

Platelet monitoring for PCI

Is it really necessary?

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Summary

Percutaneous coronary intervention (PCI) has significantly improved clinical outcomes in coronary artery disease patients. Since PCI is associated with platelet activation, antiplatelet therapy with aspirin, clopidogrel and GPIIb/IIIa inhibitors comprise the cornerstone strategy during and following PCI. The latter agents are arguably the most important drugs we administer to the patient with established coronary artery disease since they are specifically given to prevent the most catastrophic event, the formation of an occlusive arterial thrombus. Numerous clinical trials have confirmed the efficacy of antiplatelet therapy in attenuating recurrent ischaemic event occurrence.

Despite the extensive use of antiplatelet therapies, ischaemic event occurrence such as post-procedural myocardial infarction and stent thrombosis still remains an important concern and highlights the need for improved treatment strategies. A major limitation of current treatment is the application of a "one

size fits all" strategy advocated by the guidelines that completely ignores the evaluation of the individual antiplatelet response. Pharmacodynamic studies have revealed the limitations of aspirin and clopidogrel treatment that include response variability, and a high prevalence of antiplatelet non-responsiveness associated with significant risk for recurrent ischemic event occurrence. Thus, two major paradoxes in cardiovascular medicine today are: 1) despite the overwhelming evidence that platelet reactivity strongly influences the development of potentially catastrophic events including myocardial infarction and stent thrombosis in the PCI patient, no measurement is made in clinical practice to assess the presence of blood vulnerability (platelet reactivity) and 2) despite the overwhelming evidence that the effect of dual antiplatelet therapy with aspirin and P2Y₁₂ receptor blockers is variable, the guidelines largely recommend a uniform, "one size fits all" dosing of these agents in the PCI patient without any confirmation of an adequate antiplatelet effect.

Adenosine diphosphate (ADP) and thromboxane A₂ (TxA₂) are released following platelet activation. They cause the amplification of the platelet response and sustained platelet aggregation. Simultaneously, exposed tissue factor leads to small amounts of thrombin generation that further activates platelets and exposes the phosphatidyl anionic surface. The coagulation cascade taking place on the activated anionic platelet surface generates large amounts of thrombin that produces fibrin. Ultimately, there is cross-linking of fibrin that interacts with the platelet aggregate and results in a stable platelet-fibrin clot that causes both short- and long-term ischaemic complications. The rationale for antiplatelet therapy during and following PCI is to

- attenuate platelet activation and aggregation, and
- promote thrombus disaggregation.

All of the latter effects will preserve myocardial perfusion downstream from the affected coronary artery. Aspirin inhibits the cyclooxygenase-1 enzyme, P2Y₁₂ receptor blockers inhibit the ability of ADP to activate platelets and GPIIb/IIIa receptor blockers inhibit platelet binding to the dimeric fibrinogen molecule (▶ Fig. 1) (1). The achievement of optimal antithrombotic effects by the latter agents is limited by:

- a lack of knowledge of which pathway of platelet activation (COX-1, P2Y₁₂, thrombin-platelet) primarily drives thrombosis in the individual patient at the time of acute event occurrence,
- a uniform dosing (one size fits all) strategy despite the unpredictable antiplatelet response associated with two major antiplatelet agents, aspirin and clopidogrel, and
- a lack of understanding of the key pathways that influence bleeding.

Therefore, in order to improve the clinical efficacy of antiplatelet treatment and achieve the optimal balance between ischaemia and

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Patients with stable and acute coronary disease (ACS) undergoing PCI have dysfunctional endothelium associated with a diminished release of antithrombotic factors such as ecto-adenosine diphosphatase, nitric oxide, and prostaglandin-I₂ and often cause diffuse plaque formation. Although PCI and stenting provide local relief of severe arterial obstruction, these interventions result in the

denudation of endothelium and plaque rupture thereby exposing the subendothelial matrix.

Central role of platelets

Circulating platelets adhere to the exposed subendothelial matrix and undergo acti-

bleeding during and following PCI, the objective measurement of platelet function is under intensive investigation at this time.

Platelet function measurement before PCI

Platelet activation is associated with

- diabetes mellitus,
- acute coronary syndromes, and
- hyperlipidaemia.

