Review Article

High residual platelet reactivity on clopidogrel: its significance and therapeutic challenges overcoming clopidogrel resistance

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Abstract: Over the last decade, dual antiplatelet therapy has been the mainstay of the management of Acute Coronary Syndrome, with clopidogrel therapy providing clear benefits over aspirin monotherapy and becoming the agent of choice for the prevention of stent thrombosis. While newer antiplatelet agents have now become available, clopidogrel is still widely used due to its low cost and efficacy. However, many patients still experience recurrent ischemic events. A poor response of the platelets to clopidogrel, called High Residual Platelet Reactivity (HRPR), has been incriminated to account for this dilemma. Despite the absence of a universal definition of HRPR or the gold standard test to quantify it, persistent high platelet reactivity has consistently been associated with recurrence of ischemic events. Clopidogrel metabolism is highly variable, and genetics, comorbidities and drug interactions can affect it. In this article we review all definitions of HRPR, explore the available tests to quantify it, the clinical outcomes associated with it, as well as strategies that have shown success in overcoming it.

Key Words: Acute coronary syndrome; clopidogrel; platelet aggregation; platelet reactivity

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Dual antiplatelet therapy with aspirin and clopidogrel has been the cornerstone in the management of coronary artery disease in patients with Acute Coronary Syndrome (ACS) and those undergoing Percutaneous Coronary Intervention (PCI) (1-3) with clear benefits in the prevention of stent thrombosis following PCI (4). However, despite dual antiplatelet therapy, many patients continue to suffer recurrent ischemic events. This has been partly attributed to High residual platelet reactivity (HRPR) or high on-treatment platelet reactivity (HTPR). HRPR may be defined as the high level of platelet reactivity that is present hours after receiving a loading dose of an antiplatelet agent (5). In most prospective studies, resistance to clopidogrel has been the most extensively studied. The higher the residual platelet reactivity is the higher the risk of cardiovascular adverse events.

In this review we examine the clinical significance of HRPR or HTPR, the various tests commonly used to quantify it, the proposed strategies, as well as the novel therapeutic options for this clinical challenge.

Defininig clopidogrel resistance

Whereas clopidogrel resistance has been viewed as the occurrence of an adverse cardiovascular event while a patient is on clopidogrel therapy, the most acceptable definition of resistance/nonresponsiveness to an antiplatelet agent is the failure of the drug to inhibit its target of action (6). The objective criterion to verify resistance should therefore be based on a laboratory technique that can quantify the activity of the target receptor both before and after administration of the antiplatelet drug: the residual platelet reactivity. The association between high on-treatment platelet reactivity (HTPR) and future (periprocedural and long-term) ischemic risk has been strongly suggested in the literature, notwithstanding the

Table 1 Commonly used assays and their characteristics

	VASP-P	VerifyNow	LTA
Mechanism	Flow cytometric measurement of the phosphorylation of VASP, an intracellular marker of platelet reactivity	Turbidimetric measurement of platelet aggregation to fibrinogen-coated beads	A change in light transmittance, in response to platelet aggregation
Stimulus	ADP and PGE1	ADP and PGE1	ADP
Receptors involved	P2Y12	P2Y12	P2Y12 and P2Y1
Reported values	PRI	PRU	% MPA or %IPA
Cutoff by consensus (6)	50%	>235-240	46%

MPA = Maximal platelet aggregation; IPA = Inhibition of platelet aggregation

lack of an optimal method to define HTPR and risk stratify the patients. Furthermore, the exact timing of measurement of platelet reactivity is not established (6).

High Residual Platelet reactivity (HRPR) may be defined as the high level of platelet reactivity that is present hours after receiving a loading dose of an antiplatelet agent (5). In most prospective studies, clopidogrel has been most extensively studied; the higher the residual platelet reactivity the higher the risk of cardiovascular adverse events.

Available platelet functional assays

Several assays are now available and commonly used to assess platelet reactivity. The oldest and most established assay is the Light transmission aggregometry (LTA) assay, often valued as the gold standard. This assay evaluates the response of the platelet to ADP through the function of both P2Y1 and P2Y12 receptors. Most studies use doses of 5-, 10-, or 20-µmol/L ADP as agonist, which is translated into an increase of light transmittance, reported as a percentage of Maximal Platelet Aggregation (MPA). High residual platelet reactivity (HRPR) with clopidogrel treatment using this technique has been associated with recurrent ischemic events (6,7). LTA has been criticized however for its poor reproducibility and lack of specificity for the P2Y12 pathway.

The other assays which are now very widely used, and are relatively easier to perform, are vasodilator stimulated phosphoprotein phosphorylation (VASP) analysis and the VerifyNow P2Y12 bedside assay.

The Vasodilator stimulated phosphoprotein (VASP) phosphorylation assay uses flow cytometry to measure the specific inhibition of the biochemical target of clopidogrel via the P2Y12 receptor. In patients treated with P2Y12 inhibitors, the phosphorylated state of VASP is a specific intracellular marker of residual P2Y12 receptor reactivity. This assay has the advantage of specifically assessing the P2Y12 receptor activity. The results are reported as a percentage value of Platelet Reactivity Index (PRI) (8). The platelet reactivity index VASP has also been associated with recurrent ischemic events after PCI (6,7) while having a strong negative predictive power below a certain cutoff (9). Unlike the measured aggregation induced by ADP, in VASP, the measurement in this assay does not include the contribution of the P2Y1 receptor to the platelet response.

The VerifyNow platelet function assay (Accumetrics, San Diego, California), a turbidimetric assay, is a very practical bedside tool that measures platelet aggregation to fibrinogen-coated beads in whole blood in response to an ADP induced stimulus. Reported as values of P2Y12 reaction units (PRU), a higher PRU value reflects a higher P2Y12 mediated platelet reactivity. A high PRU is associated with adverse cardiovascular events (7,10).

