Optimizing Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical Pathways for Platelet Function Testing

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Current guidelines recommend dual antiplatelet therapy (DAPT), which includes aspirin and a platelet $P2Y_{12}$ adenosine diphosphate (ADP) receptor antagonist, for treatment of patients with acute coronary syndrome and following percutaneous coronary intervention (PCI). Although DAPT significantly reduces stent thrombosis and major adverse cardiovascular events (MACE), there is considerable interindividual variability in the degree of platelet inhibition achieved with the most widely used ADP receptor antagonist, clopidogrel, and high on-treatment platelet activity in the setting of clopidogrel therapy (hyporesponsiveness) is associated with increased adverse cardiovascular events following PCI. Personalized tailoring of antiplatelet therapy guided by patient management algorithms and/or platelet function testing has the potential to reduce MACE and stent thrombosis. This article outlines specific algorithms for using potent new antiplatelet agents, such as prasugrel and ticagrelor, and platelet function "test and treat-to-target" strategies to reduce adverse cardiovascular events following PCI.
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Current guidelines recommend administration of dual antiplatelet therapy (DAPT), with aspirin and a platelet $P2Y_{12}$ adenosine diphosphate (ADP) receptor antagonist to patients with acute coronary syndromes (ACS) and to those treated with percutaneous coronary intervention (PCI).[1,2] The guideline recommendations are based on data indicating that DAPT compared with aspirin alone reduces ischemic events in patients treated with PCI

and stenting.[3,4] Of the currently available ADP receptor antagonists, clopidogrel, a second-generation agent, is the most widely used, and has almost completely replaced the older first-generation drug ticlopidine because of a lower incidence of side effects. Compared with clopidogrel, the third-generation ADP receptor antagonist prasugrel has more rapid onset of action (1-2 h), a significantly greater degree of platelet inhibition, fewer drug–drug interactions, and less interindividual response variability.[5-7] In addition to clopidogrel and prasugrel, which are competitive, irreversible inhibitors of the $P2Y_{12}$ receptor, ticagrelor, is a twice-daily dosed, reversible, direct-acting, noncompetitive ADP receptor antagonist that was recently approved by the US Food and Drug Administration (FDA).[8] Ticagrelor and prasugrel are similar in the timing of their onset of action, provide a greater degree of platelet inhibition, and they have less interindividual variability when compared with clopidogrel.[9]

Compared with clopidogrel, the third-generation adenosine diphosphate receptor antagonist prasugrel has more rapid onset of action (1-2 h), a significantly greater degree of platelet inhibition, fewer drug-drug interactions, and less interindividual response variability.

Clopidogrel and prasugrel are both prodrugs; however, they have markedly different pharmacokinetic profiles of prodrug conversion to active metabolite.[5-7] A total of 85% of clopidogrel is hydrolyzed by human carboxylesterase-1 into an inactive metabolite, and the remaining 15% then undergoes a two-step hepatic cytochrome P-450 (CYP)-dependent oxidation process. The activation processes involved in clopidogrel metabolism lead to a delay in peak antiplatelet effect that varies from 6 to 9 hours, depending on the loading dose. In comparison with clopidogrel, prasugrel is converted from prodrug to an active metabolite by more efficient hepatic oxidation pathways that result in a rapid onset of prasugrel action with inhibition of more than 50% of platelet aggregation in 30 to 60 minutes. The degree of platelet inhibition achieved with clopidogrel is affected by several clinical factors, such as compliance, age, ethnicity, body weight, diabetes, dyslipidemia, renal function, myocardial infarction (MI) presentation, congestive heart failure (CHF), and interaction with drugs that alter prodrug conversion.[10-15] In addition, genetic polymorphisms of intestinal transport proteins (eg, *ABCB1*) and the P-450 system (eg, *CYP2C19*) influence clopidogrel action. Polymorphisms that reduce *CYP2C19* activity (eg, *CYP2C19**2 and *CYP2C19**3) decrease hepatic activation of clopidogrel, and carriers of these reduced-function *CYP2C19* alleles have significantly lower levels of active metabolite, diminished platelet inhibition, and higher rates of adverse cardiovascular events and stent thrombosis following PCI.[14] The prevalence of *CYP2C19* polymorphisms is significant, and varies from 30% to 55% depending on the patient's ethnic background.[5,16-18] Polymorphisms in genes that influence gastrointestinal absorption, such as *ABCB1*, have also been reported to alter PI by clopidogrel, and *ABCB1* polymorphisms may impact the risk of cardiovascular events in clopidogrel-treated patients.[19,20] Medications that inhibit CYP activity also have the potential to decrease clopidogrel efficacy by diminishing clopidogrel conversion to the active metabolite. In particular, some common proton pump inhibitors (PPIs) directly reduce the antiplatelet efficacy of clopidogrel, although there is controversy whether PPI coadministration with clopidogrel results in increased major adverse cardiac events (MACE) following PCI.[21] The potential for reduced clinical efficacy of clopidogrel in patients with CYP polymorphisms, or in patients treated with certain PPIs, led the FDA to issue specific black box warnings regarding the potential risk for increased cardiovascular events in patients who are poor metabolizers of clopidogrel or in patients who use PPIs.[18] These black box warnings suggest avoiding clopidogrel coadministration with PPIs, and further urge practitioners to consider genetic profiling, alternative dosing strategies, or use of other agents to identify or treat potential clopidogrel hyporesponders. Importantly, hyporesponsiveness appears to be a lesser problem with prasugrel and ticagrelor.[22] *CYP2C19* genetic variants do not affect active drug metabolite levels of prasugrel, and prasugrel provides more uniform and more potent inhibition of platelet aggregation compared with clopidogrel regardless of *CYP2C19* polymorphism status (Figure 1).[5,23] Prasugrel is currently

