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Role of Genetic Testing in Patients undergoing Percutaneous Coronary Intervention

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Abstract

Introduction—Variability in individual response profiles to antiplatelet therapy, in particular clopidogrel, is a well-established phenomenon. Genetic variations of the cytochrome P450 (CYP) 2C19 enzyme, a key determinant in clopidogrel metabolism, have been associated with clopidogrel response profiles. Moreover, the presence of a *CYP2C19* loss-of-function allele is associated with an increased risk of atherothrombotic events among clopidogrel-treated patients undergoing percutaneous coronary interventions (PCI), prompting studies evaluating the use of genetic tests to identify patients who may be potential candidates for alternative platelet $P2Y_{12}$ receptor inhibiting therapies (prasugrel or ticagrelor).

Areas covered—The present manuscript provides an overview of genetic factors associated with response profiles to platelet $P2Y_{12}$ receptor inhibitors and their clinical implications, as well as the most recent developments and future considerations on the role of genetic testing in patients undergoing PCI.

Expert Commentary—The availability of more user-friendly genetic tests has contributed towards the development of many ongoing clinical trials and personalized medicine programs for patients undergoing PCI. Results of pilot investigations have shown promising results, which however need to be confirmed in larger-scale studies to support the routine use of genetic testing as a strategy to personalize antiplatelet therapy and improve clinical outcomes.

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Conflict of interest

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Keywords

clopidogrel; $P2Y_{12}$ receptor antagonist; genotype; pharmacogenomics; *CYP2C19*

1. Introduction

Therapeutic inhibition of platelet activation is essential for the management of ischemic cardiovascular disease [1]. The use of platelet adenosine diphosphate (ADP) $P2Y_{12}$ receptor antagonists in addition to aspirin, also known as dual antiplatelet therapy (DAPT), has significantly contributed towards reduction in atherothrombotic events particularly in high-risk patients such as those with acute coronary syndromes (ACS) or undergoing percutaneous coronary interventions (PCI) [2–4]. Currently, three oral $P2Y_{12}$ receptor antagonists (clopidogrel, prasugrel, and ticagrelor) are commonly used in clinical practice. Although prasugrel and ticagrelor are associated with more reliable pharmacological effects compared with clopidogrel, which translates into a greater reduction of atherothrombotic events in ACS patients, clopidogrel is the most broadly utilized $P2Y_{12}$ receptor inhibitor [5,6]. Indeed, the reduced cost, ease of access, and reduced risk of bleeding complications associated with clopidogrel contribute to these observations. However, a plethora of investigations over the years has consistently shown a broad variability in interindividual response profiles among clopidogrel-treated subjects [7]. Most importantly, PCI patients with impaired clopidogrel-induced antiplatelet effects, also known as high on-treatment platelet reactivity (HPR), have an increased risk of ischemic events, including stent thrombosis [7,8]. There is also emerging evidence, albeit with conflicting data, that patients with enhanced clopidogrel-induced antiplatelet effects, also known as low on-treatment platelet reactivity (LPR), have an increased risk of bleeding complications [8,9].

Multiple mechanisms, including clinical, cellular and genetic factors, contribute to individual's response profile to clopidogrel [7,8]. Among genetic factors, a number of genes coding for enzymes or receptors that may be involved with the pharmacokinetic (PK) or pharmacodynamic (PD) profiles of clopidogrel have been investigated. However, genetic variations of the hepatic cytochrome P450 (CYP) 2C19 enzyme, a key determinant in both metabolic steps of clopidogrel transformation into its active metabolite, has been consistently associated with interindividual variability in clopidogrel's PK/ PD profile [10,11]. In particular, the presence of loss-of-function (LOF) alleles in the *CYP2C19* gene is associated with reduced metabolism of clopidogrel and lower generation of its active metabolite, which in turn leads to reduced antiplatelet effects and consequently increases the risk atherothrombotic events [11,12]. These observations have prompted studies evaluating the use of genetic tests to identify patients with a *CYP2C19* LOF allele who may be potential candidates for alternative platelet $P2Y_{12}$ receptor inhibiting therapies, such as prasugrel or ticagrelor, the effects of which are not affected by this genotype [13]. The availability of more efficient genetic tests has also contributed towards the development of a number ongoing clinical trials and personalized medicine programs for patients undergoing PCI [14]. The present manuscript provides an overview of genetic factors associated with response profiles to platelet $P2Y_{12}$ receptor inhibitors and their clinical implications, as well

as the most recent developments and future considerations on the role of genetic testing in patients undergoing PCI.

