REVIEW ARTICLE

Antiplatelet therapy beyond 2012: role of personalized medicine

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ABSTRACT

Since its first approval in 1997, clopidogrel has revolutionized interventional cardiology and transformed therapy for non-ST-segment elevation myocardial infarction (NSTEMI), STEMI, and percutaneous coronary intervention-treated patients. It enjoyed a remarkable 15-year "homerun" in the world market without any major competition. With the introduction of more potent $P2Y_{12}$ receptor blockers, the current antiplatelet strategy is undergoing a transition period. Generic clopidogrel is inexpensive and pharmacodynamically effective in at least two thirds of the patients with coronary artery disease. The unpredictable, slow onset, and overall modest pharmacodynamic effects are the major limitations of clopidogrel. The new, more potent $P2Y_{12}$ receptor blockers overcome the limitations of clopidogrel therapy and are associated with better clinical efficacy, but are more costly and associated with more bleeding. In this scenario, personalization of antiplatelet therapy based on platelet function and genetic testings to strike a balance between cost, benefit, and safety is a potential option.

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Introduction **Rationale for monitoring antiplatelet therapy** There are numerous practical and important data to support antiplatelet therapy monitoring. First, there is overwhelming evidence that thrombus generation is the primary process responsible for the occurrence of myocardial infarction (MI) and stent thrombosis and is highly influenced by platelet activation and aggregation. Second, the most widely implemented antiplatelet regimen to combat thrombus generation targets 2 key pathways that lead to platelet activation: 1) cycloxygenase-1-mediated thromboxane A_2 generation (inhibited by aspirin), and 2) adenosine diphosphate (ADP)-$P2Y_{12}$ receptor interaction (inhibited by clopidogrel). Third, although clinical efficacy has been demonstrated in a wide range of high-risk coronary artery disease (CAD) patients treated with clopidogrel, the agent is also associated with an unpredictable pharmacodynamic response. Fourth, approximately 1 in 3 clopidogrel-treated patients will have high platelet reactivity (HPR), and HPR has been linked to the occurrence of post-percutaneous coronary intervention (PCI) ischemic event in the observational studies of thousands of patients. Despite the fundamental importance of unblocked $P2Y_{12}$ receptors in the genesis of thrombosis, the clear demonstration of clopidogrel resistance, and the identification of genes associated with resistance-*CYP2C19*2* and **3*, most cardiologists do not monitor antiplatelet therapy in their high-risk patients treated with clopidogrel to ensure that an antiplatelet effect is actually present.[1] Moreover, antiplatelet agents are arguably the most important drugs given to the high-risk patient to prevent the catastrophic event – thrombosis. The whole clinical efficacy of clopidogrel has been attributed to the inhibition of $P2Y_{12}$ receptor blockade. Yet, clopidogrel, the most widely used $P2Y_{12}$ inhibitor, is administered most often with a "nonselective" or "one-size-fits-all" approach. Indeed, this nonselective approach to clopidogrel therapy is paradoxical in comparison with the objective assessments and adjustments frequently made during treatment with the majority of other cardiovascular drugs.[1,2]

Influence of single nucleotide polymorphisms on clopidogrel metabolism and its clinical efficacy Multiple lines of evidence suggested that variable and insufficient active metabolite generation were

