Sticky Platelets

Using platelet reactivity testing to guide antiplatelet therapy after PCI.

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Dual-antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the cornerstone of medical therapy for percutaneous coronary intervention (PCI) and acute coronary syndromes (ACS). By inhibiting platelet aggregation, DAPT reduces ischemic cardiac complications after PCI, but also the risk of bleeding.[1] An optimal level of platelet inhibition is needed to achieve maximal ischemic protection. However, the precise level of inhibition is not well understood.

At the same time, there is significant interpatient variability in antiplatelet response to aspirin and clopidogrel, the most common medications composing a DAPT regimen. As such, there has been a surge in the development of laboratory tests to identify individuals who respond poorly. Poor antiplatelet response, or high on-treatment platelet reactivity (HTPR), has been associated with worse ischemic outcomes following PCI.[1] Recently, several point-of-care assays have become available to measure on-treatment platelet reactivity, but large clinical trials have not yet shown a clear benefit. In this article, we review platelet reactivity testing and its potential role in guiding DAPT after PCI.

ANTIPLATELET AGENTS IN ACS/PCI: BENEFITS AND COMMON SHORTCOMINGS

Clopidogrel is a widely used antiplatelet agent for patients with cardiovascular disease. It carries a class I indication for emergent and elective stenting.[2,3] The use of clopidogrel and aspirin has shown to reduce ischemic events, including myocardial infarction (MI) and stent thrombosis (ST), after PCI.[1,4] Discontinuation of clopidogrel, as a component of DAPT, is a major contributor to the development of ST. Other risk factors for ST include the thrombogenic nature of stents, hypercoagulability, lesion anatomy, and procedure-related factors, including suboptimal stent deployment and unrecognized stent-edge dissections.[5,6] Some cases of ST have been linked to the variability in the effectiveness of clopidogrel.[7,8] There are dramatic interpatient differences in clopidogrel pharmacokinetics leading to variations in efficacy.

Clopidogrel requires a two-step hepatic bioactivation to its active thiol metabolite, which irreversibly binds to the platelet $P2Y_{12}$ receptor, thus inhibiting platelet activation and subsequent aggregation. Bioactivation of clopidogrel involves a two-step oxidative process carried out predominantly by the cytochrome P450 2C19 (CYP2C19) enzyme.[9] Reduced or absent CYP2C19 activity, secondary to genetic polymorphisms, results in decreased exposure to the active metabolite, which, in turn, diminishes clopidogrel's effectiveness, resulting in HTPR and increased risk of ST and ischemic events.[10] HTPR is broadly defined as the failure of an antiplatelet agent to inhibit its site of action or inhibit platelet activity. HTPR can be identified by assessing on-treatment platelet reactivity by various assays, each of which has different validated cutoff values (Table 1).[11]

Given that a significant proportion of patients exhibit HTPR to clopidogrel, it has been recommended to switch to an alternative thienopyridine. Prasugrel, like clopidogrel, is a thienopyridine, irreversible $P2Y_{12}$ antagonist; however, it undergoes a much more efficient bioactivation process that is not as highly dependent on CYP2C19. This results in faster and more potent platelet blockade that is not subject to variation by CYP2C19 polymorphisms.[23,24]

Ticagrelor is another recently approved $P2Y_{12}$ agent, which is a nonthienopyridine and reversibly binds the $P2Y_{12}$ receptor. It does not require hepatic bioactivation, and it exhibits fast and potent antiplatelet activity that does not vary by CYP2C19 genotype.[25] There are several other factors that contribute to HTPR to clopidogrel, which may subsequently impact clinical outcome (Table 1).