2. Pharmacologic profiles and Clinical Outcomes of $P2Y_{12}$ Receptor Inhibitors

2.1. Clopidogrel

Clopidogrel is a second-generation thienopyridine, which has largely replaced ticlopidine, a first generation thienopyridine, because of its better safety profile [1,3]. Clopidogrel is an inactive form of pro-drug, which needs to undergo an oxidative process by the hepatic CYP system to become active. The hepatic conversion of clopidogrel to its active metabolite is a 2-step biotransformation process. Since 85% of clopidogrel pro-drug is inactivated by esterases in the blood, only15% of the pro-drug is available for transformation to the active metabolite (Figure 1) [7,15,16]. The active metabolite irreversibly inhibits the platelet $P2Y_{12}$ receptor, thus exerting its antiplatelet effects for the life-span of the platelet. A number of trials conducted in high-risk patients with coronary artery disease (CAD), in particular those with ACS and/or undergoing PCI, have consistently shown that clopidogrel in addition to aspirin reduces both short- and long-term ischemic events and thrombotic complications [17–20]. For this reason, for nearly two decades, this DAPT regimen represented the standard of care in ACS and PCI patients. However, the observation that a considerable number of patients continue to experience recurrent ischemic events, including stent thrombosis, has prompted investigations to better understand the response profiles of clopidogrel, which have shown a broad variability in clopidogrel-induced antiplatelet effects [7,8]. Importantly, PCI patients with impaired clopidogrel-induced antiplatelet effects, or HPR, have an increased risk of ischemic events, including stent thrombosis, while those with enhanced clopidogrel induced antiplatelet effects, or LPR, may have an increased risk of bleeding complications [7–9]. These observations have prompted the development of newer generation oral $P2Y_{12}$ receptor inhibitors, such as prasugrel and ticagrelor [1].

2.2. Prasugrel

Prasugrel is a third-generation thienopyridine which, like clopidogrel, also is a pro-drug requiring hepatic metabolism to generate its active metabolite, which irreversibly inhibits the platelet $P2Y_{12}$ receptor [1,3,21]. However, unlike clopidogrel, prasugrel is almost completely absorbed in the intestine and hydrolyzed into a thiolactone by the intestinal esterases. This thiolactone undergoes a single-step hepatic metabolism, primarily by CYP3A and CYP2B6, with a minor role of CYP2C19 and CYP2C9, to generate its active metabolite (Figure 1) [22]. Therefore, the metabolic conversion of prasugrel is more efficient than that of clopidogrel, providing higher drug bioavailability. In turn prasugrel has a more rapid onset of action, enhanced platelet inhibition, and less inter-individual variability in effects than with clopidogrel [23]. Its more potent irreversible platelet inhibitory effects also explains the slower offset of effects compared with clopidogrel [24]. These pharmacological properties contribute to the enhanced efficacy of prasugrel to reduce ischemic recurrences, including stent thrombosis, in high-risk ACS patients undergoing PCI, albeit at the expense of increased bleeding, including fatal bleeding [25]. In clinical trial participants with a prior

cerebrovascular event, there was an increased risk of intracranial hemorrhage (ICH) and overall net harm, reason for which prasugrel is contraindicated in these patients [25]. The risk of bleeding was increased in patients of low body weight (≤60 kg) and old age (≥75 years), likely attributed to excess active metabolite formation (suggesting the need for lower doses in these patients) in whom the net effect of prasugrel was neutral [25–27].

2.3. Ticagrelor

Ticagrelor is a first in class cyclopentyltriazolopyrimidine which reversibly binds to the $P2Y_{12}$ receptor at distinct site to that of ADP [28–30]. After intestinal absorption, ticagrelor directly binds (without the need for metabolism) to the $P2Y_{12}$ receptor. However, 20–30% of the antiplatelet effects induced by ticagrelor derive from metabolites, mainly AR-C124910XX, generated by the hepatic CYP3A4 and CYP3A5 enzymes. Both the parent drug and the active metabolite have similar potency (Figure 1) [31,32]. These properties explain why ticagrelor has a more rapid onset of action, enhanced platelet inhibition, and less inter-individual variability in effects than with clopidogrel [33]. Its reversible binding property also explains the faster offset of effects compared with clopidogrel [33]. Overall, these pharmacological effects contribute to the enhanced efficacy of ticagrelor to reduce ischemic recurrences, including stent thrombosis, in ACS patients, irrespective of management (invasive or non-invasive) [34]. Moreover, it is the only $P2Y_{12}$ receptor inhibitor which, compared with clopidogrel, also reduces cardiovascular mortality. These benefits have also been attributed to the off-target effects of ticagrelor, which does not occur for thienopyridines, represented by blockade of the equilibrative nucleoside transporter-1 (ENT-1) located on erythrocytes, which in turn leads to an increase in circulating adenosine plasma levels [35]. Although there were no differences in overall bleeding complications, there was an increase in spontaneous bleeding [34]. However, there was no subgroup identified to be at increased risk for bleeding complications with ticagrelor. The other most common side effect is represented by dyspnea, which has been attributed to ticagrelor's effect on adenosine and is also the leading cause of drug discontinuation [34,36].

3. Genetic determinants of response to $P2Y_{12}$ Receptor Inhibitors

The study of genetic polymorphisms has received a lot of attention over the past years in the field of cardiovascular disease. In particular, pharmacogenetics is the study of how genetic differences influence the variability in patients' responses to drug [37]. Specific polymorphisms in genes which encode proteins or molecules associated with drug absorption, metabolism, transport, or eliciting therapeutic effects may potentially affect an individual's response to the drug and thus explain drug effectiveness and safety profiles for the individual [38]. Therefore, the ultimate goal of a pharmacogenetic study is to identify specific genetic polymorphism(s) that are able to explain the variability in individual patient response to a given drug [37]. Identification of patients with specific genetic polymorphisms may be clinically important as these subjects may benefit from alternative therapies. This approach is the foundation for the concept of personalized treatment strategies. The ever-growing knowledge in the field of pharmacogenetics has indeed contributed the development of personalized medicine programs [39].