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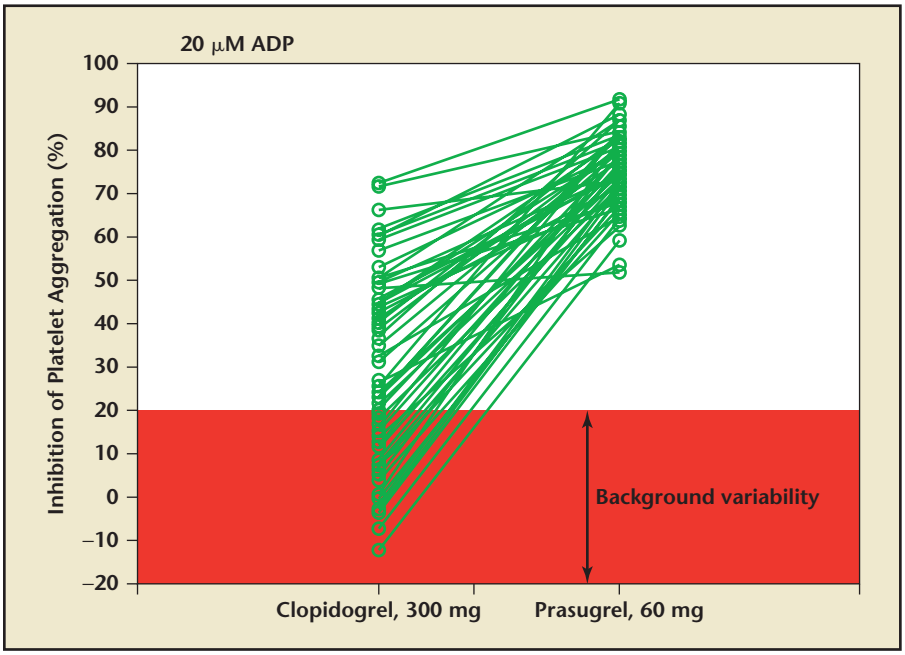

Figure 1. *Relationship between inhibition of platelet activation by clopidogrel (300 mg) versus prasugrel (60 mg) in response to 20 μmol/L adenosine diphosphate (ADP) 24 hours after loading. Subjects were administered both clopidogrel and prasugrel in a crossover fashion. These data illustrate the point that clopidogrel has significant interindividual variability compared with prasugrel. Reprinted with permission from Brandt JT et al.*[22]

approved by the FDA for DAPT in ACS patients undergoing PCI based on a significant reduction in MACE when compared with clopidogrel.[24] Ticagrelor was recently approved by the FDA as another alternative DAPT agent for ACS and PCI, because it also reduces the rate of thrombotic cardiovascular events in ACS patients when compared with clopidogrel.[9]

The presence of reduced degrees of PI in clopidogrel-treated patients is also called high on-treatment platelet reactivity (HTPR). HTPR is typically defined as > 70% ADP-induced aggregation by light transmission aggregometry or greater than 208 to 230 $P2Y_{12}$ reaction units (PRUs) by the VerifyNow P2Y12 Assay® (Accumetrics, San Diego, CA). Diminished clopidogrel response and HTPR varies with clinical factors and ethnicity (vide supra); for example, 2% of whites, 4% of blacks, and up to 20% of Asian individuals have homozygous reduced-function *CYP2C19* alleles. In addition, up to one-third of the population is heterozygous for at least one reduced-function *CYP2C19* polymorphism, suggesting that a significant number of individuals may be at risk for HTPR.[25] HTPR is associated with adverse clinical outcomes; namely, patients with HTPR have two to five times higher risk of cardiovascular death, MI, and stent thrombosis.[10,12,14,26] In addition, there appears to be a stepwise correlation between the degree of platelet reactivity and the risk of MACE in a recently published meta-analysis (Figure 2).[26]

Once HTPR patients are identified, several recent studies have demonstrated that clopidogrel hyporesponsiveness can, in some cases, be treated by increasing clopidogrel dose from standard dosing (300 mg load + 75 mg/d) to high loading (600 or 900 mg) and/or high maintenance (150 mg/d) regimens. Higher clopidogrel dosing has been shown to shorten the onset of action, reduce interindividual variability, and improve early outcomes without increasing bleeding.[25,27,28] Encouragingly, in the PCI subgroup of the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS) 7 trial, high loading- (600 mg) and short-term (7-day) high maintenance-dose clopidogrel (150 mg/d) reduced stent thrombosis and improved 30-day cardiovascular outcomes compared with standard therapy (300 mg load + 75 mg/d).[29] Although high-dose clopidogrel did not increase Thrombolysis in Myocardial Infarction (TIMI) major bleeding, there was a significant increase in bleeding using CURRENT-specific criteria. Importantly, results from CURRENT-OASIS 7 should be interpreted cautiously because the benefit of high loading- and maintenance-dose clopidogrel was negative for the entire ACS study cohort (PCI and non-PCI patients).[29]

Despite the ability of high maintenance-dose clopidogrel to increase PI, high maintenance-dosing strategies have not consistently improved cardiovascular outcomes when HTPR patients are prospectively identified with platelet function testing. Results from the Gauging Responsiveness With a VerifyNow Assay-Impact on Thrombosis and Safety (GRAVITAS)

Despite the ability of high maintenance-dose clopidogrel to increase platelet inhibition, high maintenance dosing strategies have not consistently improved cardiovascular outcomes when high on-treatment platelet reactivity patients are prospectively identified with platelet function testing.

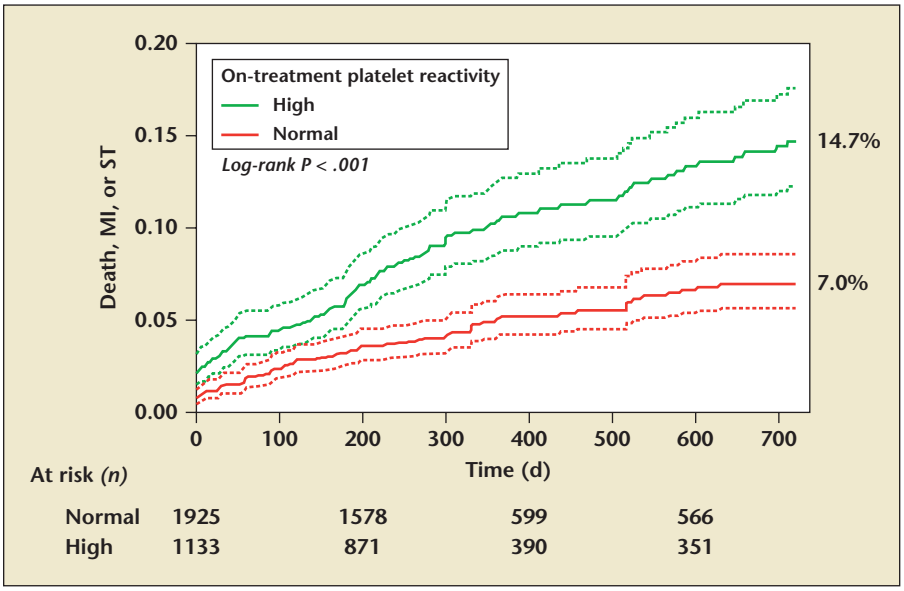

Figure 2. *Kaplan-Meier curve for high (PRU ≥ 230) versus normal (PRU < 230) on-treatment platelet reactivity. Patient level meta-analysis where the inhibitory effects of clopidogrel on platelet reactivity were quantified using the VerifyNow P2Y12 Assay® (Accumetrics, San Diego, CA). Postclopidogrel platelet reactivity was measured at least 12 hours following PCI. Kaplan-Meier curves for high and normal platelet reactivity are shown. The incidence of death, MI, or ST was 14.7% for PRU values > 230 versus 7.0% for PRU values < 230 (hazard ratio 2.13; 95% confidence interval, 1.64-2.77; P < .001). These data demonstrate that clopidogrel hyporesponsiveness is associated with increased risk of death, MI, and ST following PCI. MI, myocardial infarction; PCI, percutaneous coronary intervention; PRU, $P2Y_{12}$ reaction unit; ST, stent thrombosis. Reprinted with permission from Brar S et al.*[26]