CAUSES OF HTPR TO CLOPIDOGREL

CYP2C19 Genotype

As discussed earlier, genetic variations in CYP2C19 can significantly affect an individual's response to clopido-

TABLE 1. VARIABILITY AMONG DEFINITIONS OF HTPR FROM PUBLISHED CLINICAL TRIALS

Antiplatelet Reactivity Assay	Study Reference	Definitions of HTPR (units)
LTA	Gurbel et al[12]	> 75% post-PCI aggregation to 20 uL ADP
	Gurbel et al[13]	> 50% post-PCI aggregation to 5 uL ADP
	Bliden et al[14]	
	Lev et al[15]	Baseline minus posttreatment aggregation ≤ 10% in response to 5 and 20 uL ADP
	Breet et al[16]	LTA+20 uL ADP > 64.5% aggregation
	Cuisset et al[17]	LTA+10 uL ADP > 70% aggregation
Flow cytometry using VASP	Cuisset et al[18]	> 50% VASP-PRI
	Blindt et al[19]	> 48% VASP-PRI
VerifyNow	Price et al[20]	> 230 PRU
	Trenk et al[21]	> 208 PRU
	Patti et al[22]	> 240 PRU
	Cuisset at al[18]	
	Breet et al[16]	> 236 PRU
PFA-100	Breet et al[16]	≥ 116
Plateletworks	Breet et al[16]	80.5%

Abbreviations: ADP, adenosine diphosphate; HTPR, high on-treatment platelet reactivity; LTA, light-transmittance aggregometry; PCI, percutaneous coronary intervention; PRI, platelet reactivity index; PRU, $P2Y_{12}$ reaction units; VASP, vasodilator-stimulated phosphoprotein.

grel and, potentially, their risk of ST (Figure 1).[10,26] The patient's CYP2C19 genotype confers one of four phenotypes: rapid, extensive, intermediate, or poor metabolizer. There is an inverse relationship between the rapidity of metabolism and the risk of ST after PCI.[26] For instance, those homozygous for CYP2C19*2 are at a substantially increased risk for ST, while the gain of function provided by CYP2C19*17 places the patient at a lower risk for ST post-PCI, but potentially an increased risk of bleeding.[26,27]

Drug Interactions

CYP2C19 inhibitors can reduce the antiplatelet activity of clopidogrel. Omeprazole, a commonly prescribed proton pump inhibitor, reduces clopidogrel's active metabolite generation and antiplatelet activity.[28] Several observational studies have linked omeprazole use with an increase in ischemic outcomes in clopidogrel-treated patients; however, a recent randomized trial did not demonstrate a clinically significant interaction between omeprazole and clopidogrel. They also found a significant reduction in gastrointestinal-related bleeding with omeprazole use in the setting of DAPT.[29] However, no definite conclusions can be made from this study because it was prematurely terminated. It was terminated for having a smaller number of gastrointestinal bleeds than anticipated, which limited its power. Pantoprazole, on the other hand, does not decrease the antiplatelet effect of clopidogrel.[28] Thus, the use of proton pump inhibitors after PCI depends on the risks and benefits of therapy on an individual basis, and a preference for pantoprazole is prudent.[2,30]

Calcium channel blockers (CCBs) are also metabolized through the CYP450 enzyme pathway. In the past, there was a concern for an increased risk of ST with concomitant administration of CCBs and clopidogrel, but more recent studies have shown that there is no clinically significant interaction between CCBs and clopidogrel.[31,32]

Comorbidities

Common comorbidities found in patients with coronary artery disease, such as diabetes mellitus, chronic renal failure, and obesity, are also linked to HTPR.[33] Resistance to standard clopidogrel therapy is more prevalent in diabetic patients than in those who are not diabetic.[34] Insulin normally interacts with human platelets to decrease platelet reactivity, but due to peripheral resistance to insulin in diabetics, platelets in