3.1. *CYP2C19* gene and Clopidogrel Pharmacokinetics and Pharmacodynamics

A large number of drugs (such as clopidogrel, benzodiazepines, antidepressants, voriconazole, and some proton pump inhibitors) are metabolized by the CYP2C19 enzyme system in the liver [40]. The gene that codes the CYP2C19 enzyme is highly polymorphic, like many other CYP450 superfamily members [41]. Based on numerous studies including a genome-wide association study (GWAS), the *CYP2C19* gene is known to be the most potent genetic determinant of interindividual variability in clopidogrel response [10–12,42–46]. It is located on chromosome 10 (10q24.1– q24.3), and over 30 gene alleles have been identified [41]. Among them, the *CYP2C19*1* allele is the most prevalent and represents a normal activity allele. The *CYP2C19*2* to **8* alleles are LOF alleles. Of these, *CYP2C19*2* is the most frequently observed LOF allele [41]. There is a notable ethnic and racial difference in the frequency of *CYP2C19* LOF alleles. For the East Asian population, the frequency of **2* and **3* is much higher than the European and African ancestry populations (Table 1) [47]. The allele frequency of **2* has been reported as about 15 % in Caucasians and Africans, and range between 25% and 35% in Asians [47–49]. The **3* through **8* alleles have a low frequency in the European and the African ancestry populations (less than 1%). The *CYP2C19*3* allele is more common in East Asian populations (5–15%), and its effect on the clopidogrel response appeared greater than the *CYP2C19*2* allele in an East Asian-based study [48,50]. The *CYP2C19*17* allele results from a genetic variation in the gene promoter region associated with higher transcription rates of the gene, contributing to enhanced enzymatic activity and is thus called an increased or gain-of-function (GOF) allele [51,52]. The presence of **17* allele is significantly greater in African and European ancestry populations compared to Asian populations. The frequencies of *CYP2C19* polymorphisms in major ethnic groups are presented in Table 1[47]. The distribution of *CYP2C19* genotypes allows for individuals to be classified as follows: Ultrarapid metabolizers (UMs), Rapid metabolizers (RMs), normal metabolizers (NMs), Intermediate metabolizers (IMs), Poor metabolizers (PMs) (Table 2) [47,53]. PMs have 2 LOF alleles, and IM have one copy of a LOF allele. The **1/*1*, **1/*17*, and **17/*17* genotypes confer the NM, RM, and UM phenotypes, respectively. The prevalence of the PM phenotype is reported as 2–4% among African and Europeans ancestry populations, whereas it is 10% to 20% among East Asians [47,54].

Since there had been numerous reports that carriers of a LOF genotype (*CYP2C19*2* and **3*) have reduced capacity to produce active metabolites of clopidogrel, the Food and Drug Administration (FDA) requested that a dedicated study be performed to confirm these observations [55]. In this healthy subject study (n=40), PMs had lower conversion rate of clopidogrel to its active metabolite and HPR. This result led to the clopidogrel label change by drug regulating authorities, as described below.

In another study, carriers of a *CYP2C19* LOF allele showed a 32.4% reduction in formation of the active metabolite of clopidogrel compared with non-carriers and a 9% absolute reduction of platelet aggregation (a relative reduction of approximately 25%) in response to clopidogrel [46]. Heterozygotes of *CYP2C19* LOF alleles (e.g., **1/*2* and **1/*3*) have clopidogrel response that lies between homozygotes for the **1* allele and LOF allele homozygotes or compound heterozygotes (e.g., **2/*2* and **2/*3*) [45,46,56]. Carriers of the

**17* allele have enhanced clopidogrel metabolism and with increased production of its active metabolite and greater clopidogrel-induced antiplatelet effects. In a meta-analysis, carriers of the *CYP2C19*17* GOF allele showed lower prevalence of HPR than in non-carriers treated with standard dose clopidogrel [57].

3.2. Impact of *CYP2C19* genotype on Clinical Outcomes

Numerous observational studies have shown an association between *CYP2C19* LOF alleles and an increased risk of ischemic events [10–12,43,44,46]. However, this association has not been consistently observed across studies and may be attributed to the population under investigation. In a meta-analysis including 9 studies of 9,865 clopidogrel treated patients (54.5% with ACS and 91.3% with PCI), carriage of even one *CYP2C19* LOF allele was associated with worse outcomes, particularly stent thrombosis [12]. Another large meta-analysis study, including 32 studies of 42,016 lower risk patients (e.g. patients with stable coronary disease, ACS managed medically, or atrial fibrillation) demonstrated the significant association between carriage of 1 or more *CYP2C19* alleles and reduced clopidogrel responsiveness, however there was no significant association with adverse outcome when analyses were restricted to studies with 200 or more events (for exclusion of small-study bias) [58]. These conflicting results between two meta-analyses might be attributed to the baseline characteristics of the patients [59,60]. In fact, *CYP2C19* LOF alleles have been shown to be clinically important mainly in high-risk subset (such as PCI) or the acute phase of myocardial infarction (MI), whereas in chronic stable patients or those with other indications like atrial fibrillation, genotype does not appear to be significant [61–63]. Recently, an intriguing result from a meta-analysis (including 24 studies of 36,076 participants) on *CYP2C19* genotyping which specifically analyzed patients according to the indication for the use of clopidogrel (i.e., with or without PCI) and ethnic population (White versus Asian) was published [64]. In this analysis, the presence of a *CYP2C19* LOF allele was associated with adverse outcomes only in patients using clopidogrel because of a PCI indication. This association was more modest (RR 1.20, 95% CI 1.10–1.31) among Whites undergoing PCI and stronger among Asians (RR 1.91, 95% CI 1.61–2.27).