study, which randomized HTPR patients to standard- or high-dose clopidogrel therapy, did not show a clinical benefit.[30] Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI), which was halted early because of insufficient statistical power and lower than expected cardiovascular event rates, set out to determine whether HTPR could be used to identify patients who would benefit from intensified antiplatelet therapy with prasugrel instead of clopidogrel.[31] Taken together, the results from GRAVITAS and TRIGGER-PCI demonstrated that cardiovascular event rates are not high (< 3% for a composite of cardiovascular death, MI, and stent thrombosis) in low-risk PCI patients (only 15% of GRAVITAS patients had ACS/non–ST-elevation MI [NSTEMI]/STEMI). Furthermore, despite high-maintenance clopidogrel dosing in GRAVITAS, a significant percentage of HTPR patients failed to achieve significant reductions in platelet reactivity to levels that might be associated with improved cardiovascular outcomes.[32,33] Importantly, GRAVITAS demonstrated that patients with HTPR remained at increased risk for cardiovascular events.

Given the association between HTPR and adverse clinical outcomes, and limited clinical trial data showing that increasing clopidogrel dose reduces MACE, some interventional cardiologists continue to use platelet function testing to identify high-risk HTPR patients and then tailor antiplatelet therapy to achieve levels of PI that are associated with reduced MACE rates.[34] In contrast to the non-tailored strategy used in GRAVITAS, in which high-dose clopidogrel was often insufficient in improving the extent of platelet inhibition, a platelet function "test and treat-to-target" strategy that utilizes high-dose clopidogrel or more potent agents, such as prasugrel and ticagrelor, and serially monitors platelet function, has the potential to optimize cardiovascular outcomes following PCI.

Approaches to Tailoring Antiplatelet Therapy

Approaches to tailoring antiplatelet therapy in PCI patients integrate up-front use of potent antiplatelet agents such as prasugrel and ticagrelor, genetic testing to identify patients with *CYP2C19* polymorphisms, and phenotypic platelet function testing to identify HTPR patients who might benefit from a test and treat-to-target antiplatelet strategy.

Up-Front Use of Potent Antiplatelet Agents

In an effort to address the potential for clopidogrel hyporesponsiveness in ACS, it is possible to use an antiplatelet prescribing algorithm that favors initial use of more potent antiplatelet agents that have less interindividual variability compared with clopidogrel. An example of such a prescribing algorithm developed at the Brigham and Women's Hospital, Harvard Medical School (Boston, MA), is depicted in Figure 3.[35] The goal of the prasugrel algorithm is to harness the increased antiplatelet efficacy of prasugrel compared with clopidogrel for preventing ischemic events in ACS patients while minimizing the increased bleeding risk associated with prasugrel therapy. In this approach, clinicians take advantage of the rapid 30-minute onset of action of prasugrel as the drug is administered immediately prior to or just after PCI. In urgently treated patients who are not taking clopidogrel, the benefit of this peri-PCI load protocol is a reduction in the likelihood that a