The latter demographics are also common in patients undergoing PCI where platelet activation is marked (2, 3). Evidence for platelet activation and high platelet reactivity is

- presence of spontaneous platelet aggregation,
- high soluble p-selectin levels,
- elevated mean platelet volume,
- increased agonist-induced platelet aggregation, and
- expression of activation dependent receptors.

All of these markers have also been associated with ischaemic risk (4–7). Moreover, elevated pre-PCI platelet reactivity measured by agonist induced ex-vivo platelet aggregation and

surface activation dependent receptor expression measured by flow cytometry has been associated with increased ischaemic event occurrence following PCI (8–10). Some studies have demonstrated a relation between baseline (pre-PCI) and post-PCI platelet reactivity in patients treated with dual anti-platelet therapy. Patients with the highest pre-treatment platelet reactivity have been shown to have the highest post-treatment platelet reactivity (11, 12). High baseline platelet reactivity has been directly correlated to angiographic and clinical restenosis following bare-metal stent implantation (13).

Recently, it was demonstrated that high platelet-fibrin clot strength measured pre-PCI was associated with high platelet reactivity measured by aggregometry and inflammation marker release. Moreover, high platelet-fibrin clot strength correlated strongly with post-PCI ischaemic event occurrence (14). Based on these data it was suggested that a link exists between inflammation and heightened thrombogenicity measured pre-procedure and identified the patient at high risk for recurrent ischaemic events after stenting.

Similarly, in the TRIP (Thrombotic Risk Progression) study, multiple risk factors for ischaemic event occurrence including pla-

telet-fibrin clot strength, C-reactive protein, prothrombotic factors (VWF and fibrinogen), and platelet GPIIb/IIIa expression were studied simultaneously in patients with asymptomatic coronary artery disease (CAD) and in patients undergoing PCI for stable and unstable angina.

A distinct pathophysiological state of heightened platelet function, hypercoagulability, and inflammation marked the presence of unstable cardiovascular disease requiring intervention (15).

These studies suggest that an assessment of pathophysiology (inflammation and thrombogenicity) in the patient with CAD may assist in the identification of patients who are at greatest risk of needing future coronary intervention.

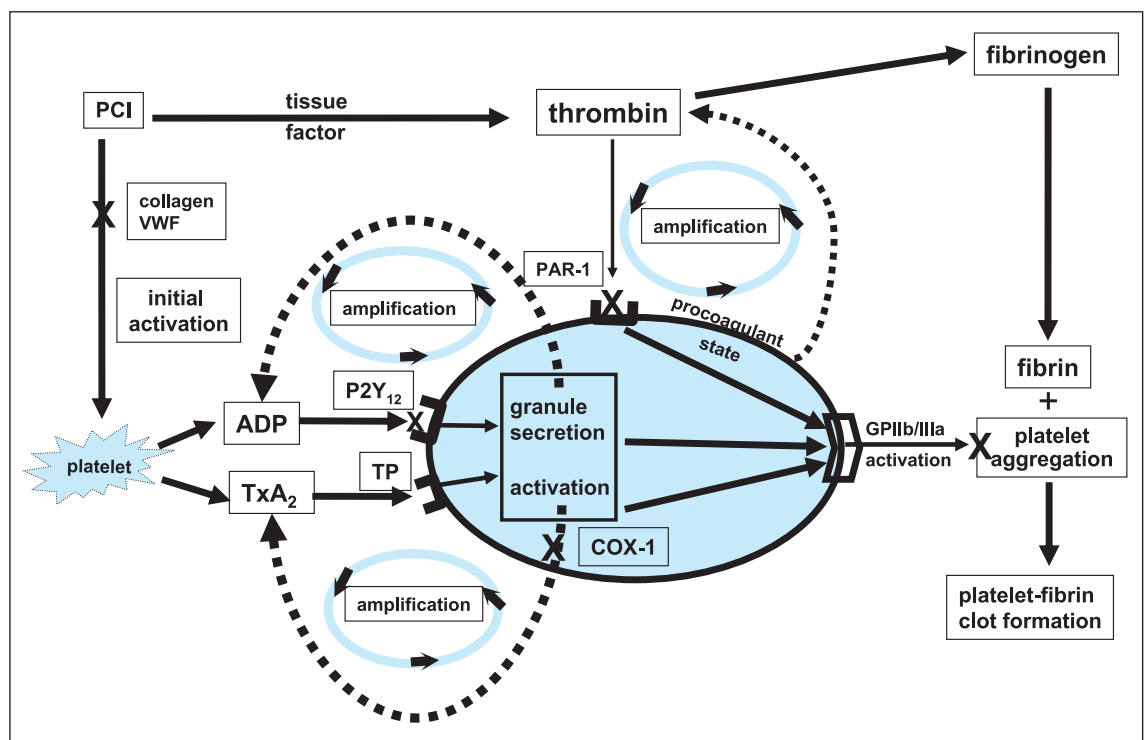
Antiplatelet response and post-PCI events