On the contrary to the *CYP2C19* LOF alleles, patients carrying the *CYP2C19* GOF (i.e., **17*) allele might be protected from ischemic recurrences but may also have a higher risk of bleeding due to the enhanced clopidogrel-induced antiplatelet effects [51,52,57,65]. Data from pooled analysis of six clinical studies showed that presence of the *CYP2C19*17* GOF allele had a benefit against recurrent cardiovascular events in patients with CAD compared with non-carriers (OR 0.82, 95% CI 0.72–0.94, p = 0.005). Conversely, carriers of the **17* allele had an increased risk of bleeding complications (OR 1.25, 95% CI 1.07–1.47, p = 0.006) [57]. However, the data on the impact of the *CYP2C19*17* allele on platelet function profiles and clinical outcomes, including bleeding risk, among clopidogrel treated patients are inconsistent [63,65,66].

Overall, the available evidence consistently supports that the presence of a *CYP2C19* LOF allele contributes to HPR and an increased risk for adverse cardiovascular outcomes, including stent thrombosis among patients undergoing PCI [10–12,43,44,46].

3.3. *CYP2C19* genotypes and Newer Generation $P2Y_{12}$ Receptor Inhibitors

Although some of the CYP450 isoenzymes contributing to clopidogrel metabolism are also required for prasugrel metabolism, genetic polymorphisms of these enzymes have not shown to affect the PK and PD profiles of prasugrel [56,67–70]. Moreover, clinical outcomes of prasugrel-treated patients were not affected by CYP450 genetic polymorphisms [70,71]. Similarly, the pharmacological properties of ticagrelor and clinical outcomes of ticagrelor treated patients have not shown to be affected by CYP450 or other genetic polymorphisms [62,72,73].

3.4. Other candidate genes

A number of other candidate genes including *ABCB1*, Carboxylesterase 1 (*CES 1*), paraoxonase-1(*PON1*), *CYP2C9*, *CYP3A4*, $P2Y_{12}$, and *PlA* genes have been proposed as genetic determinants of clopidogrel response and adverse clinical outcomes [37,56,71,74–79]. The absorption of thienopyridine is associated with an activity of the efflux pump P-glycoprotein, encoded by the *ABCB1* gene. Increased activity of this pump system may decrease the absorption of clopidogrel in the intestine. Therefore, the *ABCB1* polymorphism has been suggested to be correlated with clopidogrel intestinal efflux [71]. Carboxylesterase 1 is the main enzyme to convert the absorbed clopidogrel into an inactive form [80,81]. In one study, the presence of the *CES1 143 E*-allele led to an increase in clopidogrel active metabolite levels and enhanced platelet inhibition [74]. PON1 is associated with bioactivation of clopidogrel; PON1 catalyzes the conversion of 2-oxo-clopidogrel into active metabolite. There are some reports that *Q192R* polymorphism of *PON1* contributes to reduced clopidogrel activity and increased risk of stent thrombosis in PCI patients [77]. The CYP2C9 and CYP3A4 enzymes are also involved in the clopidogrel metabolism, and thus genes encoding these enzymes have also been implicated in clopidogrel response [75,79]. Coexisting genetic variations of $P2Y_{12}$ and *CYP2C19* seemed to be associated with platelet activation in a small study [76]. The polymorphism of the $Pl\ (A_1/A_2)$ gene-encoding glycoprotein (GP) IIIa also showed an association with clopidogrel response [78]. Although some studies have demonstrated the association between each polymorphism and clinical outcomes, most of data are inconsistent [11,62,82–87]. Importantly, GWAS showed that only *CYP2C19* is associated with meaningful variability in clopidogrel response, suggesting that if other candidate genes that predict clopidogrel response exist, they likely have a much smaller impact [10].

4. Current Guidelines for *CYP2C19* Genotyping and Assays for Bedside Genotyping

4.1. Current Guidelines for *CYP2C19* genotyping

Data on the impact of *CYP2C19* LOF alleles on the PK/PD profiles of clopidogrel and clinical outcomes have prompted drug regulating authorities including the FDA and the European Medicines Agency to issue a warning [88,89]. More specifically, they warn about the reduced effectiveness in patients who are PMs of clopidogrel and advise consideration of alternative antiplatelet agents [49]. Nevertheless, genotyping for *CYP2C19* LOF alleles in high risk patients undergoing PCI is considered a Class IIb recommendation, and routine

genotyping is not recommended (Class III) in the ACCF/AHA/SCAI guideline [2,90,91]. Similar to the ACCF/AHA/SCAI guideline, the ESC guidelines indicate that routine genetic testing is not recommended and should only be considered in selected patients treated with clopidogrel (Class IIb recommendation) [92,93]. Overall, the reason for this low level of recommendations derives from the lack of prospective randomized trial data demonstrating an impact on clinical outcomes with genotype-guided antiplatelet therapy. Moreover, it has been argued that the positive predictive value of a *CYP2C19* LOF allele is low, and this polymorphism accounts for only 12% of clopidogrel response variability [94]. Ultimately, at the time of writing of the guidelines there were no user-friendly genetic tests that would allow for having results in the acute care setting, limiting the feasibility of applying results of genetic tests in real-world practice given that several days or weeks would be necessary prior to obtaining results [49]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are available for clopidogrel use based on *CYP2C19* genotype [47]. CPIC guidelines do not provide recommendations on whether pharmacogenetic testing should be conducted, but focus on how to apply genetic test results in clinical practice for optimal antiplatelet therapy. These guidelines recommend using alternative antiplatelet agents (e.g., ticagrelor or prasugrel) for *CYP2C19* PMs and IMs in the absence of contraindications in ACS/PCI patients (Figure 2).

