resolution and clinical outcome after PCI and indicated that intensified platelet inhibition is essential in patients with STEMI undergoing PCI.⁷⁸ It may be plausible that the lack of a clear advantage of pre-treatment strategies negates or at least attenuates the importance of peri-PCI P2Y₁₂ receptor antagonism. A clear-cut benefit of pre-treatment, which is missing so far, would undoubtedly lead to a more widespread implementation of such strategies with potentially improvement in PCI's outcome.

In patients with HPR, on-treatment intensification of peri-PCI platelet inhibition (e.g. with GPIs use) has been shown to reduce 1-month post-PCI events.^{79,80} A routine assessment of platelet function testing with subsequent treatment tailoring has failed to improve outcome in randomized trials that were associated with important limitations, mainly the involvement of low-risk patients undergoing elective coronary stenting.^{37–39} This is mirrored in the current practice guidelines recommendations, where the routine clinical use of platelet function testing to adjust anti-platelet therapy before or after elective stenting is not recommended.^{81,82} In a trial confined in elderly ACS patients at increased risk of bleeding and ischaemic events, a tailored according to platelet function testing strategy also failed to improve outcomes compared with standard 5 mg of prasugrel.⁴⁰ An additional role for platelet function testing has been described in the recent Testing Responsiveness To Platelet Inhibition On Chronic Antiplatelet Treatment For Acute Coronary Syndromes (TROPICAL-ACS) trial where platelet reactivity after 1 week prasugrel followed by 1 week clopidogrel was used to de-escalate prasugrel treatment.⁸³ Guided de-escalation treatment was proved to be non-inferior to standard treatment

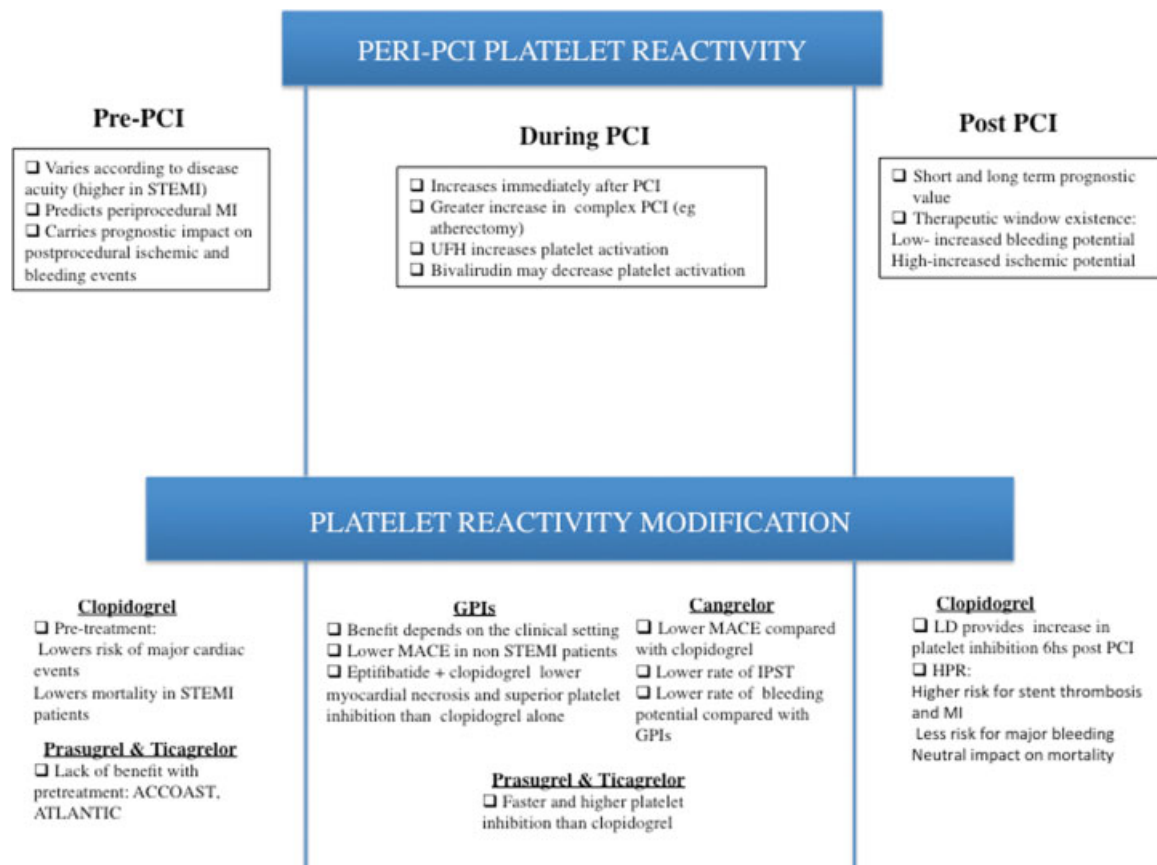


Fig. 1 Peri-PCI platelet reactivity variations and treatment-induced modifications. GPI, glycoprotein inhibitor; HPR, high platelet reactivity; IPST, intra-procedural stent thrombosis; LD, loading dose; MACE, major adverse cardiovascular event; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; UFH, unfractionated heparin.

with prasugrel at 1year post-PCI. Moreover, a genotyping strategy to tailor anti-platelet treatment is assessed in the ongoing Tailored Antiplatelet Therapy Following PCI (TAILOR-PCI, NCT01742117) and in the Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment (POPular Genetics, NCT01761786) studies.

Although ST rates have been dramatically reduced by prasugrel or ticagrelor versus clopidogrel, results from the STEMI cohorts from TRITON-TIMI 38 and PLATO trials revealed no reduction in ST with the faster and more potent acting agents (vs. clopidogrel) within the first 24 hours of PCI, the period of greatest risk.^{74,84} Furthermore, the overall benefit of faster/stronger platelet inhibition with ticagrelor appears to be attenuated in cases of primary PCI, when compared with the rest of the cases in both trials, although no treatment interaction has been reported.⁸⁵

Conclusion

Platelet reactivity assessed prior, during and post-PCI appears to carry a prognostic value, which is dependent on the acuity of the disease. Data obtained from studies with potent P2Y₁₂ receptor antagonists—administered orally or intravenously—emphasize the importance of superior inhibition of peri-PCI platelet reactivity. A better understanding of relation of peri-PCI platelet

reactivity inhibition and clinical outcome may assist in the development of more effective and safe therapeutic strategies.

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Conflict of Interest

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