Many other platelet function assays are available, but since the abovementioned assays are the most commonly used ones in research trials and clinical practice, we will limit ourselves to those. Other available assays are: Multiplate Analyzer, PFA-100, whole blood thromboelastography (TEG) (6).

However, there is no consensus yet regarding the "gold standard" test, capable of defining resistance/poor response to clopidogrel. Indeed, while PRI VASP is the most specific test to assess the clopidogrel induced activation of the platelets, most clinical studies linking low response to clopidogrel with clinical outcomes have been performed with LTA or Verify Now (7), though more and more clinical data using the PRI VASP are being published.

Given the lack of universal cutoff values, Bonello *et al.*, 2010, defined consensus values for HTPR, based on prior studies, for the most commonly used platelet function assays (6) (*Table 1*). HTPR values were defined by ROC analyses as follows: (I) PRI >50% by VASP-P analysis; (II) >

235 to 240 P2Y12 reaction units by VerifyNow P2Y12 assay; (III) >46% maximal for a 5-μmol/L ADP-induced aggregation; and (IV) >468 arbitrary aggregation units/min in response to ADP by Multiplate analyzer (6). While the authors argued against a routine use of those assays in any PCI patient, they reckoned its value in guiding personalized therapy for patients undergoing high-risk PCI or those with a known history of stent thrombosis.

They also argued that there may not be one universal cutoff value defining HTPR for each assay, considering that those values may have different weights in different settings, like urgent versus elective PCI, periprocedural setting versus maintenance treatment phase. Moreover, even though these cutoff values had very good negative predictive values for recurrence of ischemic events, their positive predictive value was low for all used assays. The study deemed that, although HTPR is a major risk factor for future thrombotic events, it is nonetheless not the only culprit responsible for these.

In a separate study, Breet *et al*. showed that most used platelet reactivity assays were only modest predictors of outcomes at 1 year follow up, advocating against routine use of platelet reactivity assays in the low-risk group of patients undergoing PCI (11,12).

Agreement among tests

Gaglia *et al*. attempted to evaluate the degree of agreement and correlation among VASP-P, LTA and VerifyNow in patients on clopidogrel therapy undergoing PCI (8). The objective was to assess platelet reactivity between 6 to 24 hours following PCI and a minimum of six hours after a loading dose of clopidogrel.

Threshold values for HPR were used according to the latest consensus recommendations (6). There were considerable differences in the proportion of patients defined as having HTPR, as follows: 39.3% with VASP, 27.3% with VerifyNow, 23.1% with LTA ADP 5 μM, and 16.2% with LTA ADP 20 μM. The weakest correlation was noted between VASP and LTA ADP 5 μM (κ=0.33, 95% CI: 0.19-0.47). It was concluded that there was at best only a fair degree of agreement between those tests and that 'platelet reactivity' is not an interchangeable term to be used among the different assays used, even when abiding with "consensus" guidelines for cutoff values for each assay. Previous studies also had yielded similar observations, however with more disparate conclusions.

Nevertheless, even though agreement among these tests may be modest, it still remains that each one of the above-mentioned tests has shown, in separate studies, a significant correlation with occurrence of adverse cardiovascular outcomes beyond a certain cutoff value adopted by consensus. Therefore any of those tests can be used reliably to prognosticate about risk stratification of patients undergoing PCI.

Clopidogrel metabolism and influencing factors

Clopidogrel is an inactive pro-drug that requires oxidation by the hepatic cytochrome P450 (CYP) system in order to become the active metabolite. It has been observed that platelet inhibition response to clopidogrel is highly heritable (73%). Two sequential cytochrome P450-dependent oxidative steps are required to convert clopidogrel to its active metabolite. The first step leads to the formation of 2-oxo-clopidogrel. This metabolite is then metabolized to the active metabolite (6). This accounts for 15% of the drug metabolism. The remaining 85% is metabolized in the blood by esterases into an inactive metabolite and therefore does not contribute to drug effect. Cytochrome P450s enzymes are a large highly polymorphic family of mono-oxygenases. Some of the alleles coding for those enzymes have been reported to modify the concentration of some metabolites as well as the activity of some proteins, thereby modifying potential drug effect.

Of relevance, loss-of-function variants in the hepatic cytochrome 2C19 (CYP2C19) system have been reported to significantly alter the metabolism of clopidogrel and therefore its drug effect. While some alleles (like *17) would lead to an increased response to clopidogrel with increased bleeding risk, others, and most notoriously the *2 allele is related with a poorer response to clopidogrel. Others alleles, as well as combinations of mutated alleles with *2 deletion have been incriminated as well. However, genetically speaking, the highest risk profile group corresponds to those who are homozygous for allele *2 (13). Other studies have nevertheless identified heterozygous status as a significant risk (13-16). Being carrier of a loss-of-function allele is translated by a higher residual platelet reactivity, which in turn is associated with adverse outcomes, namely death, myocardial infarction and stent thrombosis as seen in the AFIJI study (15) and confirmed in a recent metanalysis (17). Nevertheless, despite the significant role of hereditary component for the clopidogrel responsiveness, only 18% of it explained by identified genetic mutations (6), suggesting that response to clopidogrel is the result of a very intricate

genetic interplay.

Beside the genetic component, a controversial aspect is the drug-drug interaction at the level of the CYP3A4 enzyme activity, which is involved in the metabolism of clopidogrel into its active metabolite. This has been postulated mainly for statins metabolized by this enzyme, such atorvastatin and simvastatin (18,19). Nevertheless this has not confirmed by other studies (20,21). Similar risks have been identified about the concomitant use of proton pump inhibitors and clopidogrel (22). More so, there is also a variable intestinal absorption process, which could be affected by an *ABCB1* gene polymorphism (7). As will be stated later in this review, some co morbid conditions are also associated with a poor platelet inhibition in response to clopidogrel, like Diabetes Mellitus, high BMI, and low ejection fraction (23-25). Among those, high BMI has been identified as an independent predictor of failure to overcome HTPR, even with clopidogrel dose adjustment (26).