TABLE 2. COMPARISON OF THE MAIN PLATELET REACTIVITY ASSAYS

	Test	Method	Complexity of Sample Preparation by Specially Trained Personnel	Factors Confounding Measurements	Turn Around Time	FDA Approved	Approximate Cost per Assay
Laboratory testing	LTA	Measures low-shear, platelet-to-platelet aggregation in response to agonists	Complex	Age, sex, race, hematocrit	6 hours	Yes	$1,000
	Flow cytometry	Uses whole-blood samples to measure platelet glycoproteins and activation markers by light-emitting fluorescence and detects platelet activation in vivo or in response to agonists	Complex	None	4 hours	No	$400
	Flow cytometry using VASP	Used to monitor $P2Y_{12}$ platelet receptor inhibition	Complex	None	2 hours	No	$400
Point-of-care testing	VerifyNow	Fully automated platelet aggregometer that measures platelet reactivity by measuring the agglutination of fibrinogen-coated beads by platelets stimulated by an agonist in citrated whole blood	Easy	Use of GP IIb/IIIa inhibitors and phosphodiesterase inhibitors	1 hour	Yes	$22
	PFA-100	Measures high-shear platelet adhesion and aggregation	Easy	Patients with platelet disorders, platelet count, and hematocrit	1 hour	Yes	$154
	Platelet-works	Measures the change in the patient's platelet count secondary to aggregation of the functional platelets in the patient's whole blood sample	Easy	None	1 hour	Yes	$15.83

TABLE 3. COMPARISON OF THE MAJOR TRIALS USING PLATELET REACTIVITY TESTING TO GUIDE MANAGEMENT

	GRAVITAS (Gauging Responsiveness With a VerifyNow $P2Y_{12}$ Assay: Impact on Thrombosis and Safety) Trial	TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) Study	ARCTIC (the Double Randomization of a Monitoring-Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and an Interruption Versus Continuation of Double Antiplatelet Therapy, One Year After Stenting) Study
Objective	To compare the efficacy and safety of treating patients with high HTPR with double-dose clopidogrel compared with standard dose after PCI	To investigate the efficacy, safety, and antiplatelet effect of prasugrel as compared with clopidogrel in patients with HTPR after elective PCI	1. To demonstrate any clinical benefit to dose adjustment of aspirin and clopidogrel based on platelet reactivity testing when compared to a conventional strategy in patients scheduled for drug-eluting stent implantation and followed up for 1 year 2. To demonstrate the superiority of a strategy of pursuit of a DAPT beyond 1 year as compared to a strategy of interruption of DAPT over a period of at least 6 additional months of follow-up
Study type	Randomized controlled trial	Randomized controlled trial	Prospective double randomized trial
Population (n)	HTPR postelective PCI with DES (2,214)	Stable CAD postelective PCI with DES (212)	Stable angina/ischemia or non–ST-elevation acute coronary syndrome undergoing PCI with DES (2,466)
Platelet reactivity test	VerifyNow; HPR defined as ≥ 230 PRU	VerifyNow; HPR defined as > 208 PRU	VerifyNow; PRU value > 235 and/or a % inhibition < 15%.
Treatment	High-dose clopidogrel (600-mg initial dose, 150 mg daily thereafter) or standard-dose clopidogrel (no additional loading dose, 75 mg daily)	Prasugrel 10 mg daily or clopidogrel 75 mg daily	Adjustments to antiplatelet therapy was done based on a set algorithm for those with HTPR to clopidogrel or No platelet function testing and given standard treatment per the physician's discretion and current guidelines
Follow-up period	6 months	6 months	Hypothesis 1: 12 months Hypothesis 2: 6 additional months
Primary end points	Cardiac death, MI, ST	Cardiac death, MI	Death, MI, stroke, urgent coronary revascularization, ST
Primary safety point	Bleeding	Bleeding	Bleeding
Conclusion	There was a reduction in platelet reactivity at 30 days. There was no reduction in the incidence of cardiac death, nonfatal MI, or ST. There was no increased incidence of bleeding.	Given the low rate of adverse ischemic events after PCI with contemporary DES in stable CAD, they could not demonstrate a benefit of switching patients with stable CAD after elective PCI to prasugrel.	There were no significant improvements in clinical outcomes with platelet-function monitoring and treatment adjustment for coronary stenting, as compared with standard antiplatelet therapy without platelet function monitoring.

