Current Concepts in the Clinical Utility of Platelet Reactivity Testing

Jean-Philippe Collet

*Professeur des Universités-Praticien Hospitalier, Paris, France***Abstract**

The pharmacodynamic effect of clopidogrel varies among individuals; approximately a third will have high on-treatment platelet reactivity (HTPR) to adenosine diphosphate and may benefit from more intensive antiplatelet therapy. Platelet reactivity testing has an important role in monitoring the therapeutic efficiency of clopidogrel and the safety of more potent drugs that confer an increased bleeding risk, because it provides a direct measure of the biological effect of these drugs. Numerous studies have demonstrated an association between HTPR and the risk of cardiac events in acute coronary syndrome (ACS) or after percutaneous coronary intervention (PCI). While the prognostic value of platelet reactivity testing following PCI has been demonstrated repeatedly in cohort studies and meta-analyses, randomised controlled studies investigating the clinical utility of the technique to guide treatment decisions failed to improve clinical outcomes of clopidogrel-treated patients undergoing stent implantation. Available data suggest that platelet function monitoring may be carried out in clopidogrel-treated patients with a higher risk of thrombotic events. These include patient risk factors such as body mass index (BMI), type 2 diabetes, and those prior unexpected ischemic events such as stent thrombosis, as well as procedural risk factors. As we move towards conclusively defining a therapeutic window associated with both cardiovascular (upper threshold) and bleeding risk (lower threshold) for antiplatelet agents, platelet reactivity testing will become a central tool in the practice of personalised strategies.

Keywords

Clopidogrel, platelet reactivity testing, percutaneous coronary intervention, VerifyNow®

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The role of platelets in coronary artery thrombosis is well-established.¹ They also play a critical role in a number of cardiovascular conditions including stroke, peripheral vascular disease and diabetes, and may be involved in the pathology underlying atherosclerotic changes.¹ Antiplatelet agents such as clopidogrel, a platelet P2Y₁₂ receptor antagonist, and aspirin are used for the prevention of thrombotic conditions in patients with acute coronary syndrome (ACS) or when undergoing percutaneous coronary intervention (PCI).² Dual antiplatelet therapy (DAPT), with the combination of aspirin (75–325 milligrams [mg] daily) and clopidogrel (75 mg daily after a loading dose of 300/600 mg) has become the widely accepted regimen for stent-placement procedures. Use of these drugs is widespread – clopidogrel is one of the largest selling drugs worldwide.³

However, despite antiplatelet therapy following PCI with stent implantation, 1–5 % of patients develop stent thrombosis (ST), a feared complication that results in myocardial infarction (MI) in 80 % and mortality in up to 40 % of cases.^{4,5} Individuals receiving clopidogrel exhibit a wide variability in platelet responsiveness, resulting from a variable level of P2Y₁₂ inhibition.^{6,7} A significant number (up to a third) of patients have no measurable effect of the medication, often referred to as having high on-treatment platelet activity (HTPR) to adenosine diphosphate (ADP).⁸ The presence of HTPR has been associated with

increased rates of adverse effects, including cardiovascular death, MI and ST in patients undergoing PCI.^{9–11} Although less common, low response to aspirin has also been observed and has been associated with adverse effects.^{12–14}

Alternative therapeutic options, such as prasugrel and ticagrelor, have been shown to be successful for ACS patients irrespective of HTPR status.^{15–18} These new therapeutic options have also demonstrated superiority to clopidogrel for the prevention of ischaemic events in patients undergoing PCI for ST-elevation MI (STEMI).¹⁹ However, these therapies may confer a higher risk of bleeding and are not available everywhere due to economic constraints. Another option is increasing the dose of clopidogrel; a randomised clinical trial found that a double-dose clopidogrel regimen is associated with a reduction in cardiovascular events and ST when PCI is performed, but also an elevated risk of major bleeding.²⁰ A 'one-size-fits-all approach' is therefore not appropriate in antiplatelet therapy and personalised strategies appear attractive, identifying those patients who would benefit most from therapeutic adjustment.

A subset of patients demonstrate low on-treatment platelet reactivity or a hyper-response to clopidogrel, which has been associated with an increased risk of haemorrhagic complications following coronary

stent placement²¹ and after neurointerventional procedures.²²⁻²⁴ There is a need for larger studies to define thresholds for clopidogrel hyper-response and examine the clinical effects of dose adjustments or treatment interruption in the setting of coronary artery bypass graft (CABG) surgery in particular.