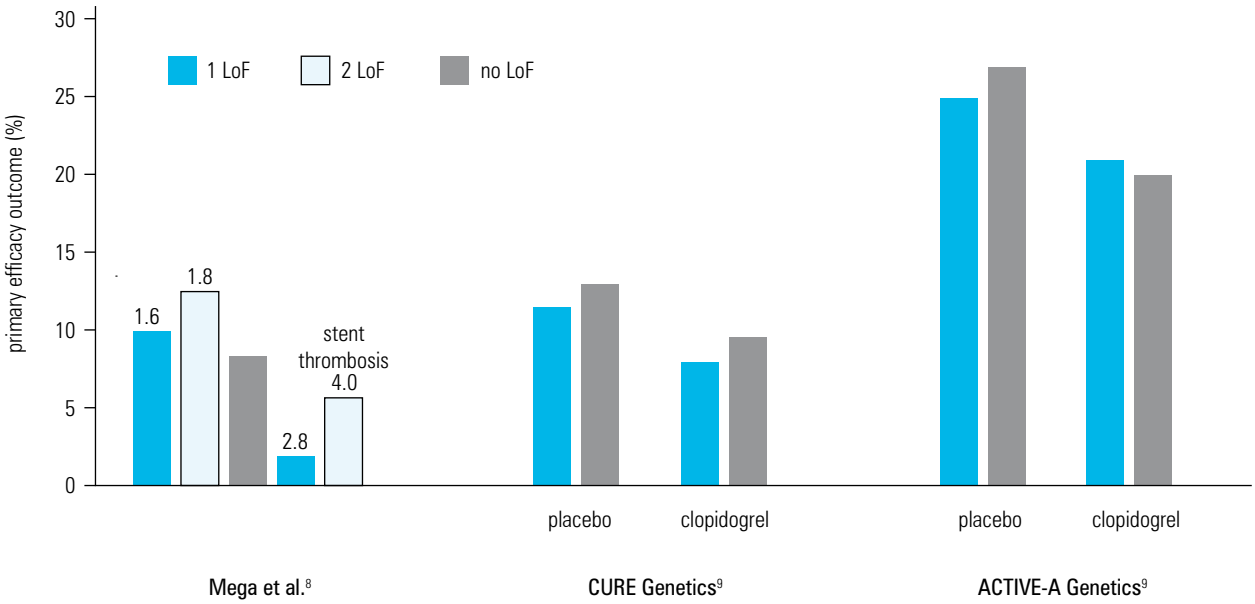

FIGURE 1 Relation of CYP2C19 loss-of-function carrier status to clinical outcomes in clopidogrel trials; hazard ratios are presented at the top of the respective columns Abbreviations: ACTIVE – Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events, CURE – Clopidogrel in Unstable Angina to Prevent Recurrent Events, LoF – loss-of-function allele

the primary explanations for clopidogrel response variability and nonresponsiveness, respectively.[3] Clopidogrel, a prodrug, is converted to an active metabolite by hepatic cytochrome (CYP) P450 isoenzymes. CYP isoenzyme activity is influenced by single nucleotide polymorphisms (SNPs) and other drugs that compete with clopidogrel for CYP-mediated metabolism or inhibit the CYP isoenzymes involved in clopidogrel metabolism. Candidate gene studies conducted in healthy volunteers demonstrated that *loss-of-function* (*LoF)* polymorphisms of *CYP2C19* were associated with decreased clopidogrel active metabolite exposure and less platelet inhibition.[4,5] In the first genome-wide association study, conducted in healthy subjects, *CYP2C19*2* was the only SNP significantly associated with clopidogrel response variability. In a replication study of PCI-treated patients, carriers of the *LoF CYP2C19*2* allele had ~2.4-fold higher cardiovascular event occurrence compared with noncarriers.[6] The influence of the *CYP2C19* genotype on clinical outcomes in patients treated with clopidogrel has been studied extensively in CAD patients undergoing stenting and also patients with acute coronary syndrome (ACS).[7] In a collaborative meta-analysis of trials primarily involving PCI-treated patients (91%), an increased risk of the composite endpoint of cardiovascular death, MI, or stroke among carriers of CYP2C19 1 *LoF* allele (1.6×) and also carriers of 2 *LoF* alleles (1.8×), as compared with noncarriers, was reported (FIGURE 1).[8]

Subsequent retrospective analyses of ACS trials involving mainly a mix of PCI and medically treated patients failed to demonstrate a significant association between *CYP2C19 LoF* allele carriage and adverse clinical outcomes (FIGURE 1).[9,10] The relation of the gain-of-function allele (*CYP2C19*17*) carrier status and *ABCB1* genotype to the antiplatelet response of clopidogrel and clinical outcomes in clopidogrel-treated patients are inconclusive at this time.[3] The relation of SNPs of the gene encoding paraoxonase-1 to the pharmacokinetic and pharmacodynamic effects of clopidogrel and clinical outcome is controversial.[11,12] In summary, the evidence to this date indicates that *LoF* allele carrier status is an important independent predictor of the pharmacodynamic response to clopidogrel and appears to influence clinical outcomes in high-risk clopidogrel-treated patients who have undergone PCI.