Abbreviations: CAD, coronary artery disease; CO, clinical outcome; DES, drug-eluting stent; HPR, high platelet reactivity; HTPR, high-treatment platelet reactivity; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRU, $P2Y_{12}$ reaction units; ST, stent thrombosis.

diabetics remain highly reactive, despite the presence of clopidogrel.[34] Additionally, there is increased risk for adverse outcomes post-PCI in diabetics independent of glycemic control or inflammatory status.[34]

Observational data suggest an association between chronic renal failure and increased risk of ST after PCI. This may be related to increased platelet turnover, poor drug absorption, and a prothrombotic state secondary to increased release of adenosine diphosphate (ADP).[35] Moreover, several observational studies have demonstrated a higher incidence of accelerated atherosclerosis and ST in patients with chronic renal failure compared to those with normal renal function.[35,36]

There are also observational studies linking obesity to HTPR to clopidogrel and treatment failure. However, other similarly designed studies have shown no association between body mass index and on-treatment platelet reactivity.[37] There is also no agreement on whether clopidogrel dosage should be adjusted for body weight.[37]

ASSOCIATION BETWEEN HTPR AND OUTCOMES AFTER PCI

The association of HTPR and ischemic events after PCI has been studied extensively. In the Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation trial (EXCELSIOR), patients were tested for platelet reactivity after the loading dose of 600 mg of clopidogrel before PCI and tested once again after the first maintenance dose of 75 mg of clopidogrel. Those with HTPR, defined as residual platelet reactivity > 14% with 5 mmol/L of ADP, were found to have three times the increased risk of death or MI compared with those with low residual platelet reactivity at 1-year follow-up post-PCI. There was also a 3.7-fold increase of ST at 1 year after PCI.[8]

In the Responsiveness to Clopidogrel and Stent Thrombosis 2–ACS (RECLOSE 2–ACS) study, patients were deemed to have HPTR or low residual platelet reactivity according to platelet reactivity testing by the use of ADP after the loading dose of 600 mg of clopidogrel prior to PCI. Based on the platelet reactivity results, patients entered one of three treatment groups: (1) received standard treatment, (2) increased daily doses (250–300 mg) of clopidogrel, and (3) switched to ticlopidine. RECLOSE 2-ACS demonstrated that HTPR was associated with an increase in the primary endpoint of MI, cardiac death, urgent coronary intervention, and stroke.[7]

On the contrary, a recent platelet function substudy of the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary

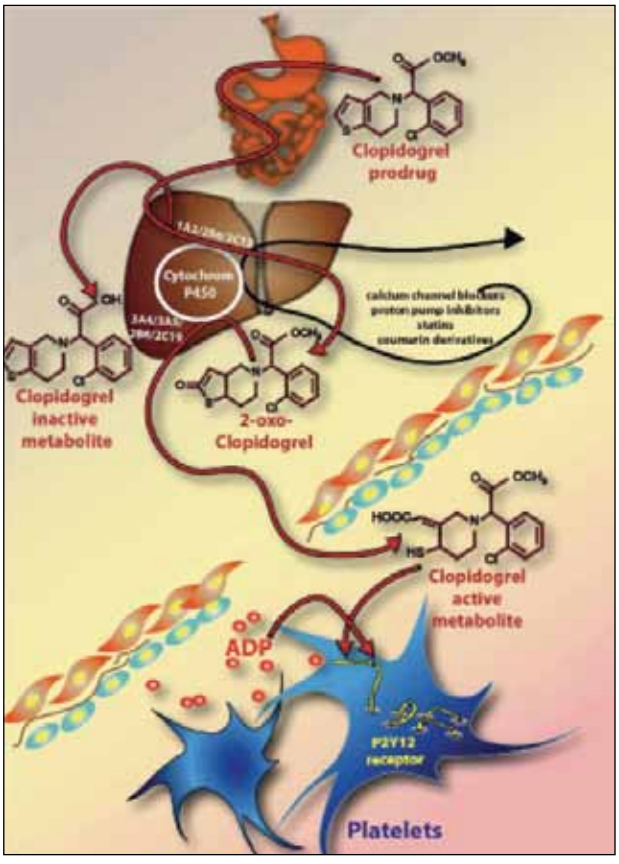

Figure 1. The metabolism of clopidogrel. Adapted with permission from Tentzeris I, Siller-Matula J, Farhan S, et al. Platelet function variability and non-genetic causes. Thromb Haemost. 2011;105 (Suppl 1): S60–S66.[33]