Platelet reactivity testing enables the identification of patients with an inadequate response to antiplatelet agents who might benefit from a more intense antiplatelet regimen, as well as those exhibiting hyper-responsiveness. While large studies and registries have clearly defined a threshold for hypo-response,^{25,26} there remains a need to definitively define a threshold for hyper-response and the clinical effects of antiplatelet dosage adjustment. This article aims to discuss advances in platelet reactivity testing and to review clinical studies investigating their use.

Platelet Reactivity Testing

In addition to its role in disorders associated with platelet dysfunction,²⁷ platelet reactivity testing is a crucial component of the management of cardiovascular disease in order to identify patients at higher risk for poor clinical outcome related to their response to antiplatelet drugs. The measurement of platelet aggregation at baseline following administration of DAPT is subject to considerable variability, therefore on-treatment platelet reactivity is the preferred means of platelet reactivity testing.²⁸ However, it is a poorly standardised process. Several studies have shown large inter-laboratory variation in platelet reactivity testing practice.²⁹ Platelet reactivity has been historically measured with light transmittance aggregometry (LTA), but this method is technically complex, time-consuming, requires sample manipulation, and is subject to operator-induced error.³⁰ Point-of-care tests have been developed that are more practical and facilitate the clinical management of patients. The VerifyNow® P2Y₁₂ assay was designed to overcome the limitations of conventional optical platelet aggregation assays. It produces results in five minutes and requires no pipetting or sample preparation, reducing the risk of error.

The VerifyNow System (Accumetrics Inc, San Diego, CA, US) is a point-of-care assay that measures agonist-induced platelet aggregation by turbidimetric based optical detection, using a four-channel disposable cartridge (see Figure 1). In the channels, platelets are activated by the presence of agonists and bind to fibrinogen-coated beads, causing agglutinates to drop out of solution. The change in optical density is then measured.³¹ Results are reported as P2Y₁₂ reaction units (PRU), a BASE (base PRU) value, and a percentage of inhibition calculated from the BASE and PRU. A lower PRU value corresponds to a higher degree of P2Y₁₂ receptor inhibition and thus a decreased possibility of platelet activation and aggregation. Advantages of the VerifyNow system include simplicity, sensitivity, speed and user-friendliness.^{32,33} The VerifyNow assay correlates well with LTA and with other point-of-care assay devices,^{34,35} and has been validated in a head-to-head comparison of platelet function tests.³⁰

Clinical Studies Involving Platelet Reactivity Testing

Testing platelet reactivity following the administration of antiplatelet agents aims to determine how the drugs affect their biological targets, which is likened to the risk for secondary ischaemic/bleeding events. It is important to evaluate the levels of platelet reactivity that may correlate with thrombotic events and to create a clinically meaningful cut-off value of platelet reactivity. According to the VerifyNow package insert,

Figure 1: The VerifyNow® Assay

the highest combination of sensitivity and specificity for identifying a measurable effect of a P2Y₁₂ inhibitor is a PRU of 208.³⁶ To date, cut-off values have mainly been investigated in patients undergoing PCI. However, platelet reactivity testing has been employed in numerous clinical indications (see Table 1).

Peripheral Angioplasty Procedures

Clopidogrel resistance, defined as ≥ 235 PRU, significantly affected clinical outcomes after peripheral angioplasty procedures.^{37,38}

Coronary Artery Bypass Graft Surgery

A strategy based on pre-operative platelet reactivity testing to determine the timing of CABG surgery in clopidogrel-treated patients was associated with the same amount of bleeding observed in clopidogrel-naïve patients and 50 % shorter waiting time than recommended in the current guidelines.³⁹ These results led to an upgrade in the guidelines, to base timing of surgery on platelet function monitoring rather than the arbitrary use of a specified period of delay.⁴⁰

Neurovascular Applications

Clopidogrel resistance, defined using a PRU cut-off value of 235, was associated with increased periprocedural thromboembolic complications following neurovascular stenting.⁴¹ Flow diversion with the Pipeline™ Embolization Device (PED) is an important treatment option for cerebral aneurysm, but it is associated with the risk of thromboembolic complications. A study of pre-procedure platelet reactivity testing using VerifyNow found that a PRU value of <60 or >240 was the strongest