Furthermore, platelet reactivity is not similar across all presentations of CAD, as we will see the studies reported in the review. A potential significant variable would be patient compliance to daily medication intake.

Does HRPR have any clinical significance?

Stent thrombosis (Table 2)

It was noted that that patients experiencing subacute stent thrombosis have significantly higher platelet reactivity (27). Muller *et al*. reported in a cohort of 105 patients undergoing PCI that patients having stent thrombosis are more likely to be non-responders to clopidogrel (28), which was also noted by Cuisset *et al*. using two different assays (31). Analysis of the CREST study established HTPR and incomplete P2Y12 receptor inhibition as risk factors for subacute stent thrombosis (29). In 2007, it was observed that in patients undergoing PCI with DES placement, HRPR following a 600 mg loading dose of clopidogrel was associated with an increased risk of stent thrombosis at 6 months following PCI (32). Therefore, having a HRPR following a loading dose of clopidogrel is associated with a higher incidence of stent thrombosis.

Recurrence of events (Table 2)

Matetzky *et al*. established that in patients with STEMI undergoing PCI, the higher the platelet aggregation (PA)as assessed by LTA (in the catheterization laboratory and then for 5 days following PCI), the higher the risk of sustaining a recurrent ischemic episode within 6 months (33), which was also confirmed by Gurbel *et al*. (34). This finding was extended to the NSTE-ACS population thanks to Cuisset *et al*., who demonstrated that in a cohort of 106 patients at 1 month follow up, patients within the highest PA quartile exhibited the highest rate of ischemic events (35). This trend is seen as early as the first few hours after PCI, with a higher incidence of periprocedural myocardial infarction (MI) among NSTE-ACS patients who demonstrate HRPR (41). The same conclusion has been drawn with patients undergoing angioplasty on elective basis, with those exhibiting HRPR on chronic clopidogrel therapy having a higher recurrence of events at 1 year (36).

A more recent study, the ARMYDA-PRO study (Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome), evaluated the use of point-of-care measurements of platelet inhibition in predicting clinical outcome in patients undergoing PCI, in a short-term follow-up (38). All patients had either received a 600 mg loading dose of clopidogrel or were on chronic clopidogrel therapy and all were maintained on aspirin and clopidogrel throughout the study. At 30-day follow up, those belonging to the highest quartile of platelet reactivity within the first 24 hours following PCI exhibited the highest rates of major adverse cardiac events (MACE) as defined by cardiac death, myocardial infarction (MI), target vessel revascularization. This difference was mainly driven by the risk of periprocedural MIs. The authors supported the use of a rapid point-of-care assay to monitor residual platelet reactivity after clopidogrel administration, which would identify the patients at a higher risk for MACE and potentiate the use of alternative antiplatelet regimen .A higher prevalence of MACE among patients with HRPR is also seen at 30-day follow up even after elective PCI (39).

These findings also hold true for the long term, with Price *et al*. noting that in patients with ACS undergoing PCI and DES placement, a HRPR following 600 mg loading-dose of clopidogrel was associated with a greater risk of cardiovascular death and stent thrombosis during a 6 months follow up (40). The higher risk incurred by HRPR also reflects on outcomes at 12 months follow up, with HRPR being predictive of MACE, as shown by Marcucci *et al*. (10).

In the RECLOSE 2-ACS study, Parodi *et al*. offered to study the role of HRPR as an independent prognostic indicator for occurrence of long term thrombotic events) (37). Prior big trials [like the GRAVITAS (Gauging Responsiveness with A VerifyNow assay — Impact on Thrombosis and

Safety) study, to be discussed later] had not included the "sicker" population like those with NSTEMI and STEMI. Most studies only had short term follow up for clinical outcomes on patients with HRPR following PCI. The study included 1789 ACS patients, including all types of presentations ranging from unstable angina to STEMI. All patients were given 600 mg clopidogrel loading dose and 325 mg of aspirin upon presentation and maintained on daily doses of aspirin (325 mg/d) and clopidogrel (75 mg/d). However patients with HRPR were placed on 150-300 mg daily doses of clopidogrel or ticlodipine (500-1,000 mg/d) and supervised by ADP guidance, with a goal of reaching a reactivity value of less than 70% platelet aggregation measured by LTA. Platelet reactivity was assessed 12-18 hours after loading with clopidogrel, or 6 days later if patients were loaded with both clopidogrel and a IIB/IIIa inhibitor. The primary endpoint was a composite of cardiac death, myocardial infarction and urgent coronary revascularization, as well as stroke at two-year follow up. Follow up examinations throughout the study period showed that the primary endpoint occurred in 14.6% of HRPR group patients versus 8.7% of LRPR group, with an absolute risk reduction of 5.9% (95%CI: 1.6%-11.1%, P=0.003). The leading difference was concerning the rate of cardiac death (9.7% *vs*. 4.3%), while other components of the primary endpoint were similar between the 2 groups.

HRPR was associated with older age, previous history of MI, diabetes mellitus, hypercholesterolemia and low ejection fraction as well as congestive heart failure. That had also been established by the RECLOSE 1 study by Buonamici *et al*. in 2007 (31). Of note, both studies had higher proportion of STEMI in the low residual platelet reactivity group.

The RECLOSE 2-ACS study showed that while only 14% of patients undergoing PCI for ACS will have HRPR following a 600 mg clopidogrel loading dose, 38% of HRPR patients will still have HRPR even after adjusting antiplatelet therapy to HRPR status. Interestingly, it confirmed a previous finding seen with GRAVITAS that normalization/decrease of platelet reactivity after treatment is not translated into a better clinical outcome (41). The study confirmed that HRPR following 600 mg loading dose of clopidogrel as an independent prognostic marker of short and long-term ischemic events and is associated with increased risk ischemic events, both in the short and the long term, including stent thrombosis.