Syndromes (TRILOGY-ACS) trial found no association between platelet reactivity and ischemic events in clopidogrel-treated ACS patients who were medically managed.[38] The main results of TRILOGY-ACS, which randomly assigned medically managed ACS patients to standard-dose clopidogrel or prasugrel, found no differences in clinical outcomes between treatment groups. These new data suggest that $P2Y_{12}$ blockade and platelet function testing may be more important in higher-risk ACS- and PCI-treated patients while being less important in lower-risk, medically managed ACS patients.

In summary, HTPR is associated with increased adverse cardiac outcomes, especially ST, in PCI-treated patients. The new data from the TRILOGY-ACS platelet substudy cast a cloud of doubt of its utility in non-PCI ACS patients. However, clinical applicability of these individual studies is limited due to the various methods used to measure platelet reactivity, as well as the variable thresholds used to define HTPR.

LABORATORY TESTING OF PLATELET REACTIVITY

Two major protocols have been used and studied extensively: light transmittance aggregometry (LTA) and vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay by standard flow cytometry.[39] LTA involves the use of an aggregometer that measures the ability of various platelet agonists to induce in vitro platelet aggregation. Aggregates absorb less light, increasing light transmission, which is detected by a photocell (Figure 2). LTA is the gold standard test, but several drawbacks to its use remain.[40] Studies have evaluated both the maximal amplitude of measured platelet aggregation in response to ADP and late (final or residual) aggregation measured approximately 5 minutes after the addition of an agonist. There is no consensus on whether measuring the maximum or late response to clopidogrel is a more accurate representation of resistance. LTA is also costly, time consuming, and labor intensive, making it a less ideal test to monitor the effects of antiplatelet therapy in a wider clinical setting.

The VASP phosphorylation assay monitors platelet responsiveness by tagging the phosphorylated form of the intraplatelet actin regulatory protein that is activated in response to platelet $P2Y_{12}$ receptor.[39] $P2Y_{12}$ receptor is inhibited by clopidogrel, and therefore in cases where clopidogrel is ineffective, there is a loss of inhibition. Increased aggregation is observed, with consequent increase in the platelet reactivity index. Similar to LTA, VASP phosphorylation assay is labor intensive, time consuming, and requires special training and expensive equipment, making it less routinely available.

POINT-OF-CARE TESTING OF PLATELET REACTIVITY

Due to the weakness of the laboratory testing methods, more practical approaches have emerged. Point-of-care assays, such as the platelet function analyzer PFA-100 System (Siemens Healthcare Diagnostics Inc, Tarrytown, NY), Plateletworks (Helena Laboratories, Beaumont, TX), and VerifyNow (Accumetrics, Inc., San Diego, CA) have been used in major trials, and the results of these assays have been shown to be well correlated with ADP-induced platelet aggregation by LTA and VASP phosphorylation assays (Figure 2).[41]

The platelet function analyzer PFA-100 is an impedance aggregometer, which utilizes collagen/ADP-based cartridges and measures shear-induced platelet aggregation.[41] The Plateletworks assay measures the change in the patient's platelet count secondary to aggregation of the functional platelets in the patient's whole blood sample, simultaneously measuring both platelet count and platelet aggregation at the patient's bedside.[41] VerifyNow measures changes in light transmission as a result of aggregation using whole blood samples in a system containing fibrinogen-coated beads.