Use of other antiplatelet agents or alternative dosing strategies of clopidogrel to overcome the influence of the *LoF* allele has been proposed.[13] However, recent evidence indicated that therapy with high maintenance-dose clopidogrel (150 mg daily) was not a highly effective strategy to overcome the influence of the *LoF* allele and, in poor metabolizers, had no enhanced effect on reducing platelet reactivity compared with standard dose clopidogrel (75 mg daily).[14,15] Therapy with the third-generation thienopyridine, prasugrel (60 mg load / 10 mg daily maintenance) resulted in a 19% relative reduction in the occurrence of the primary composite endpoint of cardiovascular death, MI, and stroke compared with clopidogrel therapy (300 mg load / 75 mg daily maintenance) in patients undergoing PCI in the TRITON-TIMI 38 trial (The TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel Thrombolysis In Myocardial Infarction 38).[16] In a randomized study of patients with stable CAD, the *CYP2C19* genotype and SNPs of genes encoding other isoenzymes influenced active metabolite formation or the magnitude of platelet inhibition during clopidogrel therapy but not during prasugrel therapy.[17] Furthermore, in a subanalysis of the TRITON-TIMI 38 trial, carriers of the *LoF* allele treated with clopidogrel had higher rates of the primary outcome and definite/probable stent thrombosis compared with noncarriers, whereas among prasugrel-treated patients, *LoF* carrier status was unrelated to outcomes.[5,18]

The *CYP2C19 LoF* genotype significantly influenced the antiplatelet effect of clopidogrel, but