4.2. Assays for Rapid *CYP2C19* Genotyping

One of the major limitations to implementing genetic testing in clinical practice has been the availability of assays that allow for obtaining results in a timely fashion. With standard genetic assays, results may not be available for days or even weeks. In addition, many centers do not have the capability of conducting genetic testing, and thus, samples must be sent to off-site laboratories for testing. Having genetic test results available in a timely fashion is critical if test results are to be considered in the setting of PCI, where prompt use of a $P2Y_{12}$ receptor inhibitor is necessary. Timing from clinical presentation to the cardiac catheterization laboratory has dramatically shortened over the years, particularly in ACS settings, and most patients undergo ad-hoc PCI procedures following diagnostic angiography [95]. Obtaining genetic test results after patients have been discharged is not practical as LOF carriers started on clopidogrel will not be optimally treated in the critical early weeks following PCI, and physicians must follow up with patients to switch to appropriate alternative therapy [96].

Recently, two rapid assays for *CYP2C19* genetic testing have reached the market: SpartanRx™ (Spartan Bioscience, Ottawa, Canada) and the Verigene® System (Nanosphere, Northbrook, Illinois) (Figure 3) [14,97]. The SpartanRx is based on polymerase chain reaction and takes only one hour to obtain genetic information. The Spartan system is a user-friendly rapid genetic testing assay, which uses a buccal swab as a specimen, thus requiring minimal training. The feasibility of using this assay in real world clinical practice was demonstrated in patients (n=200) undergoing PCI for an ACS or stable angina in the point-of-care genetic testing for personalization of antiplatelet treatment (RAPID GENE) study [14]. The Verigene CYP2C19 test, an automated microarray-based assay, uses whole blood and takes 3 hours to provide results [98].

5. Personalized Antiplatelet Treatment based on Genotype

5.1. Dosage adjustment of clopidogrel to overcome the *CYP2C19* LOF allele

Several studies using a clopidogrel dose-escalation strategy to overcome HPR in the presence of a *CYP2C19* LOF allele have been conducted. In healthy volunteers, clopidogrel dose escalation from 75mg to 150mg or 300mg per day was tested using platelet aggregation [99]. In a healthy volunteer study, the dose necessary to obtain similar inhibition of platelet aggregation as a standard 75mg/day dose in NMs was 300 mg/day in *CYP2C19*2* homozygotes (PMs) and 150 mg/day in *CYP2C19*2* heterozygotes (IMs). Therefore, a dose at least quadruple of the usual clopidogrel dose might be necessary to overcome the effect of the homozygous *CYP2C19* LOF genotype [99]. Among patients with stable cardiovascular disease, tripling the dose of clopidogrel to 225 mg daily in *CYP2C19*2* heterozygotes was shown to be required to reach similar levels of platelet reactivity as a 75 mg daily dose among non-carriers of a LOF allele. Importantly, among homozygotes for a LOF allele (PMs), a 300 mg/day dose failed to achieve the level of platelet inhibition observed with a 75 mg dose in non-carriers of a LOF allele [100]. In the Genotype Information and Functional Testing (GIFT) study (n=1,028), there was no significant PD effect with double-dose clopidogrel treatment (150mg daily) compared with a standard 75mg dosing regimen in among patients who were carriers of a *CYP2C19* LOF allele and undergoing PCI [101]. Therefore, findings from dose escalation in healthy participants might not apply to patients of CAD. In a recently published meta-analysis, high-dose clopidogrel therapy was not shown to overcome the HPR rates in *CYP2C19*2* carriers in patients undergoing PCI [102]. Overall, these findings indicate that switching to an alternative $P2Y_{12}$ receptor inhibitor (i.e., prasugrel or ticagrelor) rather than increasing the clopidogrel dose should be considered for *CYP2C19* LOF allele carriers.

5.2 Change to novel antiplatelet agent and adding another drug

Both ticagrelor and prasugrel have more potent PD effects compared with clopidogrel, and this superiority in PD has translated into better clinical outcomes in clinical studies of ACS patients [3,4]. The presence of *CYP2C19* LOF alleles has not been shown to affect the PD effects of either prasugrel or ticagrelor, and more potent platelet inhibitory effects can be achieved by both drugs compared to clopidogrel in healthy volunteers and in CAD patients with *CYP2C19* LOF alleles [56,67,72,103]. Most recently, prasugrel was shown to be superior to an escalated dosing strategy of clopidogrel in reducing HPR among patients with a ST-segment elevation myocardial infarction (STEMI) who had high risk genetic profiles identified using the SpartanRx system, further supporting the feasibility of performing genetic testing in real-world clinical practice including in the highest risk settings [104]. Although prasugrel and ticagrelor are deemed to have similar PD potency [105], it is unclear if they exert differential PD effects among carriers of *CYP2C19* LOF alleles, which is currently being tested in patients undergoing non-emergent PCI (NCT 02065479). Overall, the novel antiplatelet agents may contribute to better clinical outcomes than clopidogrel in patients with *CYP2C19* LOF alleles. Unfortunately, there are still limited data supporting improved clinical outcomes with genotype-based personalized antiplatelet therapy. Retrospective assessments of randomized controlled trial data suggest a benefit of using newer $P2Y_{12}$ inhibitors in *CYP2C19* LOF allele carriers. Specifically, the genetic sub-