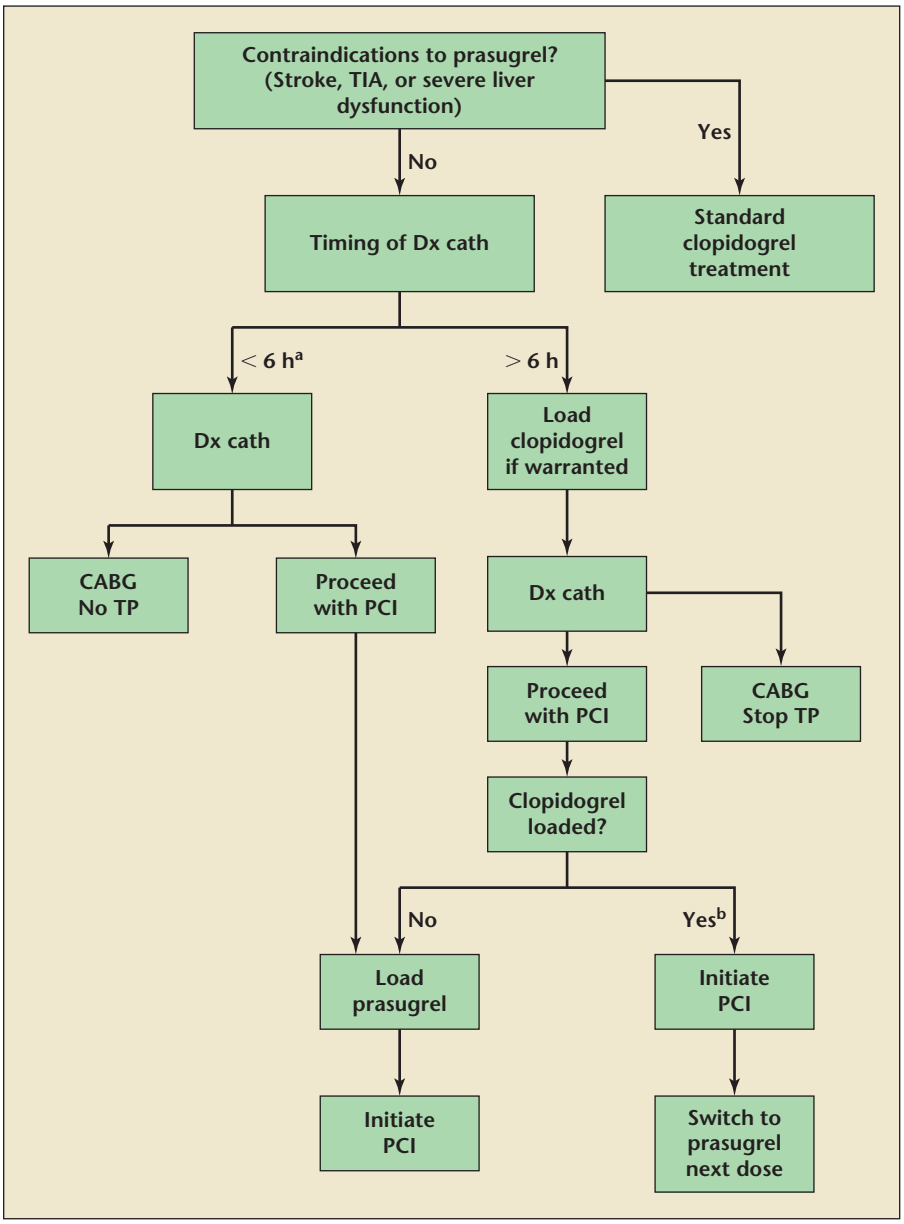

Figure 3. *Brigham and Women's Hospital prasugrel administration algorithm. For the purposes of guiding prasugrel administration, ACS patients are stratified into two groups based on the anticipated delay between their presentation and start of the cardiac catheterization. Patients with renal dysfunction, body weight < 60 kg, and history of gastrointestinal bleeding are at higher risk of bleeding, and bleeding risk is elevated with concomitant use of other medications, which increase the rate of bleeding. [a]In patients with STEMI in whom the cardiologist determines CABG is highly unlikely, upstream prasugrel loading prior to diagnostic angiogram can be considered on an individual basis. [b]The decision to load patients with prasugrel when switching from clopidogrel can be made on a case-by-case basis after considering the potential ischemic benefit and bleeding risk of a given patient. ACS, acute coronary syndrome; CABG, coronary artery bypass graft; Dx cath, diagnostic cardiac catheterization; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; TP, thienopyridine. Reprinted with permission from Marchini J et al.[35]*

patient requiring a coronary artery bypass graft will be given a thienopyridine. In this algorithm, so-called low-risk ACS patients and those receiving invasive management in a less acute time frame can still be treated with clopidogrel, and these clopidogrel-treated patients can be switched to prasugrel just before, during, or after PCI. Switching can be achieved with or without a prasugrel loading dose, as supported by the Switching Anti Platelet (SWAP) study, which demonstrated that a higher level of platelet inhibition can be quickly achieved in less than 2 hours by prasugrel "reloading" on a background of clopidogrel therapy.[36] Although clinical studies have not directly evaluated prasugrel in elective PCI, the algorithm proposes that after careful assessment of an individual patient's bleeding risk, prasugrel may be considered following elective PCI in patients who are likely to benefit from more potent antiplatelet therapy, including patients who have high-risk coronary anatomy (left main PCI, single remaining vessel PCI), patients with homozygous reduced-function CYP alleles, or patients with clopidogrel hyporesponsiveness measured by platelet function testing.

Genetic Testing for Reduced-Function CYP2C19 *Alleles*

Genetic testing for reduced function *CYP2C19* alleles can identify some patients who are at increased risk for adverse events after PCI.[14] Although not studied in clinical trials, it is possible that patients with *CYP2C19* polymorphisms might benefit from a "genotype and treat" strategy in which they receive intensification of antiplatelet therapy with high maintenance-dose clopidogrel or with prasugrel or ticagrelor. One important point to consider is that genetic testing results frequently do not predict the degree of platelet inhibition (genotype ≠ phenotype), likely because CYP polymorphisms do not detect multiple other clinical factors (eg, obesity, diabetes, ACS presentation, and drug interactions) that influence platelet activation and clopidogrel activity/metabolism. In

addition, genotyping for currently identified CYP polymorphisms that reduce clopidogrel efficacy does not address unknown or newly described genes, such as those affecting paraoxonase-1, which might influence clopidogrel responses.[37] The clinical value of genetic testing is uncertain at present. Limited clinical investigation suggests that platelet functional testing may be more useful in identifying patients with HTPR compared with genetic *CYP2C19* testing.[34,38] For example, in one study, 20% of patients who were carriers of reduced-function CYP polymorphisms had adequate responses to the first loading dose of clopidogrel, whereas 50% of patients who were not carriers of the reduced-function genotype still had > 50% platelet reactivity after the initial loading dose.[34] Finally, compared with functional testing, genetic testing does not allow for implementation of a test and treat-to-target strategy in which serial evaluations can monitor the effects of treatment modification on platelet function.

Platelet Function Testing and a Test and Treat-to-Target Strategy

Platelet function testing effectively identifies patients with HTPR.[39] Platelet reactivity testing is supported by a recommendation in the updated ACS guidelines, which state that platelet function testing to determine platelet inhibitory response in patients with unstable angina/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management (Class IIb, Level of Evidence B).[1,40] To optimize platelet inhibition following PCI, practitioners at University Hospitals Case Medical Center (UHCMC; Cleveland, OH) have implemented a platelet function testing strategy using the VerifyNow P2Y12 Assay to identify clopidogrel hyporesponders with HTPR, as outlined in Figure 4. In our geographic region of Ohio, most patients presenting to the cardiac catheterization laboratory have been preloaded with 600 mg of clopidogrel prior to diagnostic angiography and, in many cases, either due to physician preference or potential elevated bleeding risk with prasugrel (stroke/transient ischemic attack, weight < 60 kg, or age > 75 years), ACS patients will not be routinely switched to prasugrel unless results of subsequent platelet function testing dictate a change in therapy. The impact of the very recent approval of ticagrelor on clinical practice is uncertain at this time, but the treatment algorithm will likely require revisions in the future.

Although decreased responsiveness to aspirin is associated with increased CV events,[39,42,43] we do not routinely engage in aspirin sensitivity testing following PCI because the incidence of aspirin resistance and the treatment strategies to address aspirin resistance in the PCI setting are not clear. At UHCMC, aspirin resistance testing with the VerifyNow Aspirin Assay is only performed in unusual situations, such as when stent thrombosis occurs in aspirin-compliant patients without evidence of clopidogrel hyporesponsiveness. The reported prevalence of aspirin resistance varies from < 1% to 28%.[41-44] Discordant rates of high on-aspirin platelet reactivity are likely related to differences in the populations studied, where factors such as sex, obesity, diabetes, recent PCI therapy, and ACS presentation likely influence aspirin efficacy and the results of platelet function testing. Furthermore, the choice of platelet function test, testing cutoff value, and definition of resistance vary widely in published studies. Poor compliance has also been shown to be a significant cause of pseudoresistance in outpatients,[41] and coadministration of nonsteroidal anti-inflammatory drugs may also reduce aspirin inhibition of cyclooxygenase-1 (COX-1) and platelet activation. Despite uncertainty regarding the incidence of aspirin hyporesponsiveness alone, a recent investigation demonstrated that the incidence of combined aspirin and clopidogrel hyporesponsiveness can be as high as 26.9%; notably, dual nonresponders have 1-year adverse CV events rates that exceed 17%.[44] Further, clinical investigations will be required to develop evidence-based guidelines to identify and treat aspirin resistance.