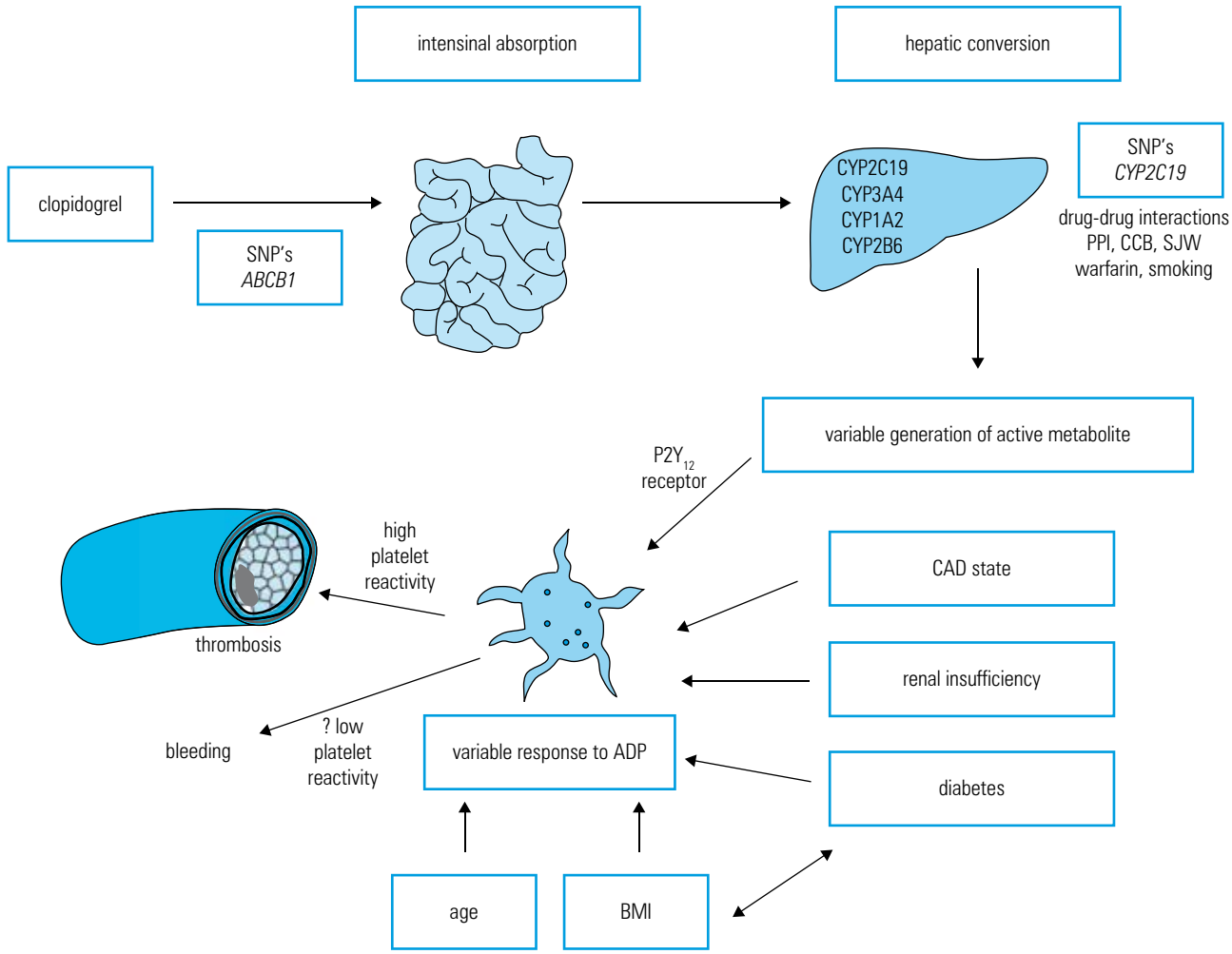

FIGURE 2 Various factors influencing platelet reactivity and clinical outcome during clopidogrel therapy (adapted from Gurbel PA, et al. Eur Heart J. 2012; 33: 1187-1189). Abbreviations: BMI – body mass index, CAD – coronary artery disease, CCB – calcium channel blocker, CYP – cytochrome P450, PPI – proton-pump inhibitor, SJW – St. John's wort, SNP – single nucleotide polymorphism

not ticagrelor, a direct-acting $P2Y_{12}$ receptor blocker, in stable CAD patients.[19] In the genetic substudy of the PLATO (Platelet Inhibition and Patient Outcomes) trial, an ACS study where ~64% of the patients underwent PCI, ticagrelor was associated with a reduced occurrence of cardiovascular events compared with clopidogrel irrespective of genotype.[20] Taken together, these data strongly suggest that prasugrel and ticagrelor are effective alternatives to overcome the influence of the *LoF* allele carrier state.

Currently, there are no data from prospective trials specifically designed to assess the clinical efficacy and safety of new $P2Y_{12}$ receptor blockers in patients identified as *LoF* allele carriers. However, the ongoing prospective randomized PAPI-2 trial (Pharmacogenomics of Anti-platelet Intervention-2) will determine the efficacy and safety of clopidogrel vs. prasugrel in *2 carriers undergoing PCI, and GeCCO (Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes Study) will compare the effectiveness of clopidogrel in CYP2C19 extensive metabolizers with prasugrel in adults recently hospitalized for ACS with primary, delayed, or planned PCI (NCT#01 452 152, NCT#00 995 514).

The fundamental reason for genotyping clopidogrel-treated patients is to identify those at risk of having high-risk phenotype, i.e., patients with HPR. However, as noted above, clopidogrel metabolism is influenced by concomitantly administered drugs and agents that either interact or compete with clopidogrel during hepatic cytochrome P450-mediated metabolism such as proton-pump inhibitors, calcium channel blockers, warfarin, and cigarette smoke. Moreover, it has been reported that on-treatment platelet reactivity to ADP is influenced by the CAD state, age, renal insufficiency, diabetes, and obesity (FIGURE 2).[21] The net effect of all of these influences is reflected in the final platelet reactivity phenotype. Although, the influence of genotype on platelet reactivity is likely stable over time, the cumulative influence of other factors is dynamic. Therefore, the assessment of platelet function may be more appropriate than genotyping to indicate the risk for ischemic event occurrence. Genotyping alone may be considered in high-risk patients to determine the optimal antiplatelet strategy.