Table 1: Clinical Settings Where Platelet Reactivity Testing has Proven Beneficial

Setting	Significant Findings	Reference
Pipeline Embolization Device procedures (pre-operative use)	Pre-procedure PRU value of <60 or >240 was the strongest independent predictor of all and major peri-operative thromboembolic and haemorrhagic complications	23
Peripheral angioplasty procedures	PRU >235 was associated with significantly more repeat interventions after peripheral angioplasty procedures	38
Platelet responsiveness to clopidogrel treatment after peripheral endovascular procedures	PRU >234 was optimal for predicting clinical outcomes of peripheral angioplasty and stenting	37
Post-clopidogrel platelet response after PCI and drug-eluting stent implantation	PRU >235 was predictive of cardiovascular events	46
Coronary artery bypass graft surgery	A platelet function measurement-based strategy reduced bleeding and waiting time in clopidogrel-treated patients undergoing CABG	39
Coronary angiography	PRU ≥275 (Asian population) after administration of antiplatelet agents is related to silent embolic cerebral infarctions after coronary angiography	51
Neurovascular stenting	Clopidogrel resistance defined using a PRU cut-off value of >235 was associated with increased periprocedural thromboembolic complications	41
Aspirin resistance after PCI	Patients with aspirin resistance as measured by a point-of-care assay have an increased risk of myonecrosis following non-urgent PCI	12, 81

CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; PRU = P2Y₁₂ reaction units.

Figure 2: Failure Rate for Normal and High On-treatment Platelet Reactivity

Kaplan-Meier curve for probability of death, MI or ST by platelet reactivity. High on-treatment platelet reactivity (blue lines) was defined as PRU values ≥230 and normal (red lines) as PRU values <230. Dashed lines = 95 % confidence intervals for each group. MI = myocardial infarction; ST = stent thrombosis. Source: Brar, et al., 2011.¹⁰

independent predictor of all major peri-operative thromboembolic and haemorrhagic complications after PED procedures.²³ In defining optimal cut-off values, it is also important to distinguish between a cardiovascular and neurovascular patient – those with a history of stroke have a greater risk of haemorrhage on more potent antiplatelet therapy and may benefit from platelet reactivity within a more narrow window.⁴²

Percutaneous Coronary Intervention

The level of platelet function inhibition as measured by a point-of-care assay is an independent predictor for the risk of major adverse cardiac events after PCI.⁴³ A recent systematic review and meta-analysis concluded that initiating intensified antiplatelet therapy on the basis of platelet reactivity testing in patients after PCI is associated with a significant reduction in cardiovascular mortality, ST and MI (p<0.01 for all).⁴⁴

A study of patients with ACS assessed the cost-effectiveness of universal clopidogrel, ticagrelor or prasugrel (given to all patients) or PRA-driven ticagrelor or prasugrel (given to patients with a PRU of >230 on the VerifyNow assay; the remainder received clopidogrel). PRA-driven ticagrelor and prasugrel were found to be cost-effective over five years compared with universal clopidogrel (incremental cost-effectiveness ratio US\$40,100 and US\$49,143/quality-adjusted life-year, respectively); however, universal ticagrelor and prasugrel were not cost-effective (incremental cost-effectiveness ratio US\$61,651 and US\$96,261/quality-adjusted life-year, respectively).⁴⁵ Thus, platelet reactivity testing has the potential to decrease the healthcare costs associated with ACS.

Defining optimal cut-offs has proved challenging in clinical studies of antiplatelet therapy following PCI. A study assessed post-clopidogrel HTPR using VerifyNow following PCI with drug-eluting stent implantation and established a cut-off of ≥235 PRU.⁴⁶ Stratifying patients according to HTPR based on this threshold proved strongly predictive of cardiovascular events. A recent meta-analysis of clinical outcomes after PCI confirmed this finding and found that every 10-U increase in PRU was associated with a significantly higher rate of the primary endpoint (hazard ratio [HR] 1.04; 95 % confidence interval (CI) 1.03–1.06; p<0.0001). A PRU cut-off of 230 was the strongest predictor of death, MI or ST (p<0.001). A PRU value ≥230 was associated with a higher rate of a composite primary endpoint of death, MI or ST (HR 2.10; 95 % CI 1.62–2.73; p<0.0001), as well as the individual endpoints of death (HR 1.66; 95 % CI 1.04–2.68; p<0.04), MI (HR 2.04; 95 % CI 1.51–2.76; p<0.001) and ST (HR 3.11; 95 % CI 1.50–6.46; p<0.002) (see Figure 2).¹⁰