studies of the PLATO and TRITON-TIMI 38 trials concluded that genetic polymorphisms of *CYP2C19* did not influence the efficacy of prasugrel or ticagrelor [62,70]. In an analysis of TRITON-TIMI 38, patients with a *CYP2C19* LOF genotype were estimated to have a substantial reduction in the risk of the composite primary outcome with prasugrel as compared with clopidogrel [106]. However, these investigations were designed to demonstrate the efficacy of these drugs irrespective of the presence of LOF allele, underscoring the need for specifically designed studies investigating whether genotype based personalized antiplatelet therapy is associated with improved outcomes.

Cilostazol, an inhibitior of phosphodiesterase type 3 and indicated for symptomatic treatment of peripheral artery disease in United States, is a unique antiplatelet agent that exerts its effects through increasing the intracellular cAMP level [107]. Intriguingly, the addition of cilostazol to DAPT showed a reduction of HPR in patients with *CYP2C19* LOF variants compared with high dose clopidogrel (150mg daily dose) [108,109]. Vorapaxar is new class of drug, which inhibited the action of thrombin in the protease activator receptors-1(PARs-1) [110]. The efficacy of this drug is demonstrated in the patients with prior MI or peripheral artery disease as an add-on therapy to standard DAPT [111]. However, the impact of adding vorapaxar among carriers of *CYP2C19* LOF variants is unknown.

5.3 Clinical outcome studies of genotype based personalized medicine

To date, data supporting the role of genotype based personalized antiplatelet therapy are limited and largely derived from registry data or small randomized studies, while there is no large randomized clinical trial demonstrating whether genotype based personalized antiplatelet therapy improve clinical outcomes or not [112–115]. A preliminary report from the University of Florida suggested improved outcomes with genotype based antiplatelet therapy. Among 412 patients who underwent PCI with genotyping, 126 (31%) had a LOF allele, and 68 (54%) of these received alternative antiplatelet therapy. On multivariable Cox regression analysis with propensity score adjustment, patients with a *CYP2C19* LOF allele who were treated with alternative antiplatelet therapy (e.g. prasugrel or ticagrelor) had a significantly lower risk for MACE (defined as the composite of cardiovascular death, MI, stroke, or stent thrombosis) over the 6-month follow-up period compared to patients with an LOF allele who were treated with clopidogrel (p=0.035) (Figure 4) [116]. More recently, this study group expanded upon these observations in the context of a larger-scale multicenter investigation. This study was conducted as part of the NIH-funded Implementing GeNomics In pracTicE (IGNITE) Network [117]. In particular, among patients undergoing PCI and clinical *CYP2C19* genotyping (n=1,815) at 7 U.S. institutions, the risk for MACE, defined as the composite of all-cause mortality, MI, or stroke, was compared between LOF allele carriers treated with clopidogrel and LOF allele carriers treated with alternative antiplatelet agent (ticagrelor, prasugrel). A total of 572 patients (31.5%) had a LOF allele, and 346 LOF allele carriers (60.5% of total carriers) received an alternative antiplatelet agent. The risk of MACE was significantly higher in LOF carriers treated with clopidogrel compared with the alternative treatment group (HR 2.3, 95% CI 1.2–4.5, p=0.015) [118]. With the recent availability of genetic tests providing results in a more timely fashion, as part of an extension of the University of Florida Health Personalized

Medicine Program [119], funded under the IGNITE Network, there is an ongoing registry (NCT02724319) implementing *CYP2C19*-guided antiplatelet therapy after PCI, which genotyping conducted using the SpartanRx system.

Currently, several ongoing studies are testing the efficacy of a genotype based approach to tailor personalize antiplatelet therapy (Table 3). The Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment (GIANT) trial (NCT 01134380) has completed patient recruitment. The GIANT trial is an observational case control study, including STEMI patients treated with primary PCI. The genetic information (*CYP2C19*2* allele) of the patients tested after primary PCI is communicated to the treating physician. At the time of primary PCI, DAPT (Aspirin + Clopidogrel/Prasugrel) was used initially, and then the physician could change or adjust the regimen after the notification of genetic test (increase of the clopidogrel dosage, switch to clopidogrel or switch to prasugrel). Public reporting of the trial results are pending.