Antiplatelet therapy monitoring: role of platelet function measurement Following the demonstration of clopidogrel-response variability, over 30 translational research studies conducted around the world involving thousands of patients utilizing multiple laboratory tests have reached the identical conclusion: patients treated with PCI who have HPR are at increased risk for both short- and long-term post-PCI ischemic event occurrence, including stent thrombosis.[3,22,23] These

TABLE Important studies linking high on-treatment platelet reactivity to ischemic events based on receiver operating characteristic curve with a specific cut-off value

Study	Assay	Cut-off value	Endpoint
Price et al.[28]	VerifyNow P2Y12 Assay	>235 PRU	6 months post-PCI CVD + MI + stent thrombosis
Gurbel et al.[25]	LTA	>46% 5 μM ADP >59% 20 μM ADP	2 years post-PCI MACE
Bonello et al.[26]	VASP-PRI	>50% PRI	6 months post-PCI MACE
Sibbing et al.[27]	Multiplate analyzer-ADP	>468 AU*min 6.4 μM ADP	30-day stent thrombosis

Abbreviations: ADP – adenosine diphosphate, AU – aggregation units, CVD – cardiovascular disease, LTA – light transmittance aggregometry, MACE – major adverse clinical events, MI – myocardial infarction, PCI – percutaneous intervention, PRU – $P2Y_{12}$ reaction units, VASP-PRI – vasodilator stimulated phosphoprotein-platelet reactivity index

studies have primarily used a single measurement of reactivity determined either immediately before PCI or at the time of hospital discharge. A recent consensus statement proposed cut-off values based on the receiver operating characteristic (ROC) curve analysis for different platelet function assays to be used in future studies of personalized antiplatelet therapy (**TABLE**).[3,24–27]

There has been a long-term reluctance to monitor antiplatelet therapy. The potential introduction of artifacts by the laboratory methods, incomplete reflection of the actual in-vivo thrombotic process, and failure to unequivocally establish a causal relation between the results of the test and thrombotic event occurrence are some reasons for this reluctance. In recent years, our understanding of platelet receptor physiology has markedly improved and more user friendly platelet function assays have been introduced. But still we lack the golden evidence from a large-scale prospective trial that changing antiplatelet therapy based on a platelet function test result actually helps the patient. And this is the most important reason why platelet function testing in the PCI population is not the standard of care.

The only completed randomized large personalized antiplatelet therapy trial, GRAVITAS (Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety), conducted in elective PCI patients with HPR, was neutral.[28] In this trial, many patients were low risk, the event rates were very low, and the regimen to combat HPR (double-dose clopidogrel) was pharmacodynamically suboptimal. The latter factors may have affected the ability to assess the utility of personalization, but it may also be possible that HPR is a nonmodifiable risk factor.[29] However, the result of the large-scale PLATO and TRITON trials, which demonstrated a greater antithrombotic effect associated with $P2Y_{12}$ inhibitors that have more potent ex vivo antiplatelet effects than clopidogrel, argues strongly against HPR being a nonmodifiable risk factor.[16,30]

It has also been argued that stent thrombosis rates are so low now in the era of third generation drug-eluting stents that the magnitude of the clinical problem is not as great as before. A common response from the interventionalist is, "I just don't see stent thrombosis in my practice." Finally, it may be impossible now to conduct any prospective personalized antiplatelet therapy trial where there is randomization to a known inferior pharmacodynamic regimen once high on-treatment platelet reactivity is identified. The latter was demonstrated in the aborted TRIGGER-PCI (Testing platelet Reactivity In patients undergoing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel) trial where about one third of the patients declined randomization once they knew they had HPR.[31]

Small translational research studies have demonstrated that ischemic risk is not linearly related to on-treatment platelet reactivity but rather occurred above a moderate level of platelet reactivity to ADP and also that very low platelet reactivity is associated with bleeding. The concept of a "therapeutic window" of $P2Y_{12}$ receptor reactivity associated with both ischemic event occurrence (upper threshold) and bleeding risk (lower threshold) has been proposed that is similar to the international normalized ratio range used for coumadin therapy. Currently, the absence of HPR is probably the best reassurance that future ischemic events, particularly stent thrombosis, will not occur.[32]