As mentioned previously, according to the VerifyNow package insert, the highest combination of sensitivity and specificity for identifying a measureable effect of a P2Y₁₂ inhibitor is a PRU of 208.³⁶ However, among clinical studies, a consensus has not yet been reached on optimal cut-off values. One small study of patients with stable angina suggested that a cut-off of ≤15 % inhibition or >213 PRU may be optimal for the identification of patients with HTPR.⁴⁷ Another study of patients with stable coronary artery disease (CAD) found that cut-off levels of 256 PRU and 26.5 % inhibition identified carriers of reduced-function cytochrome P450 2C19 (CYP2C19) allele on antiplatelet therapy, which is associated with a higher rate of clinical risk.^{48,49} As the prevalence of the CYP2C19 variant is higher in Asian population compared with the prevalence in Westerners, PRU ≥275 has predicted clinical events more accurately in this population.^{50,51} For low-risk patients, lower PRU values (180–210) have been used.^{18,52} However, the recommended cut-off of 208 was found to be significantly associated with the risk of ST at 30 days (HR 3.9, p=0.005) in the Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents (ADAPT-DES) registry study (n=8,583), which included a higher risk population (~50 % with ACS).²⁶ A recent study found that HTPR decreases from baseline to one month, a trend that is partly influenced by genotype. The study found that HTPR at one month was the strongest predictor of adverse outcomes.⁵³

While platelet activity appears to correlate with the risk of cardiovascular events and ST following PCI, studies investigating the use of platelet reactivity testing to guide treatment have had mixed results.^{18,44,54,55} The Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety (GRAVITAS) trial investigated a strategy based on high-dose clopidogrel in patients with HTPR (defined as ≥ 230 PRU).²⁵ However, this strategy of a fixed higher dose, regardless of the achieved level of platelet inhibition, did not reduce cardiovascular death, MI and ST after PCI compared with standard-dose clopidogrel.²⁵ However, a subsequent analysis of GRAVITAS data found that achievement of <208 PRU was significantly and independently associated with a markedly lower risk of cardiovascular events at 60 days (adjusted HR 0.23; 95 % CI, 0.05–0.98; $P=0.047$).⁵⁶ The lower cut-off may be due to the fact that this trial enrolled a relatively low-risk population. Consequently the trial showed low overall event rates. Furthermore, patients were randomised to single or double-dose clopidogrel rather than targeting to a specific inhibition level. Other studies have suggested that a triple dose may be needed in patients exhibiting variants in the CYP2C19 gene.⁵⁷

The Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI) trial, a randomised trial of prasugrel versus clopidogrel in patients with HTPR after PCI, was terminated early after a preliminary, blinded analysis indicated that the trial would not meet its primary endpoints. The rate of adverse ischaemic events was very low in the sample cohort, making it difficult to achieve statistical significance.⁵⁴ However, the study enrolment was biased towards very low risk populations – approximately 30 % of the study population did not go on to randomisation after it was established that they had HTPR on clopidogrel.

The Assessment by a double Randomization of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation one year after stenting (ARCTIC) trial randomised patients scheduled for coronary stenting to platelet function monitoring with the VerifyNow and adjusting antiplatelet therapy accordingly versus no monitoring and conventional clopidogrel therapy. HTPR was defined as ≥ 230 PRU or a percent inhibition <15 %. In the monitoring arm, serial platelet function tests (before stent implantation and during the maintenance phase) and treatment adjustments using a predefined treatment algorithm were performed. In addition to treatment intensification due to high on-treatment platelet reactivity, patients could be switched back from prasugrel to clopidogrel after PCI if low on-treatment platelet reactivity was measured. Despite halving the rate of high platelet reactivity to adenosine diphosphate, the primary endpoint of death, MI, ST, stroke or urgent revascularisation was similar after one year with the two strategies (HR 1.13, 95 % CI 0.98–1.29; $p=0.10$).⁵⁸ The risk level of the population, the cut-off value used to define HTPR, the heterogeneity in treatment adjustment (or lack of adjustment) in deemed non-responders, the rare use of prasugrel, which became available late after study initiation, and the lack of impact of treatment adjustment on other major determinants of platelet reactivity (such as treatment compliance) may account for the lack of benefit. However, ARCTIC is the only study that has evaluated by randomisation to the use of a platelet function test. It was appropriately powered to test the hypothesis of treatment monitoring. One-third of the randomised patients had an ACS, and one-year mortality was 2 %. Eight of 10 patients deemed non-responders were reloaded with clopidogrel and were given a glycoprotein IIb/IIIa inhibitor; 22 % of patients with