Although more than five methods for assessing platelet function are available, the results of the VerifyNow P2Y12 Assay correlate well with light transmission aggregometry; importantly, the VerifyNow P2Y12 Assay has demonstrated ability to identify HTPR patients at heightened risk for cardiovascular events.[26,39] Compared with other methods, it is rapid, inexpensive, reproducible, and simple to use in a variety of clinical settings, such as the coronary care unit, cardiac catheterization laboratory, or outpatient clinic. In the UHCMC program, one VerifyNow P2Y12

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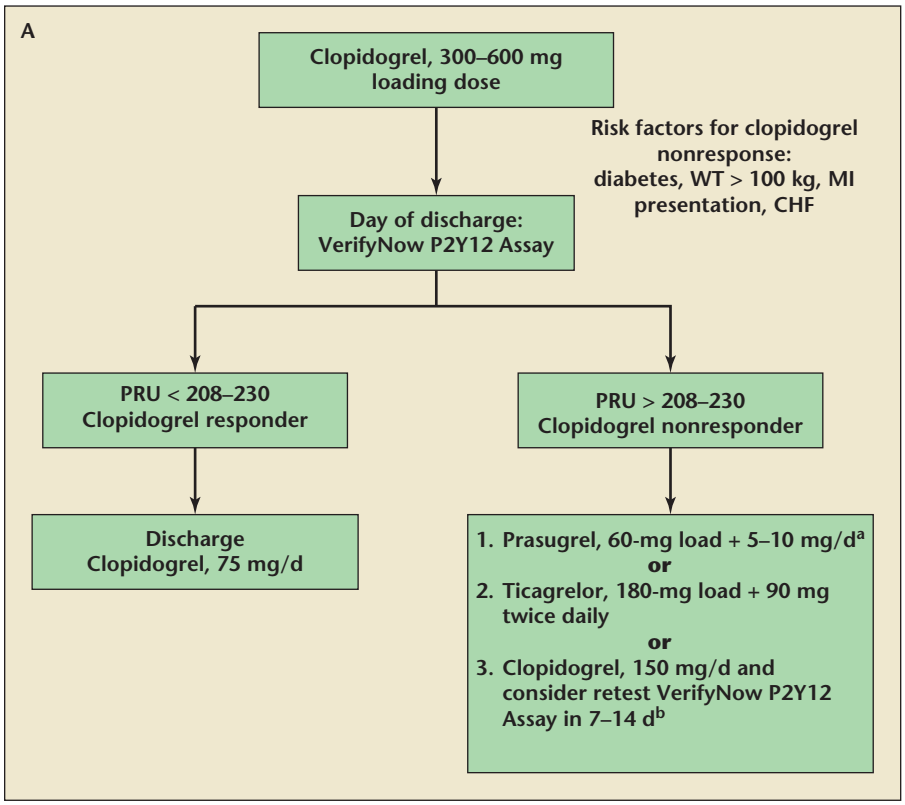

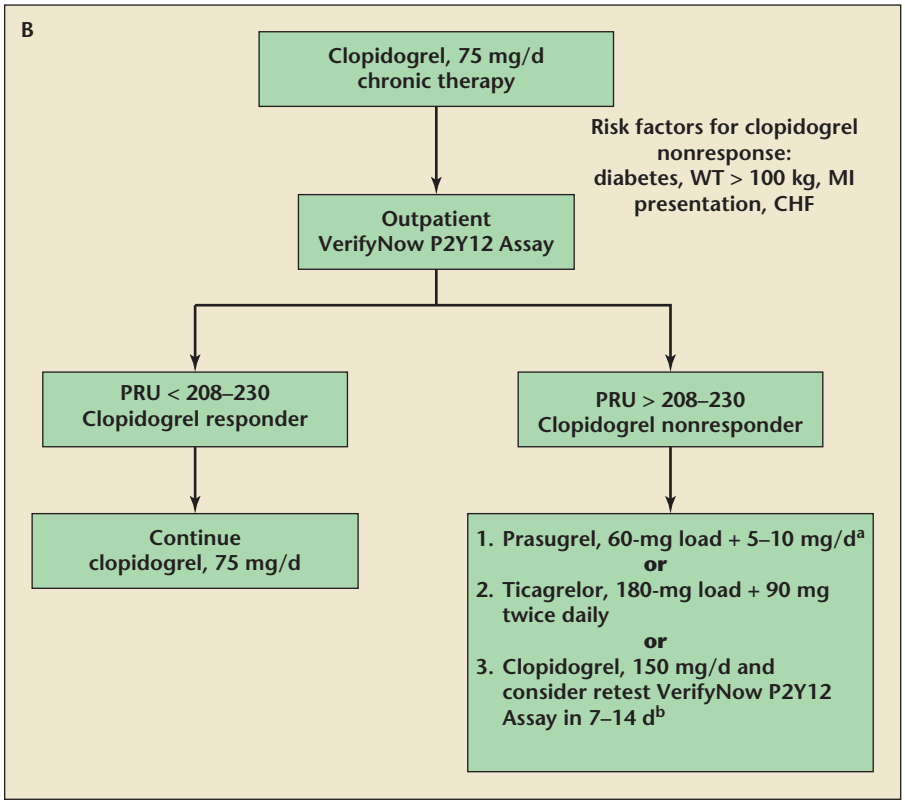

Figure 4. *University Hospitals of Cleveland, Case Medical Center platelet function testing algorithm.* **(A)** *VerifyNow P2Y12 Assay® (Accumetrics, San Diego, CA) platelet function testing algorithm following PCI in stable CAD and ACS patients.* **(B)** *VerifyNow P2Y12 Assay® platelet function testing algorithm for patients on maintenance clopidogrel therapy.* [a]*Prasugrel should not be used in patients with prior stroke/TIA, and caution should be used in patients > 75 years or with weight < 60 kg because these patient subsets had increased rates of bleeding when treated with prasugrel (Effient [package insert]. Daiichi Sankyo Inc. and Eli Lilly and Company: Indianapolis, IN; 2011).* [b]*It is reasonable to reload HTPR clopidogrel nonresponders with 600 mg or 900 mg of clopidogrel prior to initiating 150 mg/d dosing. ACS, acute coronary syndromes; CAD, coronary artery disease; CHF, congestive heart failure; HTPR, high on-treatment platelet reactivity; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRU, $P2Y_{12}$ reaction units; TIA, transient ischemic attack; WT, weight.*

Assay is kept in the catheterization laboratory, and another P2Y12 Assay is kept in a clinic location to accommodate outpatient testing needs. Specimens require approximately 15 minutes to process from time of phlebotomy to test result, and this rapid turnaround time allows for prompt therapeutic decision making.