Indeed, the results of these observational studies are of interest, but warrant confirmation in randomized control studies which are currently ongoing. The Tailored Antiplatelet Therapy Following PCI (TAILOR-PCI, NCT 01742117) is currently recruiting participants. Patients who undergo PCI are randomized to a conventional treatment arm (clopidogrel 75 mg once daily without prospective genotyping guidance) versus tailored therapy based on *CYP2C19* genotype using SpartanRx (ticagrelor 90 mg twice daily for carriers of a *CYP2C19* LOF allele, clopidogrel 75 mg once daily for non-carriers). The Assessment of Prospective *CYP2C19* Genotype Guided Dosing of Anti-Platelet Therapy in Percutaneous Coronary Intervention (ADAPT, NCT 02508116) trial is also ongoing, and will test a similar concept using rapid genetic testing with SpartanRx™. The Patient Outcome after primary PCI (POPular) Genetics study (NCT01761786) is a prospective, randomized, controlled trial of 2,700 STEMI patients undergoing primary PCI investigating the efficacy, safety and cost-effectiveness of the *CYP2C19* genotype guided antiplatelet treatment strategy, using prasugrel or ticagrelor in carriers of a *CYP2C19* LOF allele and clopidogrel in non-carriers of a *CYP2C19* LOF allele.

Unfortunately a number of clinical trials using genetic testing have terminated prematurely (Table 3). The GeCCO (NCT 00995514), PAPI-2 (NCT 01452152), TARGET-PCI (NCT 01177592) have been terminated prematurely because of administrative reasons, problems with the sponsor, or lack of financial support.

6. Conclusions

The use of DAPT composed of aspirin and a $P2Y_{12}$ receptor inhibitor is the standard of care for patients undergoing PCI to prevent the risk of thrombotic events. Clopidogrel is the most broadly utilized $P2Y_{12}$ receptor inhibitor. Despite the clinical benefits associated with the use of clopidogrel, numerous studies have shown that a considerable number of patients may have impaired clopidogrel-induced antiplatelet effects and persist with HPR leading to an increased risk of thrombotic complications. *CYP2C19* LOF alleles have been associated with HPR and increased thrombotic event rates, prompting a number of investigations assessing the use of genetic tests to identify these patients who may be potential candidates

for alternative platelet $P2Y_{12}$ receptor inhibiting therapies (i.e., prasugrel and ticagrelor) not affected by these genotypes. The availability of more user-friendly genetic tests able to provide results in a timely fashion have indeed contributed towards the development of a number of ongoing clinical trials and personalized medicine programs for patients undergoing PCI. Findings from observational studies have thus far shown promising findings suggesting better outcomes with a personalized antiplatelet treatment approach using genetic testing to guide clinical decision making. However, results of large-scale randomized trials, currently ongoing, are needed to define whether genetic testing should be implemented routinely in clinical practice in patients undergoing PCI.

7. Expert commentary

7.1. Future directions and perspectives on personalized antiplatelet therapy

The well-established association between the presence of certain genotypes, HPR and increased risk of atherothrombotic events among clopidogrel-treated patients undergoing PCI as well as the encouraging preliminary clinical outcomes study results associated with the use of alternative therapies according to the results of genetic testing are indeed promising for the future personalizing antiplatelet treatment regimens [120]. Indeed, while many Institutions have already implemented the routine use of genetic testing to personalize antiplatelet therapy in PCI patients based on these observations, data from currently ongoing large scale randomized clinical trials are warranted to support their utilization. Practice guidelines, particularly in the field of cardiology, strongly rely on evidenced-based data and strategies that fall within high levels of recommendations derive from large scale randomized comparisons, which often need to be replicated in order to also obtain high level of evidence. Unfortunately, such data from large randomized controlled trials in the field of genetic testing in patients undergoing PCI are lacking. The use of genetic testing as a tool to incorporate into routine clinical practice is also challenged by the fact that a parallel line of research focused on personalizing antiplatelet therapy based on results of platelet function testing has provided thus far disappointing results [121–124]. In fact, although observational studies in high-risk PCI settings have shown that modification of antiplatelet therapy based on results of platelet function studies are associated with favorable outcomes, these findings have not been corroborated within a number of randomized clinical trials [125]. It may be argued that these trials were flawed by target population, antiplatelet medications, platelet function assay, HPR cut-off values, timing of testing, among other variables, which were not adequate to test for the study hypothesis [125]. Indeed, lessons learned from these studies have led to the development of perhaps more appropriately designed trials, such as the TROPICAL-ACS which will determine whether individualizing antiplatelet therapy based on platelet function tests remains an arena to nurture further research [126].

Genetic testing in PCI is still in its very earlier phases. In fact, while observational data have been thus far encouraging, results of large randomized clinical trials are still not available [116,118]. Moreover, the fact that more user-friendly genetic tests that can be used in daily clinical practice have not become available until recently may have hampered the evolution of this field of investigation. Therefore, the field of genetic testing in PCI has much room for future growth. Indeed, the use of genetic testing as a strategy to personalize antiplatelet

therapy rather than platelet function testing has the advantage that while results of platelet function tests are subject to a lot of variability, which may thus lead to both false-negative and false-positive results, the genotype of an individual does not change. Moreover, the advantage of genotyping compared with platelet function testing is that results can be obtained prior to initiating treatment. Therefore, genetic testing becomes an attractive option to consider. In particular, the use of genetic testing would allow for identifying patients who have adequate clopidogrel metabolism and less likely to have HPR and atherothrombotic events. Importantly, such strategy would favor the use of a drug such as clopidogrel known to have less bleeding complications compared with prasugrel or ticagrelor. It is important to underscore that a bleeding complication has prognostic implications as detrimental as a recurrent atherothrombotic event [9,127]. Ultimately, there is an opportunity for cost savings given that clopidogrel is broadly available in a generic formulation.