Caution is nonetheless in order as lower reactivity following a loading dose of clopidogrel has been associated with up to 4.5 fold increased risk in the 30-day incidence of major bleed (42). Patti *et al*. observed that this primary end point happened more frequently in patients within the lowest quartile of preprocedural PRU levels as compared to those in the highest quartile (10.1% *vs*. 1.3%, P=0.043), mainly due to entry-site hemorrhages. The optimal cutoff for the primary end point was a pre-PCI PRU value <189. Therefore, an enhanced response to clopidogrel may lead to with higher incidence of early major bleeding or entry-site complications in patients who undergo PCI.

High residual platelet reactivity and atherosclerotic burden and calcification

In a recent study, the correlation between high platelet reactivity (HPR) and its potential burden of atherosclerotic disease was investigated (44). Patients undergoing PCI according to guidelines (excluding STEMI) underwent pre-intervention volumetric intravascular ultrasound (IVUS) imaging, the gold standard modality to assess plaque atherosclerosis burden and calcification. Patients with HPR (>230 PRU) 16 hours following PCI and a first loading dose of clopidogrel had significantly greater calcification lengths, calcification arcs, and calcium indexes. Moreover, they had longer lesions and volumetric dimensions. Nonetheless plaque burden did not differ in the two groups. However after adjusting for univariate parameters, HRPR was found to be an independent predictor of the plaque findings. The study concluded that HPR is associated with a higher atherosclerotic burden and plaque calcification.

Different strategies to overcome high platelet reactivity

Is there a clinical benefit in double-dosing?

The CURRENT-OASIS 7 had ascertained that in patients with ACS following PCI, double-dose clopidogrel for at least the first 7 days was superior to standard-dose clopidogrel in reducing the incidence of a composite of cardiovascular death, myocardial infarction, or stroke and stent thrombosis at 1 month follow up (45). Moreover, a higher loading-dose of clopidogrel (600 *vs*. 300 mg) had been shown to achieve greater reduction in platelet reactivity in NSTE-ACS patient undergoing PCI (46). Nevertheless it was still unknown whether double-dosing clopidogrel maintenance therapy would have a clinical benefit in patients found to have HTPR.

The GRAVITAS randomized trial attempted to study

Table 2 HRPR on clopidogrel and clinical outcomes

Study	Platelet function assay	Cut-off	Outcome studied	Results
Barragan *et al*. (27)	VASP-P	>50%; comparing HTPR between treatment groups	Subacute stent thrombosis (SAT)	Patients with SAT are more likely to have HRPR
Muller *et al*. (28)	Optical aggregometry (using ADP 5 and 20 μmol/L)	IPA <10%	SAT	HRPR is associated with stent thrombosis
Gurbel *et al*. (30)	LTA and VASP-P	>75th percentile ADP-induced aggregation (ADP-Ag) in the group without SAT	SAT	Patients with SAT have higher mean platelet reactivity; 60% has HPR
Sibbing *et al*. (43)	Multiple electrode platelet aggregometry (MEA)	Highest quintile of MEA measurements	ST at 30 days	HRPR is a strong predictor of ST at 30 days
Cuisset *et al*. (29)	ADP-induced Platelet aggregation (PA) and VASP-P	PA >67%	Acute or subacute ST	Patients with ST are more likely to have HRPR than those with no ST
Buonamici *et al*. (31)	LTA	PA ≥70%	Stent thrombosis at 6 months	Patients with HRPR have a much higher incidence of stent thrombosis
Matetzky *et al*. (32)	Turbidimetric PA using ADP	Highest quartile of ADP-Ag	Recurrence of cardiovascular event at 6 months	Patients in the first quartile had the highest rate of events
Gurbel *et al*. (33)	LTA	Highest quartile of PA	Recurrence of ischemic events over 6 months	Patients within highest quartile had highest event rates
Cuisset *et al*. (34)	LTA	Highest quartile of ADP-Ag	Adverse CV events at 1 month follow up	Highest CV event rates in the first quartile
Bliden *et al*. (36)	LTA and TEG	≥50% ADP-Ag by LTA and ≥70% by TEG	Occurrence of MACE at 1 year follow up	Patients with MACE exhibited higher ADP-Ag
Parodi *et al*. (40)	LTA	≥70% ADP-Ag	Occurrence of MACE at 2 years follow up	Higher rates of cardiac death in patients with HRPR
Patti *et al*. (37)	VerifyNow	PRU ≥240	Occurrence of MACE at 30 days follow up	Higher occurrence of MACE, essentially periprocedural MI, within highest quartile
Hochholzer *et al*. (38)	Optical aggregometry	Quartiles of ADP-Ag	Occurrence of MACE at 30 days follow up	Highest occurrence of MACE in first 2 quartiles
Price *et al*. (39)	VerifyNow	PRU ≥235	Occurrence of MACE at 6 months follow up	HRPR associated with higher MACE rate at 6 months
Marcucci *et al*. (10)	VerifyNow	PRU ≥240	CV death, nonfatal MI, and target-vessel revascularization at 12 months follow up	HRPR associated with higher rates of CV death and nonfatal MI

the effect of high-dose clopidogrel versus standard-dose clopidogrel on platelet reactivity (41). This multicenter double blind trial enrolled 2,214 patients with stable CAD or non-ST-elevation ACS and HTPR 12 to 24 hours after undergoing PCI with drug-eluting stents. The VerifyNow assay, with a cutoff PRU≥230 was used to identify high platelet reactivity. Patients with HTPR were given high-dose platelet (600 mg loading dose and 150 mg daily doses) versus a placebo loading dose and then 75 mg daily. 586 patients were also selected form a cohort of 3,215 patients with no HTPR and were followed throughout the study. These were administered a standard daily dose of clopidogrel. Meanwhile all patients concomitantly received Aspirin doses ranging from 75 to 162 mg daily. Follow up visits and VerifyNow assay were subsequently performed at 30 days and 6 months.