As outlined in the platelet testing algorithm depicted in Figure 4, the goal of the test and treat-to-target strategy is to achieve a PRU cutpoint of less than 230. A PRU value of 230 was initially chosen as the target because receiver-operating characteristic curve (ROC) analyses have demonstrated that a PRU value of 230 provides the maximal sensitivity and specificity for the prediction of MACE events following PCI, and this 230 PRU cutoff value is consistent with or approximate to ROC cutoffs used in several major clinical studies.[10,39,45] In addition, a PRU value of 230 is able to effectively identify patients at risk for cardiovascular death, MI, or stent thrombosis with composite endpoint rates of 14.7% for PRU values > 230 versus 7.0% for PRU values < 230 (hazard ratio [HR] 2.13; 95% confidence interval [CI], 1.64-2.77; $P < .001$) (Figure 2).[26] Recently, post hoc analysis

of the GRAVITAS trial demonstrated that a PRU cutpoint of 208 may be more clinically useful to identify HTPR patients at risk for MACE, and it is now reasonable to consider treating to a target PRU of 208 when tailoring antiplatelet therapy.[46] The platelet function testing algorithm used at UHCMC is presented in Figure 4. The algorithms are stratified for testing stable coronary artery disease (CAD) and ACS patients following PCI (Figure 4A) or for testing stable patients who are on maintenance clopidogrel therapy (Figure 4B).

Platelet function testing following PCI in stable CAD and ACS patients. In the post-PCI platelet function testing algorithm, the majority of patients who are treated with coronary stenting and DAPT with clopidogrel will undergo platelet function testing with the VerifyNow P2Y12 Assay, and there is a concerted effort to test all patients who are at high risk for stent thrombosis or for whom stent thrombosis would be catastrophic. The high-risk groups that uniformly undergo platelet function testing include patients at risk for clopidogrel nonresponse (eg, those with ACS, diabetes, weight $>$ 100 kg, CHF), patients treated with unprotected left main coronary stenting or last patent coronary vessel stenting, patients at high risk for stent thrombosis (eg, bifurcation stenting, stenting of long artery segments, or implantation of stents in multiple coronary arteries), and patients with a prior history of stent thrombosis.

Twelve hours following PCI and clopidogrel load (and frequently after the initial maintenance dose), the $P2Y_{12}$ PRU is measured, and responders with PRU values $<$ 208 to 230 remain on their current therapy. If HTPR is present as evidenced by a PRU value $>$ 208 to 230, patients are either reloaded with 300 or 600 mg of clopidogrel and started on a high maintenance dose of 150 mg/d, or they are switched to prasugrel (60 mg load + 10 mg/d) or ticagrelor (180 mg load followed by 90 mg twice daily). The decision to use high maintenance-dose clopidogrel versus prasugrel or ticagrelor in an individual patient is made by weighing factors that increase cardiovascular risk (ACS presentation, diabetes, obesity, high-risk coronary anatomy, CHF, history of stent thrombosis) versus factors that influence risk of bleeding (age $>$ 75 years, body weight $<$ 60 kg, renal failure, history of stroke/transient ischemic attack). If the HTPR patient remains hospitalized, a second platelet function test will be performed 12 to 24 hours later to assess the adequacy of intensified therapy; however, we do not delay discharge to enable testing because patients are retested in the outpatient setting 10 to 14 days later, as outlined below.

At Case Medical Center, University Hospitals of Cleveland, many patients are treated with OASIS-7 dosing (600 mg load + 150 mg/d) for 7 days following PCI prior to switching to the standard 75-mg maintenance dose for chronic therapy. Because many patients have an in-hospital platelet function test while taking the initial 7-day 150-mg dose, we routinely repeat platelet function testing at 10 to 14 days after discharge to ensure adequate platelet inhibition after step-down to the 75-mg chronic clopidogrel dose. If patients are found to have HTPR at the 10- to 14-day time point, antiplatelet therapy is intensified as outlined above, with the goal of treating to a target PRU below 208 to 230. In patients with HTPR for whom prasugrel is contraindicated because of prior stroke or transient ischemic attack, ticagrelor now seems to be a reasonable option. Of note, recent evidence indicates that on-treatment platelet reactivity is higher at baseline compared with platelet reactivity measured 1 or 6 months following PCI. This same study also demonstrated that 1-month on-treatment platelet function testing better predicts bleeding and ischemic events compared with baseline testing.[38] Despite this new information about the superior predictive power of platelet function testing 1 month after PCI, a test and treat-to-target strategy based on baseline PRU values is more practical in positively impacting clinical outcomes because stent thrombosis has the highest incidence in the first 30 days following PCI.

Platelet function testing during maintenance therapy. Although the need to test patients on chronic clopidogrel maintenance therapy is less frequent than the need to test acutely following PCI, there are several instances when ascertaining HTPR status on chronic therapy may be useful (Figure 4B). In the outpatient setting, it is reasonable to test PCI-treated patients who carry reduced-function *CYP2C19* alleles, who have a prior history of stent thrombosis, or who are taking lifelong clopidogrel therapy for complex anatomic stenting, stenting for in-stent restenosis, or unprotected stenting of the left main coronary artery. In addition, we frequently test platelet inhibition in clopidogrel-treated patients who are referred for coronary angiography with possible PCI before the diagnostic angiogram, because high platelet reactivity is associated with MACE and increased rates of periprocedural MI.[47] In this precatheterization setting, a test and treat-to-target strategy for elective PCI patients has the potential to identify HTPR patients so that

antiplatelet therapy can be intensified prior to initiation of PCI.