Table 2: Risk Factors for Future Thrombolytic Events in Patients Following Percutaneous Coronary Intervention

Risk Factor	Reference
Advanced age (>65 years)	82, 83
Diabetes	82–85
ACS at presentation	82
Previous MI	83, 86, 87
Unstable angina	85, 86
Adherence to antiplatelet medication	66
Diffuse disease	85, 87
Complex anatomy	82, 84, 85, 87, 88
Bifurcations	89
Vessel size	82, 84, 85, 87
Long lesions	84, 85, 87
Stent type	4, 90
Multiple stents	84–87
Concomitant medications	67, 68
Renal insufficiency	86
Current smoker	83, 84
Hypertension	86

ACS = acute coronary syndrome; MI = myocardial infarction.

high on-treatment platelet reactivity were on prasugrel at the end of the study. The rate of poor response was halved after treatment adjustment for both P2Y₁₂ inhibition and aspirin pathway, further highlighting an aggressive approach.

Perspectives

Personalised therapeutic strategies based on platelet reactivity testing have yet to improve clinical outcomes in low-risk groups, perhaps due to the already low event rates observed in this patient population. However, it has been hypothesized that the approach may be more beneficial in high-risk patient populations.^{8,54} In addition to responsiveness to antiplatelet medication, there are numerous risk factors for future cardiovascular (CV) events following PCI; these are summarised in *Table 2*. Risk factors for non-response to antiplatelet therapy include advanced age,⁵⁹ type 2 diabetes,⁶⁰ particularly if treated with insulin,⁶¹ overweight patients,⁶² genetic factors^{49,63–66} and concomitant medications, particularly proton pump inhibitors.^{67,68}

The Concept of a Therapeutic Window for Antiplatelet Therapy

The concept of a therapeutic window of P2Y₁₂ reactivity defining the upper threshold as HTPR associated with ischaemic events and a lower threshold based on bleeding risk has been suggested.²⁸ A study using the VerifyNow assay established a therapeutic window of 86–238 PRU at a one month time-point that minimised both ischaemic and bleeding events (see *Figure 3*). At the time of PCI, the suggested cut-offs were 95 PRU for hyper- and 214 for hypo-response.⁵³

There is a need to target high-risk patients groups to optimise the clinical utility of platelet reactivity testing. Recent American and European guidelines have included Class IIb recommendations for platelet reactivity testing in high-risk patients if the results may impact on patient management.^{69,70} Adjusting medication based on the results of platelet reactivity testing is already being carried out in some outpatient ST clinics and hundreds of US hospitals.⁷¹ It must be stressed that this approach has not been conclusively validated, though it is logical based on the desire to observe evidence of treatment success in patients treated with antiplatelet agents.

Figure 3: Adverse Events and Response to Platelet Reactivity Testing

Patients were stratified into groups of enhanced responders (PRU ≤85), normal responders (PRU 86-238) and poor responders (PRU ≥239). PRU = P2Y₁₂ reactivity unit. Source: Adapted from Campo, et al., 2011.⁵³

Figure 4: The ANTARCTIC Study

CV = cardiovascular; BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiovascular events; MI = myocardial infarction; PRU = P2Y₁₂ reaction units.

The ongoing Assessment of a Normal versus Tailored Dose of Prasugrel after Stenting in Patients Aged >75 Years to Reduce the Composite of Bleeding, Stent Thrombosis and Ischemic Complications (ANTARCTIC) study (ClinicalTrials.gov number: NCT01538446) will assess the value of platelet function testing in older ACS patients, a complex population whereby major bleeds are as frequent as ischaemic events (see Figure 4). An ongoing phase of the ARCTIC trial, ARCTIC-2, will aim to determine the most effective duration of treatment.