The primary endpoint was the 6-month incidence of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis. There was a significantly higher reduction in on-treatment reactivity at 30 days and at 6 months with high dose clopidogrel than with standard-dose clopidogrel (80 PRU *vs*. 37 PRU with P<0.0001 and 85 PRU *vs*. 44 PRU; P<0.001, respectively). There was no difference in the rate of discontinuation of study drug due to GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) severe or moderate bleeding across all 3 groups. High-dose clopidogrel led to an absolute 22% (95% CI: 18-26% and 24%, 95%CI: 20-28%) lower rate of HTPR compared with standard-dose clopidogrel at 30 days and 6 months. However this was not translated into a benefit in the primary endpoint at 6 month follow up with similar occurrence rates [2.3% *vs*. 2.3%; hazard ratio (HR), 1.01; 95% CI: 0.58-1.76; P=0.97].The primary endpoint occurred more frequently in patients with HTPR as opposed to those without (586 patients), although this did not reach statistical significance [25 (2.3%) *vs*. 8 (1.4%); HR, 1.68; 95% CI: 0.76-3.72; P=0.20].In other words, the study reconfirmed the association between HTPR and adverse cardiovascular events. Important limitations of the study were the fact that the study did not observe a high enough number of events to reach its targeted power of detecting 50% relative risk reduction following the study intervention. To note, the study population excluded the highest risk patients, namely those with NSTEMI and STEMI. This could potentially limit the use of this data for the abovementioned higher risk populations. Lastly, the baseline characteristics (and comorbidities) of patients with HTPR and no HTPR differed greatly, and the analysis was not adjusted for these differences.

The GRAVITAS study showed that despite significantly reducing platelet reactivity, therapy with high-dose clopidogrel following a loading dose in patients with HTPR is not translated into a reduction of primary endpoint at 6 months follow up.

Tailored clopidogrel loading?

Bonello *et al*. hypothesized that controlling residual platelet reactivity via tailored clopidogrel loading-doses would decrease the incidence of stent thrombosis (47). In a multicenter study, 429 patients with poor clopidogrel response after a 600-mg loading dose undergoing PCI (VASP index ≥50%) were randomized to a control group [214] and to a vasodilator- stimulated phosphoprotein (VASP)-guided group [215]. In the VASP-guided group, patients received up to 3 additional 600-mg loading doses of clopidogrel in order to achieve a VASP index <50% before PCI. The primary end point was the rate of stent thrombosis at 1 month. The secondary end points were the rates of major adverse cardiovascular events (MACE) and bleeding. There was a significantly lower rate of stent thrombosis at 1 month in the VASP-guided group (0.5% *vs*. 4.2%, P<0.01). The rate of MACE was also higher in the control group (8.9% *vs*. 0.5%, P<0.001). The rate of bleeding was similar in both groups. Of relevance, even after a 2,400-mg loading dose of clopidogrel, 8% of patients in the VASP-guided remained resistant to clopidogrel. The authors concluded that tailoring the clopidogrel loading doses according to platelet reactivity monitoring decreases the rate of early stent thrombosis after PCI without increasing bleeding.

In a similar study (48), Bonello *et al*. demonstrated that 86% of patients with clopidogrel resistance achieve a target VASP index <50% after receiving additional boluses of clopidogrel and demonstrate a lower rate of MACE occurrence at 1 month follow up, with similar rates of bleeding.

In view of the current evidence, it is safe to say that this strategy reduces the rate of major cardiac events and stent thrombosis in the short term without increasing the risk of bleeding, pending further studies to prove its sustained benefit in the long term.

Furthermore Bonello *et al*. (49) demonstrated that increasing loading doses of clopidogrel in NSTE-ACS patients with CY2C19*2 loss-of-function polymorphism,

could achieve a reduction of platelet reactivity to 50% PRI. In contrast, Cuisset *et al*. showed that only a small portion of carriers of the CYP2C19*2 allele would show a significant reduction of HRPR even with 600 mg loading-doses and 150 mg daily doses (50).

Therefore it is safe to conclude that at present no consensus exists as to the impact of platelet function assays on predicting outcome with perhaps some impact on stent thrombosis.

A newer thienopyridine: prasugrel

With growing evidence concerning the limitations of clopidogrel therapy and clinically severe outcomes with recurrence of ischemic insults, researchers have focused their attention on developing new agents that would achieve a faster and higher degree of platelet inhibition.

One of those agents is prasugrel, a third generation thienopyridine agent. It is a prodrug that requires conversion to an active metabolite which will bind to the P2Y12 receptor and inhibit platelet activity. At currently used doses, prasugrel inhibits ADP – induced platelet aggregation more rapidly, more consistently, and has a higher potency when compared to both standard and higher doses of clopidogrel among healthy volunteers as well as patients with stable CAD (51,52). Moreover, a 60mg loading dose of prasugrel achieves higher and more consistent levels of the active metabolite than those achieved with a 300 mg loading dose of clopidogrel (51). Pharmacodynamics show that the degree of inhibition of platelet aggregation achieved with prasugrel within 30 minutes after treatment is comparable to the peak effect of clopidogrel 6 hours after administration (51), thus bypassing the need of prolonged pretreatment before PCI to achieve a clinical benefit.

The PRINCIPLE-TIMI 44 trial proved the greater degree of inhibition of platelet aggregation achieved by prasugrel (60 mg loading dose followed by 10 mg daily) as compared to high-dose clopidogrel (600 mg loading dose then 150 mg daily) (53). The study populations were patients presenting with angina within the last 14 days and planned for PCI. This effect was seen as early as 30 minutes after administration of the drug, and was sustained during the maintenance dose, as ascertained by LTA platelet assay, and confirmed by VerifyNow and VASP-P assays. The authors concluded that prasugrel, as compared to high-dose clopidogrel, achieves an earlier, greater and sustained platelet inhibition. Nevertheless the study was not powered to study clinical outcomes.