Case Studies Examining Platelet Function Testing Following PCI

The following clinical vignettes highlight opportunities to use newer antiplatelet agents (prasugrel, ticagrelor) and/or platelet function testing to reduce HTPR in PCI patients:

Case 1

A 42-year-old white man with a history of dyslipidemia, hypertension, and morbid obesity (> 200 kg) presented with a hemodynamically stable inferior STEMI while working as a firefighter. The patient was transferred by air ambulance directly to a catheterization laboratory after receiving 325 mg of aspirin and 4000 units of intravenous (IV) unfractionated heparin. Clopidogrel was not given prior to diagnostic angiography. Transradial catheterization was performed to reduce the risk of bleeding. Angiography revealed minimal left coronary atherosclerosis and a 100% mid right coronary artery (RCA) occlusion with significant thrombus. The patient was treated with IV bivalirudin and was loaded with 60 mg of prasugrel prior to initiating PCI. Following aspiration thrombectomy, a 95% stenosis was stented with a 3.5 × 28 mm drug-eluting stent (DES). PI was measured 12 hours after PCI with the VerifyNow P2Y12 Assay, and the patient had a PRU of 71 with 87% inhibition of platelet function. Repeat testing performed 11 days later revealed similar on-treatment prasugrel responsiveness. Prasugrel was chosen as an initial therapy for this patient because morbid obesity and ACS presentation are associated with increased risk of HTPR, he was at low risk for bleeding complications, and clinical trial evidence supported prasugrel over clopidogrel in the STEMI subgroup analysis of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial.[48] Platelet function testing was performed to ensure adequate response to prasugrel, because recent studies have demonstrated that up to 25% of prasugrel-treated ACS patients have HTPR.[49]

Case 2

An 89-year-old white woman with a history of prior MI, hypertension, and type II diabetes presented to a referring hospital with 3 hours of unremitting chest pain and anterior ST-segment elevation. The patient weighed 92 kg, was previously active, and lived independently. Prior to urgent transfer to our tertiary center for cardiac catheterization, she was treated with 325 mg of aspirin, 600 mg of clopidogrel, and IV unfractionated heparin. Transfemoral catheterization and angiography demonstrated moderate RCA and left circumflex disease, and a 100% occlusion of the left anterior descending artery (LAD). The patient was treated with IV unfractionated heparin to maintain an activated clotting time greater than 250, and following aspiration thrombectomy, the diffusely diseased LAD was stented 2.75 × 28 mm and 2.5 × 23 mm overlapping DES. Initial VerifyNow P2Y12 testing 12 hours postprocedure revealed the presence of HTPR with a PRU of 258. Implementing a test and treat-to-target strategy, the patient was switched to the lower 5-mg dose of prasugrel without prasugrel loading. The 5-mg versus 10-mg dose of prasugrel (without loading) was chosen in an attempt to reduce the risk of bleeding in this elderly patient. Repeat VerifyNow P2Y12 testing was performed 3 days later with the presumption that the heightened prasugrel antiplatelet effect would be at steady state. The repeat PRU on 5 mg of prasugrel remained in the HTPR range at 260. Weighing the risk of HTPR and stent thrombosis following complex PCI (51 mm of DES in the LAD) versus potential for bleeding in this elderly patient, the decision was made to further intensify antiplatelet therapy by loading the patient with 60 mg followed by maintenance dosing at 10 mg/d. Two days after transitioning to 10 mg of prasugrel, repeat VerifyNow P2Y12 testing showed resolution of HTPR with a PRU of 208 and 47% inhibition of platelet function. The patient had several risk factors for HTPR, including diabetes, obesity, and ACS presentation. Ticagrelor was not FDA-approved at the time this patient was treated, but is now a reasonable therapeutic alternative.

Case 3

A 54-year-old Asian man with a history of hypertension and dyslipidemia was referred to outpatient cardiovascular clinic 26 months following placement of 2.5 × 18 mm and 3.0 × 28 mm DES into his left circumflex and RCA respectively in the setting of an ACS. The patient weighed 70 kg and was a primary care physician with no history of diabetes. He had been chronically maintained on 325 mg of aspirin and 75 mg of clopidogrel daily. He was doing very well from a cardiovascular perspective and recent noninvasive testing did not show evidence of myocardial ischemia. After reading the clopidogrel FDA boxed warning, the patient requested genetic testing and was found to be homozygous for the *CYP2C19**2 and *3 reduced-function alleles. To determine if he phenotypically had HTPR, VerifyNow P2Y12 platelet function testing was performed, and testing showed a PRU of 387 with only 6% inhibition of

platelet function. Given the clinical stability, absence of angina symptoms or ischemia, and completion of > 12 months of clopidogrel therapy following DES implantation, the patient accepted the recommendation to reduce aspirin to 81 mg/d and to discontinue clopidogrel therapy. If the patient requires PCI and stenting in the future, he will be treated with a next-generation ADP receptor antagonist such as prasugrel or ticagrelor. This case illustrates concordance between *CYP2C19* genetic testing and phenotypic assessment with VerifyNow. Although treatment recommendations would have been the same if platelet phenotyping rather than genetic testing was done, information about the patient's genotype is useful in this case because, if necessary, future PCIs will be supported with non–CYP-dependent ADP receptor antagonist agents. In the convalescent phase 26 months after ACS presentation, the patient's only risk factor for HTPR was Asian descent because of the high prevalence of homozygous reduced-function alleles in Asian individuals.

Conclusions

There is considerable interindividual variability in the degree of platelet inhibition achieved with the ADP receptor antagonist clopidogrel, and HTPR is associated with increased MACE and elevated risk of stent thrombosis following PCI. Therapeutic strategies that combine potent third-generation antiplatelet agents, such as prasugrel and ticagrelor, and/or test and treat-to-target platelet testing algorithms have the potential to decrease HTPR and reduce MACE and stent thrombosis. Ongoing clinical research will further refine the optimal strategy for tailoring PI following PCI so that therapeutic interventions can provide maximal cardiovascular benefit while minimizing the risk of bleeding. ■

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References

1. Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2009;54: 2205-2241.
2. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med*. 1996;334: 1084-1089.
3. Mehta SR, Yusuf S, Peters RJ, et al; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527-533.
4. Sabatine MS, Cannon CP, Gibson CM, et al; Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA*. 2005;294: 1224-1232.
5. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation*. 2009;119:2553-2560.
6. Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. *J Clin Pharmacol*. 2010;50:126-142.
7. Huber K, Yasothan U, Hamad B, Kirkpatrick P. Prasugrel. *Nat Rev Drug Discov*. 2009;8:449-450.
8. Brilinta (ticagrelor) [package insert]. Astra Zeneca LP: Wilmington, DE; 2011.
9. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361: 1045-1057.
10. Price MJ, Endemann S, Gollapudi RR, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. *Eur Heart J*. 2008;29:992-1000.
11. Buonamici P, Marcucci R, Migliorini A, et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol*. 2007;49:2312-2317.
12. Marcucci R, Gori AM, Paniccia R, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by

Main Points

- There is considerable interindividual variability in the degree of platelet inhibition achieved with the most widely used adenosine diphosphate (ADP) receptor antagonist clopidogrel.
- High residual platelet activity in the setting of clopidogrel therapy is associated with increased adverse cardiovascular events following percutaneous coronary intervention.
- The third-generation ADP receptor antagonists, prasugrel and ticagrelor, are more potent, have a faster onset of action, and achieve more uniform platelet inhibition when compared with clopidogrel.
- Personalized tailoring of antiplatelet therapy guided by patient management algorithms and platelet function testing have the potential to reduce major adverse cardiac events and stent thrombosis.

residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. *Circulation*. 2009;119:237-242.
13. Cuisset T, Frere C, Quilici J, et al. High post-treatment platelet reactivity identified low-responders to dual antiplatelet therapy at increased risk of recurrent cardiovascular events after stenting for acute coronary syndrome. *J Thromb Haemost*. 2006;4:542-549.
14. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360:354-362.
15. Hochholzer W, Trenk D, Fromm MF, et al. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. *J Am Coll Cardiol*. 2010;55:2427-2434.
16. Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *Eur Heart J*. 2009;30: 916-922.
17. Kim IS, Choi BR, Jeong YH, et al. The CYP2C19*2 and CYP2C19*3 polymorphisms are associated with high post-treatment platelet reactivity in Asian patients with acute coronary syndrome. *J Thromb Haemost*. 2009; 7:897-899.
18. Plavix (clopidogrel bisulfate) [package insert]. Bristol-Myers Squibb, Sanofi-aventis: Bridgewater, NJ; 2011.
19. Simon T, Verstuyft C, Mary-Krause M, et al; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360:363-375.
20. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet*. 2010;376:1312-1319.
21. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol*. 2008;51:256-260.
22. Brandt JT, Payne CD, Wiviott SD, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J*. 2007;153:66.e9-66.e16.
23. Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost*. 2007;5:2429-2436.
24. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.
25. Collet JP, Hulot JS, Anzaha G, et al; CLOVIS-2 Investigators. High doses of clopidogrel to overcome genetic resistance: the randomized crossover CLOVIS-2 (Clopidogrel and Response Variability Investigation Study 2). *JACC Cardiovasc Interv*. 2011;4:392-402.
26. Brar SS, ten Berg J, Marcucci R, et al. Impact of clopidogrel on-treatment platelet reactivity on stent thrombosis after percutaneous coronary intervention: results from a collaborative meta-analysis of individual participant data. *J Am Coll Cardiol*. In press.
27. Cuisset T, Frere C, Quilici J, et al. Benefit of a 600-mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing coronary stenting. *J Am Coll Cardiol*. 2006;48:1339-1345.
28. Patti G, Colonna G, Pasceri V, et al. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation*. 2005; 111:2099-2106.
29. Mehta SR, Tanguay JF, Eikelboom JW, et al; CURRENT-OASIS 7 trial investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet*. 2010;376:1233-1243.
30. Price MJ, Berger PB, Teirstein PS, et al; GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA*. 2011;305:1097-1105.
31. ClinicalTrials.gov Web site. Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI). http://clinicaltrials.gov/ct2/show/NCT00910299. Accessed September 1, 2011.
32. Angiolillo DJ, Costa MA, Shoemaker SB, et al. Functional effects of high clopidogrel maintenance dosing in patients with inadequate platelet inhibition on standard dose treatment. *Am J Cardiol*. 2008;101:440-445.
33. Jeong YH, Hwang JY, Kim IS, et al. Adding cilostazol to dual antiplatelet therapy achieves greater platelet inhibition than high maintenance dose clopidogrel in patients with acute myocardial infarction: Results of the adjunctive cilostazol versus high maintenance dose clopidogrel in patients with AMI (ACCEL-AMI) study. *Circ Cardiovasc Interv*. 2010;3:17-26.
34. Bonello L, Armero S, Ait Mokhtar O, et al. Clopidogrel loading dose adjustment according to platelet reactivity monitoring in patients carrying the 2C19*2 loss of function polymorphism. *J Am Coll Cardiol*. 2010;56:1630-1636.
35. Marchini J, Morrow D, Resnic F, et al. An algorithm for use of prasugrel (effient) in patients undergoing cardiac catheterization and percutaneous coronary intervention. *Crit Pathw Cardiol*. 2010;9:192-198.
36. Angiolillo DJ, Saucedo JF, Deraad R, et al; SWAP Investigators. Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes: results of the SWAP (SWitching Anti Platelet) study. *J Am Coll Cardiol*. 2010;56: 1017-1023.
37. Bouman HJ, Schömig E, van Werkum JW, et al. Paraoxonase-1 is a major determinant of clopidogrel efficacy. *Nat Med*. 2011;17:110-116.
38. Campo G, Parrinello G, Ferraresi P, et al. Prospective evaluation of on-clopidogrel platelet reactivity over time in patients treated with percutaneous coronary intervention relationship with gene polymorphisms and clinical outcome. *J Am Coll Cardiol*. 2011;57:2474-2483.
39. Breet NJ, van Werkum JW, Bouman HJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA*. 2010;303:754-762.
40. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2011;57:e215-e367.
41. Tantry US, Bliden KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonic acid stimulation. *J Am Coll Cardiol*. 2005;46:1705-1709.
42. Krasopoulos G, Brister SJ, Beattie WS, Buchanan MR. Aspirin "resistance" and risk of cardiovascular morbidity: systematic review and meta-analysis. *BMJ*. 2008;336:195-198.
43. Breet NJ, van Werkum JW, Bouman HJ, et al. High on-aspirin platelet reactivity as measured with aggregation-based, cyclooxygenase-1 inhibition sensitive platelet function tests is associated with the occurrence of atherothrombotic events. *J Thromb Haemost*. 2010;8:2140-2148.
44. Breet NJ, van Werkum JW, Bouman HJ, et al. High on-treatment platelet reactivity to both aspirin and clopidogrel is associated with the highest risk of adverse events following percutaneous coronary intervention. *Heart*. 2011; 97:983-990.
45. Patti G, Nusca A, Mangiacapra F, et al. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. *J Am Coll Cardiol*. 2008;52:1128-1133.
46. Price MJ, Angiolillo DJ, Teirstein PS, et al. Platelet Reactivity and Cardiovascular Outcomes After Percutaneous Coronary Intervention: A Time-Dependent Analysis of the Gauging Responsiveness With a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety (GRAVITAS) Trial. *Circulation*. 2011;124:1132-1137.
47. Gaglia MA Jr, Torguson R, Xue Z, et al. Periprocedural myocardial infarction and high on-treatment platelet reactivity. *J Am Coll Cardiol*. 2011;57(suppl 1):E1897.
48. Montalescot G, Wiviott SD, Braunwald E, et al; TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009;373:723-731.
49. Bonello L, Pansieri M, Mancini J, et al. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. *J Am Coll Cardiol*. 2011; 58:467-473.