Clopidogrel

Multiple pharmacodynamic studies have confirmed clopidogrel response variability

Fig. 1

Central role of platelets and interaction with coagulation in the genesis of thrombosis during percutaneous intervention; ADP: adenosine diphosphate; COX-1: cyclooxygenase 1; P2Y₁₂: ADP receptor; TP: thromboxane A₂ receptor; TxA₂: thromboxane A₂; PAR-1: protease activated receptor 1; GPIIb/IIIa: glycoprotein IIb/IIIa receptor



and its relation to adverse clinical outcome in patients undergoing PCI. In an initial study, platelet inhibition was detectable at two hours after a 300 mg clopidogrel load, and a steady state of ~30–40% inhibition was reached at 24 hours that remained stable for 30 days during a 75 mg daily dose. The prevalence of non-responsiveness defined as a $\leq 10\%$ absolute change in 5 and 20 $\mu\text{mol/l}$ ADP-induced platelet aggregation (11) was

- 53% and 63% at two hours,
- 31% and 35% at 24 hours,
- 31% and 32% at five days and
- 13% and 21% at 30 days post-treatment.

Wide response variability was observed in this study that followed a normal distribution. In a subsequent study, we demonstrated that a higher loading dose (600 mg) was associated with enhanced platelet inhibition at 24 hours, less non-responsiveness (8% compared to 24% with 300 mg loading dose), and less response variability (16). Following these initial observations, other studies demonstrated response variability to clopidogrel therapy using the same and other methods, including point-of-care assays, that indicate P2Y₁₂ reactivity. The prevalence of non-responsiveness reported in these studies is approximately 8–30% depending upon the dose and time of measurement in relation to dosing (17).

Subsequent translational research studies have demonstrated the association of clopidogrel non-responsiveness and high on-treatment platelet reactivity to post-PCI adverse event occurrence. Matetzky et al. found that patients who exhibited the lowest quartile of platelet inhibition, had a 40% probability for a recurrent cardiovascular event within six months of undergoing stenting for acute ST-elevated myocardial infarctions (18). Given the variability in baseline platelet function as mentioned, it has been proposed that measurement of on-treatment aggregation is a better indicator for the risk for ischaemic event occurrence rather than non-responsiveness (19).

Translational research studies have established the relation between high on-treatment platelet reactivity to post-PCI ischaemic risk (20). The first prospective demonstration of the link between high on-treatment platelet reactivity to ADP and the occurrence of six months' post-discharge is-

chaemic events after stenting came from the PREPARE POST STENTING (Platelet Reactivity in Patients and Recurrent Events Post-Stenting) study (21). In the CLEAR PLATELETS Study it was also demonstrated that high on-treatment platelet reactivity to ADP was associated with the occurrence of a periprocedural MI (22–24). In the CLEAR-PLATELETS-2 study, in addition to high on-treatment platelet reactivity, high post-PCI platelet-fibrin clot strength was also associated with periprocedural MI.

The association of high on-treatment platelet reactivity to the occurrence of stent thrombosis has been explored in other studies by measuring ADP-induced platelet aggregation, VASP phosphorylation and ADP-stimulated active GPIIb/IIIa expression. More recently, the point-of-care VerifyNow P2Y₁₂ assay has also been used to link high on-treatment platelet reactivity to risk of thrombosis (▶ Tab. 1) (9, 18, 21–44). In addition, a recent study demonstrated that high on-treatment platelet reactivity measured before discharge is strongly associated with 2-year post-PCI adverse clinical outcome (31). All of these studies highlight the importance of identifying high on-treatment platelet reactivity to ADP in the PCI patient since it marks both periprocedural and long-term adverse clinical event occurrence.