Overcoming the barriers of genotype

With the known limitations of clopidogrel among CYP2C19*2 carriers (50), the RAPID GENE study (54) explored the effect of prasugrel therapy (versus standard clopidogrel therapy) on HRPR following PCI for ACS (excluding STEMI patients) or stable angina. The patients were randomly assigned to rapid point-of-care genotyping or to standard treatment. People in the rapid genotyping group underwent screening for the *CYP2C19*2* allele via a novel point-of-care genetic test for the *CYP2C19*2* allele with a buccal swab. Those found to be carriers were started on 10mg prasugrel daily, while non-carriers as well as patients in the standard treatment group were placed on 75 mg clopidogrel daily. All patients received 600 mg of clopidogrel at least 24 hours before PCI. All patients were tested for a baseline platelet reactivity immediately after PCI and had not significantly different PRU values at baseline, with CYP2C19*2 carriers having higher PRU compared to non-carriers.

The primary endpoint was the proportion of *CYP2C19*2* carriers with HTPR (with a (PRU) value >234 using the VerifyNow assay), after 1 week of dual antiplatelet treatment, assuming that stabilization of platelet inhibition by clopidogrel and prasugrel is achieved by that time. There was a significant decrease in the rate of HTPR in *CYP2C19*2* carriers in the rapid genotype testing group compared to those receiving standard treatment. The authors concluded that rapid genetic testing followed by a personalized treatment reduces the number of *CYP2C19*2* carriers patients undergoing PCI who would still have HTPR. They added that the use of this kind of test can identify a population at increased risk of adverse ischemic events and overcome it via the use of prasugrel. However, a major limitation of the study was that a decrease of platelet reactivity was used as the surrogate for clinical benefit, assuming that HTPR is equivalent to increased risk of MACE.

Clinical superiority of prasugrel

The first trial to assess the clinical outcomes of prasugrel was the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 (55). 13,608 patients presenting with

moderate- to-high- risk ACS syndromes for scheduled PCI were randomly assigned to receive prasugrel (a loading dose of 60 mg and then 10 mg/day as maintenance dose) or clopidogrel (300 mg loading dose, followed by 75 mg/day) for a period of 6 to 15 months. All patients concomitantly received aspirin throughout the study.

The results of the study showed a significant difference in the occurrence of the primary end point (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke over the next 15 months) with 9.9% in the prasugrel group versus 12.1% in the clopidogrel group, and a hazard ratio for prasugrel *vs*. clopidogrel of 0.81 (95% CI: 0.73 to 0.90; P<0.001). Similarly, there was a significant reduction in the rate of myocardial infarction with 9.7% for clopidogrel *vs*. 7.4% for prasugrel (P<0.001), urgent target-vessel revascularization (3.7% *vs*. 2.5%; P<0.001), as well as stent thrombosis (2.4% *vs*. 1.1%; P<0.001). Nevertheless, there was a higher propensity for major bleed in the prasugrel group, with an incidence of 2.4% of patients on prasugrel *vs*. 1.8% of patients receiving clopidogrel (hazard ratio, 1.32; 95% CI: 1.03 to 1.68; P=0.03). Moreover, the rate of life-threatening bleeding was also higher (1.4% *vs*. 0.9%; P=0.01), as well as nonfatal bleeding (1.1% *vs*. 0.9%; hazard ratio, 1.25; P=0.23) and fatal bleeding (0.4% *vs*. 0.1%; P=0.002).

While the rapid onset of action with prasugrel may explain the reduction in the rate of early MI (before day 3) observed in this trial, this significant reduction in the rate of endpoints persisted even after 3 days (assuming both drugs would have achieved peak effect), proving the continued benefit and superiority of prasugrel over clopidogrel during maintenance therapy. The estimated number needed to treat to prevent one primary endpoint with prasugrel at the studied dosage, compared with standard-dose clopidogrel, during a 15-month period was 46 patients. On the other hand, the number needed to harm, as defined by non-CABG-related TIMI major hemorrhage was 167 patients. The authors concluded that prasugrel does reduce the rate of recurrence of ischemic events in patients with ACS undergoing scheduled PCI, however at the expense of an increase in the incidence of major bleeding. Hence, contraindications for the use of prasugrel are: age older than 75 years old, weight less than 60 kg (with a recommended decreased dose of 5 mg, though no efficacy is proven), history of TIA or stroke or pathologic active bleed (56).

However, even though prasugrel achieves greater platelet inhibition and is superior to clopidogrel in preventing ischemic events, resistant platelet reactivity while on prasugrel therapy still remains a cause of concern. It was found that in patients undergoing PCI in the setting of ACS who receive prasugrel, 25.2% would still maintain HTPR (as defined VASP index >50%) after 60 mg loading dose (57). It was also found that these patients have higher incidence of MACE during the first month.

In a small study including 80 patients, Lhermusier *et al*. studied the usefulness of prasugrel reloading in ACS patients planned for PCI who had already received a 300 mg loading dose of clopidogrel (58). Various doses of prasugrel loading were used (10, 30, 60 mg) at least 3 hours after the clopidogrel dose. The assays used were VASP-P with cutoff PRI >60% and VerifyNow with a cutoff PRU>235). Although nearly all patients achieved the desired inhibition, 30 mg was the most adequate reloading dose in achieving the desired platelet inhibition with an efficacy sustained for 12-18 hours. Although no major TIMI bleed was seen in the 3 groups, the study did not assess any clinical outcomes or safety parameters.