Switching Strategies

Prasugrel has been associated with lower platelet reactivity than clopidogrel,⁷² providing evidence to support the rationale for switching therapies. The PLATElet inhibition and patient Outcomes (PLATO) study found that ticagrelor improved outcomes but did not increase the risk of major bleeding compared with clopidogrel for patients with ACS for whom an early invasive strategy was planned.¹⁷ The platelet substudy of the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to

medically manage Acute Coronary Syndromes (TRILOGY ACS) trial found that among patients with ACS without ST-segment elevation who were not treated with revascularisation, prasugrel use was associated with lower platelet reactivity compared with clopidogrel, irrespective of age, weight and dose. However, no significant differences between prasugrel versus clopidogrel in the occurrence of the primary efficacy endpoint, a composite of cardiovascular death, MI or stroke, were found. There was a univariate association between platelet reactivity and ischaemic outcomes that lost significance in an extensive multivariate analysis after adjustment of several factors, including variables associated with on-treatment platelet reactivity.⁷³ Switching strategies have proved that switching from clopidogrel to prasugrel or ticagrelor results in decreased platelet function and is well-tolerated without any major safety events.⁷⁴ The Randomised, Double-Blind, Outpatient, Crossover Study of the Anti-platelet Effects of Ticagrelor Compared With Clopidogrel in Patients With Stable Coronary Artery Disease Previously Identified as Clopidogrel Non-responders or Responders (RESPOND) study found that treatment of clopidogrel non-responders with ticagrelor in a >10 %, >30 % and >50 %, decrease in platelet aggregation from baseline in 100 %, 75 % and 13 % of patients, respectively, and its antiplatelet activity was the same in responders and non-responders. Almost all clopidogrel non-responders and responders treated with ticagrelor had platelet reactivity below the cut-points associated with ischaemic risk.⁷⁵ The ADAPT-DES study demonstrated that patients with a detectable drug effect on clopidogrel (PRU <208) represent a lower risk cohort than do those with no effect, and as a result, the ischaemic benefit with the newer, more expensive P2Y₁₂ inhibitors will be smaller than that in patients without a detectable drug effect, but will potentially expose them to a greater bleeding risk.^{26,76}

Combining Platelet Reactivity Testing with Point-of-care Genetic Testing

The Spartan RX CYP2C19 assay is a point-of-care genetic test that identifies carriers of the CYP2C19 mutation. A prospective, randomised proof-of-concept trial found that the test was specific and sensitive for measuring the genotype, compared to sequencing, and could be performed at the bedside.⁷⁷ Several larger clinical trials are currently investigating this technique.⁷⁸⁻⁸⁰ Combining platelet reactivity testing with point-of-care genetic testing may provide a personalised approach to guiding treatment with antiplatelet therapies

Summary and Concluding Remarks

Platelet reactivity testing using VerifyNow has an important role in monitoring the therapeutic efficiency of clopidogrel and the safety of therapeutic escalation to more potent drugs that confer an increased bleeding risk. It has found to be predictive of clinical outcomes in numerous cardiovascular and neurovascular interventions where antiplatelet therapies are employed. However, further study is needed to fully assess its prognostic role. While the prognostic value of testing in PCI has been demonstrated repeatedly in cohort studies and meta-analyses, randomised controlled studies investigating the clinical utility of the technique to guide treatment decision have had mixed results. Reasons may include a lack of consensus on the optimal method to quantify high on-treatment platelet reactivity and the cut-off value associated with clinical risk. At present, it seems reasonable to assess platelet function in high-risk patient groups. A combination of platelet tests may be useful to further define a high-risk population, together with the assessment of demographic and genetic factors associated with high risk. Point-of-care genetic testing may also be

combined with platelet reactivity testing. Clinical trials using a combined genotyping and phenotyping approach are underway to better define the role of such tests in guiding antiplatelet therapy in clinical practice.

The advent of the stronger P2Y₁₂ inhibitors such as prasugrel and ticagrelor and their increased cost and bleeding risk compared with

clopidogrel, will necessitate the establishment of a therapeutic window to achieve optimal and cost-effective platelet inhibition while minimising bleeding risk.^{2,3} As we move towards conclusively defining a therapeutic window for antiplatelet agents, platelet reactivity testing will become a central tool in the practice of personalised antiplatelet strategies. ■

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