Aspirin resistance

Similar to clopidogrel non-responsiveness, aspirin non-responsiveness has also been associated with post-PCI ischaemic events. The antiplatelet effect of aspirin is attributed primarily to the irreversible inhibition of platelet cyclooxygenase (COX)-1 by acetylation of the serine residue 529 resulting in downstream reduction in the synthesis of TxA₂ and resultant TxA₂-induced platelet activation/aggregation. However, recent studies indicate that the antiplatelet effect of aspirin may also involve inhibition of pathways distinct from COX-1 (non-COX-1 pathways) (45).

Recent pharmacodynamic studies have demonstrated that low-dose aspirin has variable effects in inhibiting platelet non-COX-1 pathways as measured by ADP-, collagen-, and shear-induced platelet aggregation. The prevalence of aspirin resistance is dependent on both assay and dose. The definition of aspirin

resistance is arbitrary and varies between methods and studies (45). In a recent prospective, randomized, double-blind, double cross-over investigation studying aspirin dosing (81 mg, 162 mg, 325 mg) using multiple assays in patients with stable coronary artery disease (n = 120), it was found that aspirin non-responsiveness was rare (1–6%) using methods that employed arachidonic acid stimulation (light transmittance aggregometry, VerifyNow Aspirin assay, TEG) at all doses of aspirin. When other agonists were used, the prevalence of resistance was 1–27%. Moreover, a dose dependent response to aspirin treatment was observed when collagen, ADP, and shear were used to activate platelets. The latter occurred in the presence of near complete inhibition of the COX-1 enzyme activity as measured by arachidonic acid-induced platelet aggregation, indicating that aspirin has non-COX-1 mediated dose dependent effects in platelets (46). More importantly, these dose dependent effects were more pronounced in patients with diabetes where treatment with higher doses was found to be more effective in inhibiting platelet function (47).

Platelet aspirin resistance was found to be uncommon in complaint patients undergoing PCI treated with high dose aspirin (325 mg per day) when measured by COX-1 specific assays such as using AA-induced light transmittance aggregometry (LTA) and TEG (48). Aspirin resistance as indicated by both COX-1 specific and non-specific assays have been associated with both periprocedural ischaemic events, including stent thrombosis and one year adverse cardiovascular events (49–51). Recurrent post-PCI ischaemic event occurrence is also higher in patients found to be aspirin resistant by COX-1 non-specific assays (52–53).

Dual non-responsiveness to clopidogrel and aspirin, measured during PCI, has been associated with periprocedural as well as 6-month adverse clinical event occurrence (25, 38).

Platelet reactivity threshold concept

A potential threshold level of on-treatment platelet reactivity to ADP associated with increased post-PCI risk was first demonstrated in the CLEAR PLATELETS study and sub-

Tab. 1

Studies linking high on-treatment platelet reactivity to ADP and clopidogrel non-responsiveness to Post-PCI Adverse Clinical Event Occurrence

study (ref.)	results	clinical relevance
Matzesky et al. (18)	↓ platelet inhibition	6 month cardiac events
Gurbel et al. (21)	↑ platelet aggregation	6 months post-PCI events
Gurbel et al. (22–24)	↑ periprocedural platelet aggregation	post-PCI myonecrosis
Bliden et al. (9)	↑ platelet aggregation (pre-PCI) on chronic clopidogrel therapy	1 year post-PCI events
Lev et al. (25)	clopidogrel/ aspirin resistant patients	post-PCI myonecrosis
Cuisset et al. (26)	↑ platelet aggregation	30 day post-PCI events
Geisler et al. (27)	clopidogrel low responders	3 months MACE and death
Hocholzer et al. (28)	↑ platelet aggregation (upper quartile)	30 day MACE
Frere et al. (29)	↑ platelet aggregation	30 day MACE
Price et al. (30)	↑ post-treatment platelet reactivity (VerifyNow assay)	6 months post-PCI events including stent thrombosis
Gurbel et al. (31)	↑ periprocedural platelet aggregation	2-year ischaemic events
Barragan et al. (32)	↑ P2Y ₁₂ reactivity ratio (VASP-P assay)	stent thrombosis
Gurbel et al. (33)	↑ P2Y ₁₂ reactivity ratio (VASP-P assay) ↑ platelet aggregation ↑ stimulated GPIIb/IIIa expression	stent thrombosis
Buonamici et al. (34)	↑ platelet aggregation	stent thrombosis
Bonello et al. (35)	↑ P2Y ₁₂ reactivity ratio (VASP-P assay)	post-PCI MACE
Cuisset et al. (36)	↑ platelet reactivity (VerifyNow P2Y12 assay)	post-PCI myonecrosis
Wang et al. (37)	clopidogrel resistant patients	1 year post-PCI events
Gori et al. (38)	clopidogrel/ aspirin resistant patients	6 month DES thrombosis
Marcucci et al. (39)	↑ post-treatment platelet reactivity (VerifyNow P2Y12 assay)	12-month ischaemic event
Bonello et al. (40)	↑ P2Y ₁₂ reactivity ratio (VASP-P assay)	1 month ischaemic event
Bonello et al. (41)	↑ P2Y ₁₂ reactivity ratio (VASP-P assay)	early stent thrombosis
Valgimigli et al. (42)	clopidogrel/ aspirin resistant patients (VerifyNow assay)	post-PCI myonecrosis
Patti et al. (43)	↑ pre-PCI platelet reactivity (VerifyNow P2Y12 Assay)	1 month major cardiovascular event occurrence
Sibbing et al. (44)	↑ platelet P2Y ₁₂ reactivity (Multiplate Analyzer)	1 month definite stent thrombosis