Switching from prasugrel to clopidogrel remains a valid option for ACS patients even during the maintenance clopidogrel therapy. The SWAP (Switching Antiplatelet) study demonstrated further degree of platelet inhibition achieved once patients are switched to prasugrel, with or without a loading dose of prasugrel (59). This benefit was observed as early as 2 hours after a loading dose of prasugrel.

Ticagrelor: a step further?

Ticagrelor, also known as AZD6140, is a novel oral P2Y12 receptor antagonist that reversibly binds to the P2Y12 receptor, thus preventing the binding of ADP. This new drug does not require metabolic activation, in order to exert its effect. Among patients with stable CAD, ticagrelor showed a greater degree of platelet inhibition compared to clopidogrel (60,61). The inhibitory effect of 180 mg loading dose of ticagrelor is superior to that achieved by 600 mg clopidogrel. More so, its inhibitory effect weans faster than with clopidogrel (61).

These findings were extended to the NSTE-ACS population with the DISPERSE (Dose confirmation Study assessing anti-Platelet Effects of AZD6140 *vs*. clopidogrel in non-ST-segment Elevation myocardial infarction)-2 study (62). The study compared different doses of AZD6140 (90 and 180 mg twice daily) with clopidogrel in patients with presenting with NSTE-ACS. It showed that ticagrelor exerts a greater platelet inhibitory effect

compared to clopidogrel in ACS patients. This finding was noted both during maintenance therapy and in the early hours of treatment.

The Study of Platelet Inhibition and Patient Outcomes (PLATO), compared ticagrelor (with a 180 mg loading dose, then 90 mg twice daily) and clopidogrel (300-to-600-mg loading dose, then 75 mg daily) among 18,624 patients admitted to the hospital with an ACS, including STEMI, for the prevention of cardiovascular events in this population (63). Problems encountered with ticagrelor are dose-related (i.e. more with 180 than 90 mg) and consist of episodes of dyspnea and ventricular pauses on Holter monitoring. All patients also received daily aspirin for the study period. The occurrence of the primary end point (time to occurrence of a composite of death from vascular causes, myocardial infarction, or stroke) was significantly less in the ticagrelor group than in the clopidogrel group (9.8% of patients *vs.* 11.7% at 12 months follow up; HR of 0.84; 95% CI: 0.77 to 0.92; P<0.001). The difference in treatment effect was noticeable from the first 30 days of treatment and sustained till the end of the study period. Similar reductions were seen with the ticagrelor group in regards to the rates of the composite end point of death from any cause, MI, or stroke (10.2% *vs.* 12.3%, P<0.001) as well as in the rate of death from any cause with ticagrelor as well (4.5%, *vs.* 5.9%; P<0.001).

The rate of stroke was comparable in both treatment groups, although more hemorrhagic strokes occurred with ticagrelor than with clopidogrel [23 (0.2%) *vs.* 13 (0.1%), nominal P=0.10]. Among patients who underwent invasive treatment, the rate of the primary end point was also lower with ticagrelor (8.9% *vs.* 10.6%; P=0.003).There was a lower incidence of definite stent thrombosis in the ticagrelor group than in the clopidogrel group (1.3% *vs.* 1.9%, P=0.009).

The rates of major bleeding were not significantly different between ticagrelor and clopidogrel groups whether using the criteria defined in the trial (P=0.43) or the Thrombolysis in Myocardial Infarction (TIMI) criteria (P=0.57). Neither was there a difference in fatal or life-threatening bleeding (5.8% in both groups, P=0.70). However, in the ticagrelor group, there was a higher rate of non-CABG-related major bleeding according to the study criteria (4.5% *vs.* 3.8%, P=0.03) and the TIMI criteria (2.8% *vs.* 2.2%, P=0.03).Moreover, the ticagrelor group had a higher incidence of intracranial bleeding [26 (0.3%) *vs.* 14 (0.2%), P=0.06], including fatal intracranial bleeding [11 (0.1%) *vs.* 1 (0.01%), P=0.02]. However, there were fewer episodes of other types of fatal bleeding in the ticagrelor group [9 (0.1%), *vs.* 21 (0.3%) in the clopidogrel group; P=0.03]. Notable side effects of ticagrelor during the study were dyspnea and asymptomatic ventricular pauses in the first week. Of note, ticagrelor use also had a higher incidence of creatinine and uric acid increase.

A significant advantage which ticagrelor possesses as opposed to thienopyridines is that its action is reversible, which may be a very significant parameter for control of bleeding.

The PLATO study shows us that in patients ACS with or without ST-segment elevation, treatment with ticagrelor, compared to clopidogrel, significantly reduces the rate of death from vascular causes, MI, or stroke, without increasing the overall rate of major bleeding with a sustained benefit throughout the study period (360 days), nevertheless with an increase in the rate of non–procedure-related bleeding.

A PLATO substudy by Storey *et al*. (64) showed that ticagrelor achieves a greater inhibitory response than clopidogrel with the mean maximum LTA responses (using ADP 20 μM) post maintenance dose of 44±15% for clopidogrel and 28±10% for ticagrelor (P<0.001). High platelet reactivity was seen more frequently with clopidogrel than ticagrelor following a loading dose and during the maintenance therapy. The conclusion was that in patients with ACS ticagrelor achieves greater platelet inhibition, starting in the early hours following loading, with a sustained effect throughout maintenance phase.

Ticagrelor versus prasugrel

Most recently, Alexopoulos *et al*. proposed to compare the antiplatelet effects of ticagrelor and prasugrel in patients with high on-clopidogrel platelet reactivity 24 hours following PCI (65). 44 patients with HTPR, PRU ≥235, were randomized to either 10mg daily dose of prasugrel or 90 mg twice daily of ticagrelor. After 15 days of treatment, a crossover was performed from each treatment group to the other. The primary endpoint was platelet reactivity assessed at 2 different times (the first was pre-crossover, the second was post-crossover).