EVIDENCE VALIDATING THE USE OF POINT-OF-CARE TESTS

Several studies aimed to determine whether HTPR, as measured by point-of-care platelet function assays, is also associated with ST post-PCI. A large, prospective, single-center study of 1,069 patients evaluated the capabilities of eight different platelet reactivity tests to predict a composite of death, MI, ST, and stroke at 1 year in patients taking clopidogrel and undergoing elective PCI. In addressing the question of which assay best predicts outcome, they found that LTA, Plateletworks, and VerifyNow had a modest ability to successfully

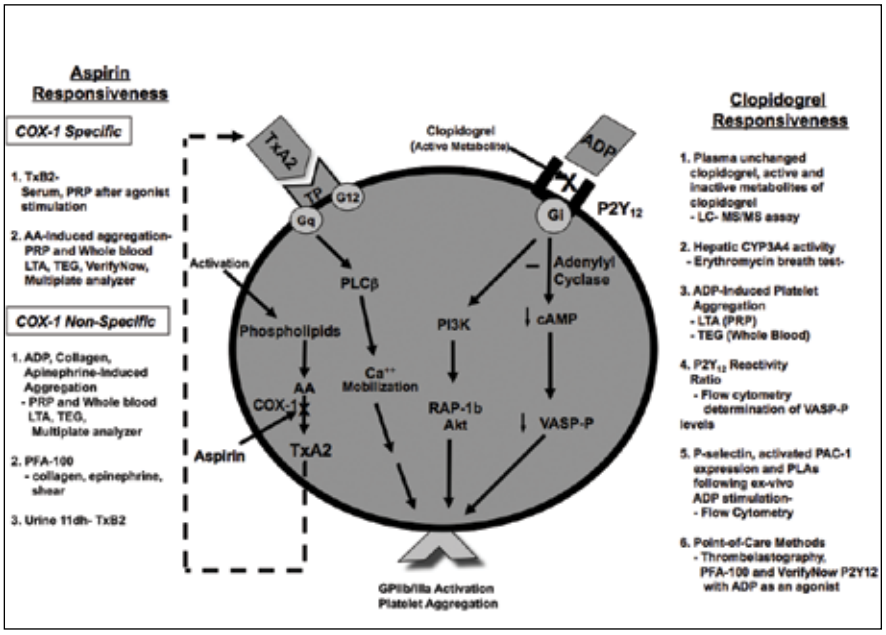

Figure 2. The mechanism of action and laboratory evaluation of clopidogrel and aspirin responsiveness. Adapted with permission from Gurbel PA, Tantry US. Aspirin and clopidogrel resistance: consideration and management. J Interv Cardiol. 2006;19(5):439–448.[42]

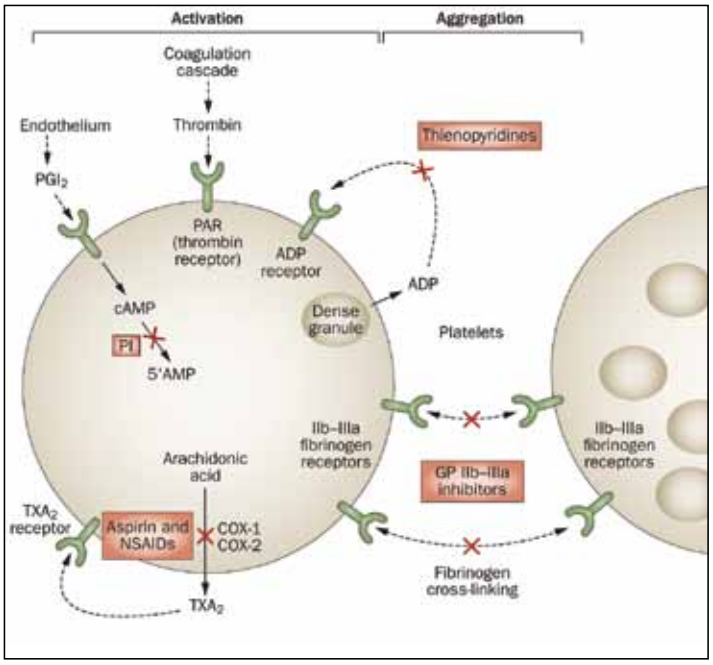

Figure 3. The mechanism of action of antiplatelet therapies. Adapted with permission from Kavanagh LE, Jack GS, Lawrentschuk N. Prevention and management of TURP-related hemorrhage. Nat Rev Urol. 2011;8:504–514.[43]