It should be taken into consideration that the currently accepted HPR cut-off values have been associated in many studies with modestly increased odds ratios for ischemic event occurrence and are associated with high negative predictive values and low positive predictive values (PPV). However, given the overall low prevalence of thrombotic events in these studies, the low PPV is understandable. Moreover, there is debate about whether diagnostic test statistics were appropriately used to describe the utility of prognostic tests, such as platelet function tests. Furthermore, in the recently presented ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) study (n = 8349), an investigation of the relation of post-PCI platelet reactivity measured by the VerifyNow assay to thrombotic event occurrence, patients with >208 $P2Y_{12}$ reaction units (PRU) had a 3-fold adjusted hazard for the occurrence of 30-day stent thrombosis.[33] Fifty percent of 30-day definite or probable

stent thrombosis occurrence was solely attributable to HPR by a multivariate analysis. Thus, the current data indicate that although platelet reactivity plays a major role in ischemic event occurrence (up to 50% of the attributable risk of 30-day stent thrombosis in the ADEPT-DES), other factors including demographic and clinical factors must be taken into consideration to optimally define the patients at greatest risk. Along this line, recent studies also suggest that adding clinical variables and genotype to platelet reactivity measurements (combined risk factor) will improve risk prediction.[34,35]

Based on the vast amount of accrued observational data, the recent 2011 American and European guidelines have given a class IIb recommendation in the high-risk patient for platelet function testing or genotyping if the results of testing may alter management.[36,37] At this time it appears less certain that we will witness the "proof" from an adequately powered randomized trial of personalized antiplatelet therapy. Certainly, a superiority trial seems unlikely given the above facts. However, a future study demonstrating noninferiority from the selective use of generic clopidogrel and the new $P2Y_{12}$ inhibitors may be more likely. However, low event rates in current practice would require enrollment of a very large number of patients and the prospect of finding funding for this type of endeavor is not promising. Thus, at this time we must rely on the guidelines and the existing observational data while keeping fully in mind the role that platelet physiology plays in catastrophic event occurrence in the PCI patient.

There are many gaps in our knowledge regarding the role of platelet function and genetic testing to optimize antiplatelet therapy including 1) no information in stable CAD patients, 2) no information on the relation of phenotype to event occurrence in medically managed ACS patients, 3) few data on the relation of long-term platelet reactivity to both ischemic and bleeding event occurrences, 4) preliminary data only on the relation of phenotype and genotype to bleeding, 5) limited data on the utility of combining genotype and phenotype data for prognosis, 6) uncertainty regarding the variability of platelet function over time, 7) limited data relating platelet function to clinical outcomes in a major clinical trial of antiplatelet therapy, and most importantly, 8) very limited evidence from a large-scale trial that personalization of antiplatelet therapy enhances efficacy and improves safety. Ongoing studies, including the TRILOGY ACS (TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes) (NCT#00 699 998) Platelet Function Substudy, and future studies will provide valuable information and potentially influence the field of personalized antiplatelet therapy.

The HPR threshold mentioned in the consensus statement was determined by the ROC curve analysis and is only applicable to the PCI population. However, based on the group of patients from GRAVITAS treated with standard-dose clopidogrel, an even lower threshold defining HPR (~170 PRU) was associated with optimal identification of patients destined to experience ischemic event occurrence. It was suggested that this "immunity to thrombosis" cut-off should be considered as the new therapeutic target in the PCI patient.[38]

Personalized antiplatelet therapy in the surgical patient Irreversible inhibition of platelet function associated with thienopyridine therapy carries a substantial risk of bleeding, particularly in patients undergoing coronary artery bypass graft surgery (CABG). Up to 15% of the patients presenting with ACS will require CABG, and bleeding complications and transfusion of red blood cells in these patients have been associated with adverse outcomes. The 2011 American College of Cardiology Foundation / American Heart Association Guidelines for the Management of Patients with Unstable Angina / Non-ST-Elevation Myocardial Infarction has a class I recommendation for withdrawing clopidogrel for 5 days and prasugrel for 7 days to allow for the recovery of platelet function before planned CABG.[39] In the TARGET-CABG (Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to CABG) study, the first prospective investigation of a platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing surgery, 180 patients on background aspirin with/without clopidogrel therapy undergoing elective first-time isolated on-pump CABG were enrolled. Clopidogrel responsiveness (ADP-induced platelet-fibrin clot strength [MA_{ADP}]) was determined by thrombelastography; CABG was performed within 1 day, 3–5 days, and >5 days in patients with an MA_{ADP} >50 mm, 35–50 mm, and <35 mm, respectively. Mean 24-hour chest tube drainage in clopidogrel-treated patients, the primary endpoint, was 93% (95% confidence interval, 81%–107%) of the amount observed in clopidogrel-naive patients, and the total amount of red blood cells transfused did not differ between the groups (1.80 U vs. 2.08 U, respectively, $P = 0.540$). An overall 46% shortening of the guideline recommended preoperative waiting period for clopidogrel-treated patients (mean 2.7 days vs. 5 days per patient) resulted from the platelet function assessment strategy employed in TARGET-CABG.[40]