The results were heavily in favor of ticagrelor as far the primary endpoint was concerned. At the end of the 2 treatment periods PR was lower with ticagrelor (32.9 PRU, 95% CI: 18.7 to 47.2) compared with prasugrel (101.3 PRU, 95% CI: 86.8 to 115.7) with a mean difference in least squares of –68.3 PRU (95% CI: –88.6 to –48.1; P<0.001).

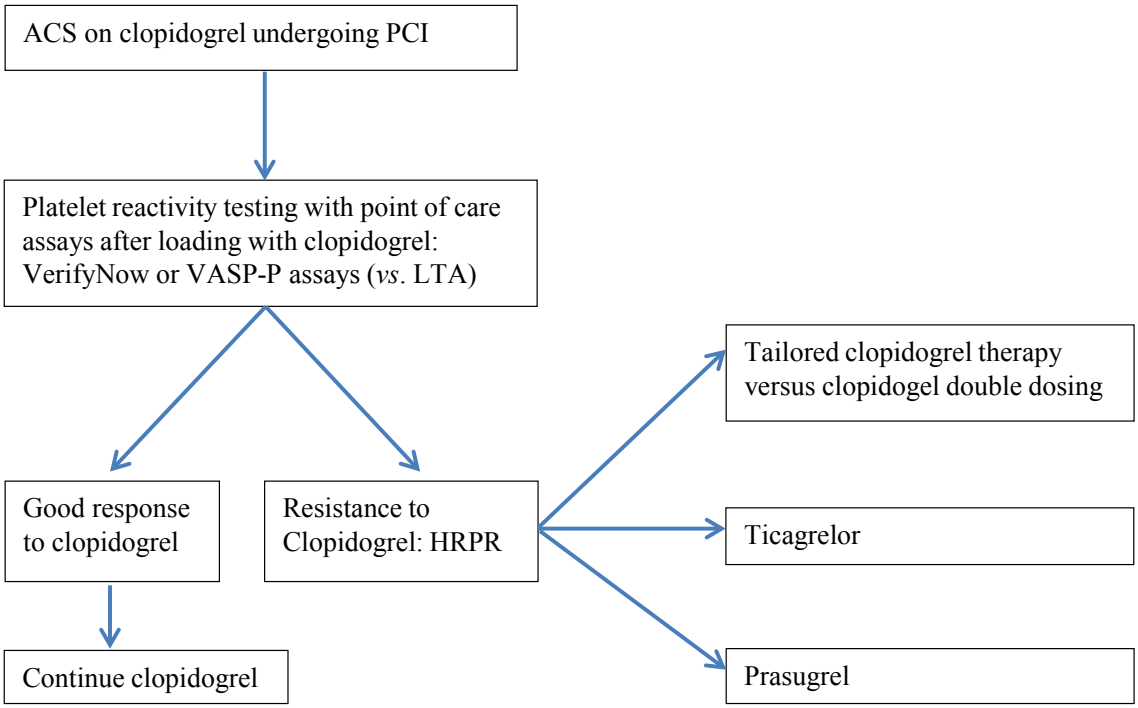

Figure 1 Conceptual algorithm for the use of platelet function assays and different therapeutic options

The secondary endpoint, which was the rate of HTPR, was found to be 0% for ticagrelor versus 2.4% for prasugrel (1 of 42, P=0.5).

No patients had any MACE in either study group during the study period, and no TIMI major bleed was observed in either group. The study was not powered to assess the association between the primary endpoint and clinical outcomes. The study shows that ticagrelor achieves a significantly greater platelet inhibition as compared to prasugrel in ACS patients with HTPR 24 hours post PCI while on clopidogrel undergoing PCI. It also shows that patients on prasugrel can directly be switched to clopidogrel and vice versa (65).

Modifying HTPR with adjunctive antiplatelet therapy

The impact of adjuvant antiplatelet or anticoagulant on patients with HRPR following clopidogrel loading dose in the PCI setting was studied. The ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-4) study looked at the efficacy of abciximab plus unfractionated heparin versus bivalirudin in NSTEMI patients undergoing urgent PCI who had HPR following a loading-dose of clopidogrel (66). The study showed no difference in the rate of occurrence of the primary combined efficacy endpoint (death, any recurrent MI, urgent target-vessel revascularization) during a 30-day follow-up period. Nevertheless, bivalirudin showed a significantly reduced risk of major bleeding.

In the ISAR- REACT4 substudy, Sibbing *et al.* showed that for patients having received abciximab with Heparin, there was no difference in the incidence of the efficacy endpoint in HPR versus no-HPR patients (9.4% *vs.* 6.7%; OR: 1.4; 95% CI: 0.6 to 3.5; P=0.43) (67). However, for bivalirudin, there was a significantly higher incidence of the efficacy endpoint in HPR versus no-HPR patients (22.0% *vs.* 5.0%; odds ratio: 5.4; 95% CI: 2.4 to 12.1; P<0.0001). They concluded that the impact that HPR has on clinical outcomes may be determined by the type of adjunctive antithrombotic therapy that was used during PCI.

Conclusions (*Figure 1*)

While platelet reactivity is not routinely tested in ACS patients undergoing PCI, HRPR to clopidogrel is a clinical conundrum for interventional cardiologists. Despite the fact that higher doses of clopidogrel have shown some benefit in that regard, the choice of alternative agents may be the preferred practice. Recent guidelines have

upgraded prasugrel and ticagrelor as superior alternatives to clopidogrel in STEMI (68) as well as in Unstable Angina/NSTEMI (69).Weighing the risk of bleeding is clearly required under these circumstances. At present, prasugrel use only applies to patients undergoing PCI, while the twice daily dosing with ticagrelor raises an issue of patient compliance. In addition, these drugs are a more expensive and less available option in many countries. Nevertheless, these two potent antiplatelets provide a breakthrough against the poor response to clopidogrel and may soon replace clopidogrel in routine clinical practice.

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