predict HTPR that was associated with reduced survival and increased rates of nonfatal acute myocardial infarctions, ST, and ischemic stroke. More precisely, high platelet reactivity was associated with a 12.1% incidence of major CV events, as compared with a rate of 6% in patients without high platelet reactivity on one of these tests.[41] As shown in Table 2, point-of-care assays are inexpensive, quick, and require less expertise to perform in contrast to LTA and VASP phosphorylation assays.

THE USE OF PLATELET REACTIVITY TESTING TO GUIDE DAPT AFTER PCI

Increasing the Clopidogrel Dose

As a consequence of wide interpatient variability in response to clopidogrel and evidence suggesting increased risk of adverse events with HTPR, there has been an interest in identifying those with HTPR and offering alternative treatment with the hopes of improving clinical outcomes. One hypothesis was to increase the clopidogrel dose. The Gauging Responsiveness With A VerifyNow $P2Y_{12}$ Assay: Impact on Thrombosis and Safety (GRAVITAS) trial was a multicenter, randomized, double-blinded study of 2,214 patients undergoing elective or urgent PCI with drug-eluting stents (DES). Using the VerifyNow assay, platelet reactivity was measured 12 to 24 hours after PCI. Patients with HTPR (on clopidogrel) were randomly assigned to 75 mg daily of clopidogrel with no loading dose or a 600-mg loading dose followed by 150 mg of clopidogrel daily. During the 6-month follow-up period, there was no significant difference in death secondary to cardiovascular causes, nonfatal MI, or ST observed between the two treatment groups.[20,44] Therefore, this trial did not support a double-dose clopidogrel strategy for elective PCI patients with HTPR to clopidogrel.

A recently published study, the ARCTIC trial, compared platelet function testing with treatment modification to standard treatment. The study included 2,466 patients undergoing PCI with DES (70% elective, 30% ACS) from 50 different centers. In one group, platelet function was monitored using VerifyNow, and adjustments to antiplatelet therapy were performed based on a set algorithm. In the conventional treatment group, platelet function testing was not performed, and patients received standard treatment per the physician's discretion and current guidelines.[45]

Adjustments for HTPR (defined at PRU ≥ 235) included use of glycoprotein IIb/IIIa inhibitors, additional loading doses of clopidogrel, or switching to prasugrel. Thirty-four percent of the monitoring group had HTPR after randomization. Eighty percent of these were given additional clopidogrel loading doses. Prasugrel was used in only 10% of study patients due to late availability and off-label use in clinically stable patients. At 2 to 4 weeks after randomization, there was a 50% relative reduction in HTPR in the platelet-monitoring arm. However, the drop in HTPR did not result in differences in the rate of clinical outcomes compared to those with standard treatment. At 1 year, rates of death from any cause, MI, stroke or transient ischemic attack, urgent coronary revascularization, and ST were similar between groups. In summary, the results from the prospective randomized ARCTIC trial do not support the use of platelet reactivity treatment to guide antiplatelet therapy after PCI.