sequently supported in the CLEAR PLATELETS-2 study where ~50% mean platelet aggregation in response to 5 µmol/l ADP was a threshold for the occurrence of periprocedural myocardial infarction (22, 24). In the PREPARE POST-STENTING study ~50% periprocedural platelet aggregation in response 20 µmol/l ADP (approximately the upper quartile) was independently associated with 6-month ischaemic event occurrence (20). In another study of patients treated with long-term dual antiplatelet therapy prior to non-emergent stenting, a threshold of ~40% periprocedural 5 µmol/l ADP-induced platelet aggregation was associated with 12-month ischaemic event occurrence (9).

Cuisset et al. demonstrated that 10 µmol/l ADP-induced platelet aggregation >70% was associated with an increased risk of recurrent ischaemic events in NSTEMI-ACS patients undergoing PCI (25). Similarly, in a study by Frere et al. 20 µmol/l ADP-induced platelet aggregation ≥70% and VASP-platelet reactivity index >53% were associated with 30 day recurrent ischaemic events (29). A cutpoint of ≥240 VerifyNow P2Y₁₂ reaction units has been associated with 12 month ischaemic events in patients with acute coronary artery syndromes (29). Finally, long-term post-PCI risk has been associated with high on-treatment platelet reactivity measured at discharge.

In a recent study of patients undergoing stenting, measurement of periprocedural platelet reactivity to ADP was associated with two years clinical outcomes. Using a ROC curve analysis, cutpoints of >46% aggregation following 5 µmol/l ADP stimulation and >59% aggregation following 20 µmol/l ADP stimulation, were associated with 58% and 54% of ischaemic events, respectively. High post-procedural platelet reactivity to ADP was independently associated with a nearly four-fold increased risk of ischaemic events within two years of non-emergent PCI (31). Using the multiplate analyzer, Sibbing et al. demonstrated that high on-treatment ADP-induced platelet reactivity was strongly

associated with the occurrence of 30-day stent thrombosis in 1608 patients undergoing PCI treated with a 600 mg clopidogrel loading dose before PCI. Moreover, a cutpoint of 468 based on ROC analysis was associated with the occurrence of stent thrombosis (44). All of these studies therefore may provide a target level of platelet reactivity for future investigations, similar to the INR (international normalized ratio) used for warfarin therapy.