Conclusions The evidence to this date indicates that *CYP2C19 LoF* allele carrier status is an important independent predictor of the pharmacodynamic response to clopidogrel. HPR and *CYP2C19 LoF* carriage are associated with clinical outcomes in high-risk clopidogrel-treated patients who have undergone PCI. Data from TRITON-TIMI 38 and PLATO trials strongly suggest that prasugrel and ticagrelor are effective alternatives to 150 mg high-dose clopidogrel to overcome the influence

of the *LoF* allele carrier status, and pharmacodynamic studies suggest that prasugrel and ticagrelor are effective in overcoming HPR status during clopidogrel therapy.[41,42]

Therefore, it may be reasonable at this time to assess platelet function in high-risk clopidogrel-treated patients (patients with current or prior ACS, history of stent thrombosis and target vessel revascularization, poor left ventricular function, multivessel stenting, complex anatomy [e.g., bifurcation, long, small stents], high body mass index, diabetes mellitus, and patients cotreated with proton-pump inhibitors) and treat with more potent $P2Y_{12}$ receptor therapy selectively. Clopidogrel is pharmacodynamically effective in about two thirds of the patients undergoing PCI; these patients do not have HPR. Ischemic risk is much greater in patients with HPR. Therefore, selectively treating two thirds of the patients with generic clopidogrel may provide significant cost savings. Unselected therapy with the new $P2Y_{12}$ receptor blockers is associated with increased bleeding. Clinicians should strive to find the antiplatelet therapy that achieves the optimal level of platelet inhibition for the patient, regardless of the cost. If generic clopidogrel is indeed pharmacodynamically effective in the patient, offering them this less expensive option appears to be a win/win. The introduction of generic clopidogrel holds a strong possibility of inducing a change in practice, whereby genetic and platelet function testing is performed more frequently in patients receiving a stent. This will allow the patient's platelet physiology decide the course of treatment instead of the price tag on the pill bottle.

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ARTYKUŁ POGLĄDOWY

Leczenie przeciwpłytkowe po 2012 r. – rola medycyny personalizowanej

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SŁOWA KLUCZOWE

blokery recetora $P2Y_{12}$, klopidogrel, leczenie przeciwpłytkowe, prasugrel, tikagrelor

STRESZCZENIE

Klopidogrel zrewolucjonizował od chwili pierwszego zatwierdzenia go w 1997 r. kardiologię inwazyjną i odmienił leczenie chorych z zawałem serca bez uniesienia odcinka ST (*non-ST-segment elevation myocardial infarction* – NSTEMI), z zawałem serca z uniesieniem odcinka ST (STEMI) oraz tych, u których przeprowadza się przezskórne interwencje wieńcowe. Przez 15 lat był on niekwestionowanym liderem na światowym rynku, nie mając żadnej większej konkurencji. Wraz z wprowadzeniem skuteczniejszych blokerów receptora $P2Y_{12}$ obecna strategia leczenia przeciwpłytkowego znalazła się w okresie przejściowym. Generyczny klopidogrel jest niedrogi i skuteczny farmakodynamicznie u co najmniej 1/3 chorych na chorobę wieńcową. Jego głównymi ograniczeniami są nieprzewidywalne, wolne działanie na początku oraz ogólnie rzecz biorąc umiarkowane efekty farmakodynamiczne. W nowych, skuteczniejszych blokerach receptora $P2Y_{12}$ udało się przezwyciężyć ograniczenia występujące przy leczeniu klopidogrelem, a ich stosowanie powoduje lepszą skuteczność kliniczną, ale ma ono większy koszt i wiąże się z częstszym krwawieniem. Wobec takiego scenariusza indywidualizacja leczenia przeciwpłytkowego w oparciu o testy czynności płytek krwi i badania gentyczne, aby znaleźć równowagę między kosztami, skutecznością i bezpieczeństwem, jest możliwą opcją postępowania.

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