Switching to an Alternative Antiplatelet Agent

Prasugrel. Prasugrel, like clopidogrel, is a thienopyridine that irreversibly inhibits the $P2Y_{12}$ ADP receptor (Figure 3). However, it only requires a one-step liver bioactivation, resulting in more efficient active metabolite generation, and therefore faster and more potent antiplatelet response, as well as minimal interpatient

variability. Prasugrel is not affected by CYP2C19 loss-of-function variants. These advantageous pharmacological properties translated into decreased ischemic events but increased bleeding risk in a large randomized clinical trial of ACS patients managed with PCI.[46] The Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI) trial tested the hypothesis that prasugrel is superior to clopidogrel in PCI patients with HTPR.[21] PCI patients with HTPR to clopidogrel were randomly assigned to standard dose prasugrel or standard dose clopidogrel. The primary endpoint was CV, death, or MI at 6 months. Unfortunately, this study was stopped prematurely for futility because of a lower-than-expected incidence of cardiovascular death or MI during the follow-up period, providing us with little additional insight. Table 3 compares and contrasts the characteristics of the GRAVITAS, TRIGGER-PCI, and ARCTIC trials.

Ticagrelor. Ticagrelor is a recently approved reversible nonthienopyridine $P2Y_{12}$ antagonist that, unlike previous $P2Y_{12}$ antagonists, does not require hepatic bioactivation and has minimal interpatient variability. In a randomized trial of ACS patients managed with and without PCI, ticagrelor was associated with lower adverse cardiac outcomes and all-cause mortality compared with standard dose clopidogrel.[47] There was no increase in the rate of major bleeding overall, but there was an increase in the rate of non–procedure-related bleeding. Given its proven efficacy and favorable pharmacokinetic profile, ticagrelor may be an attractive option for individuals with HTPR to clopidogrel.

The RESPOND (Response to Ticagrelor in Clopidogrel Non-Responders and Responders and Effect of Switching Therapies) trial had a two-way crossover design; 41 clopidogrel nonresponders (identified by LTA) and 57 responders were randomized to clopidogrel (600-mg load/75 mg once daily) or ticagrelor (180-mg load/90 mg twice daily) for 14 days during the first period. In the second period, all nonresponders switched treatment; half of the responders continued the same treatment, and the other half switched treatment. The study showed that inhibition of platelet aggregation was higher in clopidogrel nonresponders treated with ticagrelor, and this platelet inhibition was comparable to that seen with clopidogrel responders.[48] These results taken together with the PLATO study suggest that ticagrelor may be more effective than clopidogrel in platelet inhibition with no associated increased incidence of bleeding. Furthermore, a randomized pharmacodynamic study suggests that ticagrelor may be even more potent than prasugrel in ACS patients with HTPR to clopidogrel.[49] However, no firm conclusions or recommendations can be made based on these studies. Large clinical outcome studies directly comparing ticagrelor and prasugrel would be needed to demonstrate any difference in outcome and potential benefit favoring the use of any one of these antiplatelets in the clinical setting.

PLATELET REACTIVITY TESTING AND CLINICAL PRACTICE GUIDELINES

Platelet reactivity testing was mentioned in the most recent ACCF/AHA PCI guidelines from 2011. Platelet function testing received a class IIb recommendation for patients at high risk for poor clinical outcomes.[2] For patients with high platelet reactivity on clopidogrel, alternative agents such as prasugrel or ticagrelor can be considered. However, routine testing of platelet function is not recommended. The European Society of Cardiology guidelines for revascularization from 2010 do not mention platelet reactivity testing, and the ACS guidelines from 2011 state that routine testing cannot be recommended at this time.[50,51] In light of the recent results from the ARCTIC trial and TRILOGY-ACS platelet substudy (which were not available for the above guidelines), it is possible that platelet function testing will be downgraded in future guidelines.

CONCLUSION

Antiplatelet therapy is a critical component in the management of patients with ACS and patients who undergo PCI. However, despite DAPT, particularly with aspirin and clopidogrel, ischemic complications continue to occur. HTPR is multifactorial and may be due to genetic predisposition, drug-drug interaction, or the presence of comorbidities. Although platelet reactivity correlates with the risk of cardiac events in PCI patients, escalating antiplatelet therapy or the use of more potent agents in such patients does not appear to reduce this risk. Large studies incorporating laboratory and point-of-care assays to guide therapy have not demonstrated meaningful improvements in clinical outcomes. The clinical utility of platelet reactivity testing is therefore unclear and should not be done routinely. ■

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