Strategies to address high platelet reactivity

Personalized antiplatelet therapy

Higher clopidogrel loading doses have been associated with enhanced overall platelet inhibition and a lower prevalence of non-responsiveness. Bonello examined VASP-phosphorylation levels in patients prior to stenting and identified high risk patients using a cutoff platelet reactivity index (PRI) > 50%. In a randomized fashion half of the patients were repeatedly loaded with clopidogrel (up to a total of 2400 mg) in order to achieve a PRI below the cutpoint. The latter strategy was successful in bringing 86% of the patients below the cutpoint. None of the patients who were treated with personalized therapy had a 30 day post-discharge thrombotic event, whereas 10% of the patients in the group without dose escalation had events (40). The same group also demonstrated a similar personalized antiplatelet therapeutic strategy before PCI was associated with the reduced occurrence of stent thrombosis (41). Valgimigli et al. demonstrated that treatment with the GPIIb/IIIa inhibitor, tirofiban, in patients identified as non-responders by the VerifyNow Aspirin and/or P2Y₁₂ receptor assay during PCI, was associated with a significant decrease in periprocedural MI as compared to non-responders treated with placebo (42). The addition of the phosphodiesterase inhibitor cilostazol has also been studied to overcome low responsiveness to clopidogrel. Triple antiplatelet therapy with aspirin, clopidogrel and cilostazol was associated with reduced short-term as well as long-term clinical outcomes that was associated with greater platelet inhibition (54–56).

The antiplatelet effect of aspirin is dose independent when assessed by methods that di-

rectly indicate COX-1 activity. An 81 mg per day dose is sufficient to inhibit >95% of COX-1 activity in most subjects. However, it has been suggested that doses of more than 81 mg per day may be required to inhibit aspirin non-responsiveness as indicated by COX-1 non-specific assays. This may be particularly true for high risk patients where platelet aggregation induced by agonists that activate COX-1 non-specific pathways is enhanced. Moreover, in patients with diabetes, it was suggested that a P2Y₁₂ receptor blocker may be needed to overcome the high ADP-induced platelet aggregation associated with aspirin therapy alone (47). It was subsequently demonstrated in diabetic patients with coronary disease, the addition of 75 mg/d clopidogrel to 300 mg/d aspirin was associated with superior platelet inhibition as measured by ADP- and collagen-induced platelet aggregation compared to aspirin alone (57). These data suggest that high dose aspirin or the addition of a P2Y₁₂ receptor blocker are needed in selected patients and this strategy should be based on objective measurements of platelet function in the individual patients rather than the uniform usage of high dose aspirin or dual antiplatelet therapy. It should be noted that post-hoc analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) study indicated that high dose (=100 mg/d) aspirin was associated with an increased prevalence of bleeding events but no additional benefit in reducing ischaemic event occurrence (58). Finally, there are ongoing studies employing point-of-care testing to tailor antiplatelet therapy with clopidogrel.

In order to address whether dose adjustment based on objective platelet function measurements affects outcomes, the ongoing study GRAVITAS (Gauging Responsiveness with A VerifyNow assay – Impact on Thrombosis And Safety) is measuring platelet reactivity in 2800 patients with stable angina / ischaemia or non-ST-elevation acute coronary syndrome undergoing PCI with DES 12–24 hours post-PCI. Patients with high residual platelet reactivity on clopidogrel therapy 12 to 24 hours post-PCI will be randomized to standard maintenance clopidogrel therapy (75 mg/d) or high-dose clopidogrel therapy (additional loading dose followed by 150 mg/d) for six months. Randomly selected

patients without high residual reactivity will be followed and treated with a standard clopidogrel therapy for six months and evaluated for the primary end point of cardiovascular death, nonfatal myocardial infarction, or definite/probable stent thrombosis. Platelet function analyses will also be performed at 30 days and six months (59). The CURRENT-OASIS-7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent Events-organization to Assess Strategies in Ischemic Syndromes) study will examine the effect of 300 mg and 600 mg loading doses and the effect of a 150 mg maintenance dose compared to the standard maintenance dose in patients with acute coronary syndromes. In addition, a 2×2 factorial design will compare low and high dose aspirin. However, the above study will administer the same “one size fits all” prevalent in all of the major clinical trials of dual antiplatelet therapy. Therefore, an understanding of the relation of platelet reactivity to treatment failure (ischaemia and/or bleeding) will not be possible based on the results of the CURRENT trial (61).

New P2Y₁₂ receptor blockers

Prasugrel, a third generation thienopyridine, is a more potent P2Y₁₂ inhibitor associated with less response variability than clopidogrel. In the TRITON-TIMI 38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38) trial, prasugrel treatment was associated with a greater reduction in long-term ischaemic events in patients with acute coronary syndromes undergoing PCI as compared to clopidogrel. Although bleeding events were more pronounced during prasugrel therapy, selected patients benefited from treatment (60). Since a „one size fits all“ approach without the guidance of platelet function testing was also used in TRITON-TIMI 38, as in all previous large scale investigations of antiplatelet agents, it is impossible to determine whether insufficient blockade of P2Y₁₂ was the cause of treatment failure (~10%); and conversely, whether excessive blockade was the cause of bleeding. In the ongoing TRILOGY (TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medically manage Acute Coronary Syndromes) study,

platelet function testing using the Verify Now P2Y₁₂ assay will be performed in a large number of patients in order to better understand the relation between treatment effects of clopidogrel and prasugrel and the occurrence of ischaemic and bleeding events. In order to optimally determine the mechanism of treatment failure, it is mandatory that platelet function testing be implemented in future trials. Preclinical data suggest that there may be a wider therapeutic window associated with the use of a direct-acting reversible P2Y₁₂ inhibitor, ticagrelor as compared to clopidogrel. At doses associated with 90% inhibition of thrombosis in an animal model, there was significantly less bleeding with ticagrelor as compared to clopidogrel (62). The PLATO (Study of Platelet Inhibition and Patient Outcomes) trial has completed enrollment and compared ticagrelor to clopidogrel in ACS patients. The results of PLATO will determine whether the wider therapeutic window observed in the animal study translates to the clinical scenario.

Bleeding and the therapeutic window for P2Y₁₂ Inhibitors

In the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial, dual antiplatelet therapy was associated with a 38% increased relative risk of major bleeding compared to aspirin monotherapy (63). In the TRITON-TIMI 38 trial, prasugrel treatment was associated with a 32% and 52% increased relative risk of non-CABG related TIMI major and life-threatening bleeding, respectively (61). The discordance between lower ischaemic endpoints and higher bleeding rates in the prasugrel group compared to the clopidogrel group suggest that improved clinical efficacy by use of a more potent thienopyridine will be accompanied by reduced safety. A major goal is the identification of a therapeutic window for P2Y₁₂ receptor blockade. A large body of available data strongly suggest that post-stenting ischaemic events are associated with a P2Y₁₂ reactivity cutpoint. However, there is a very large gap in our understanding of the relation between P2Y₁₂ reactivity and bleeding.

Platelet function measurement in patients undergoing CABG

Both clopidogrel and aspirin are irreversible inhibitors associated with an increased risk of bleeding especially among high-risk patients. The latter is a major concern in patients on dual antiplatelet therapy requiring immediate CABG (Coronary Artery Bypass Surgery). Preoperative clopidogrel therapy was associated with a 30% relative increased risk of major bleeding demonstrated in the in CURE trial. Specifically, in the 2077 patients undergoing CABG there was a non-significant 2.1% absolute difference in major bleeding, which was confined to patients, who continued clopidogrel within five days before CABG (63). Based on the CURE Study observations, the current guidelines consider it is “*reasonable to discontinue thienopyridines five to seven days before cardiac procedures to limit blood loss and transfusion (IIa recommendation, level of evidence B)*”. Since approximately 8–30% of patients treated with clopidogrel treatment exhibit a limited or no antiplatelet response, these patients may be eligible for urgent CABG based on platelet function measurements. Moreover, variability exists in the recovery of platelet function following withdrawal of clopidogrel treatment. Serial preoperative measurements of platelet function may allow patients to under CABG earlier than five days without an increased risk of bleeding and thus decrease hospitalization time. The latter strategy is being tested in the ongoing TARGET CABG trial that employs thrombelastography to measure platelet function.

Conclusions

Since the antiplatelet response to aspirin and clopidogrel is variable, a “one-size-fits-all” approach to therapy has major limitations. Therefore, it is not surprising that uniform antiplatelet dosing strategies employed in large-scale studies have been associated with high treatment failure rates and excessive bleeding.

All of the current data support the measurement of on-treatment platelet reactivity as a major diagnostic strategy in patients treated with PCI.

Ongoing studies are modifying the “one-size-fits-all”, guideline-based therapeutic approach to an individualized-guided therapeutic approach based on objective platelet function analysis that may reveal a therapeutic threshold and window. If a therapeutic window can be demonstrated by these studies, then ischaemic as well as bleeding risks will be balanced by the adjustment of antiplatelet therapies to place the patient within the window. Platelet function measurements will also help physicians select patients for treatment with the new P2Y₁₂ inhibitors.

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