7.1. Five-year view

In the upcoming years results of trials of testing personalized antiplatelet therapy approaches based on the results of genetic testing will become available (Table 3). Additional data from pragmatic studies, such as those from the IGNITE Network, are also expected. Moreover, user-friendly genetic testing assays will also become more broadly available. Evolution in such technology may also be paralleled by reduced cost of performing these tests. Indeed, the need for antiplatelet treatment strategies in PCI patients that are associated with improved efficacy and safety profiles still represents an area of unmet need. Therefore, amongst the various approaches currently being tested, such as testing new drugs, alternative combination therapies, and platelet function testing, the use of genetic tests falls within the viable options for the future pending results of ongoing randomized clinical trials.

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Key issues

- Cytochrome P450 2C19 gene polymorphism contributes the wide variability in interindividual response to clopidogrel-induced antiplatelet effects.
- Increasing clopidogrel dosing is overall ineffective in overcoming impaired clopidogrel-induced antiplatelet effects among carriers of *CYP2C19* LOF alleles, underscoring the need for alternative drugs.
- Prasugrel and ticagrelor are newer generation $P2Y_{12}$ receptor inhibitors and their effects are not affected by *CYP2C19* LOF alleles.
- Findings from observational studies have shown promising findings suggesting better outcomes with a personalized antiplatelet treatment approach using genetic testing to guide clinical decision making.
- Results of large-scale randomized trials, currently ongoing, are needed to define whether genetic testing should be implemented routinely in clinical practice in patients undergoing PCI.

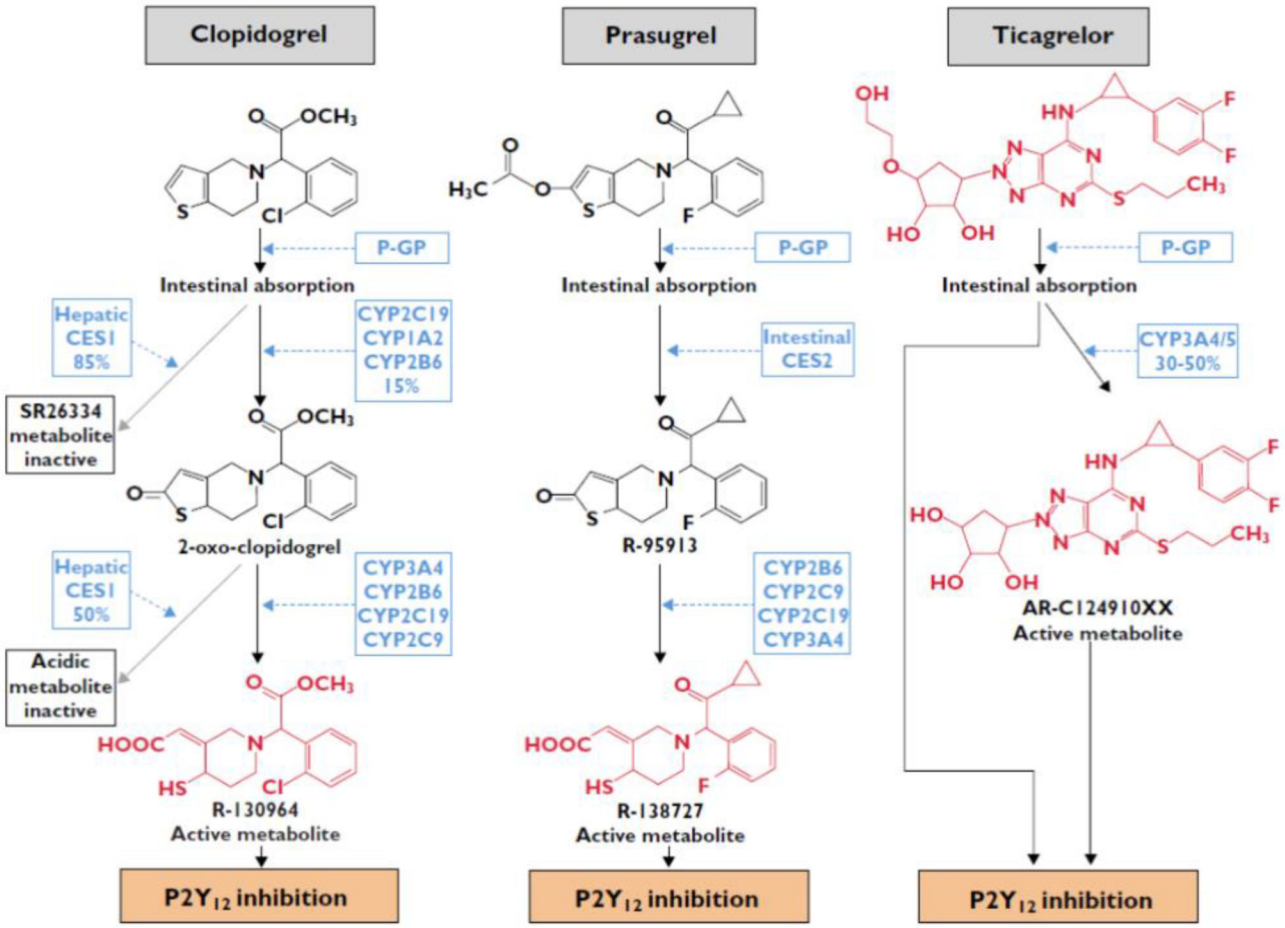
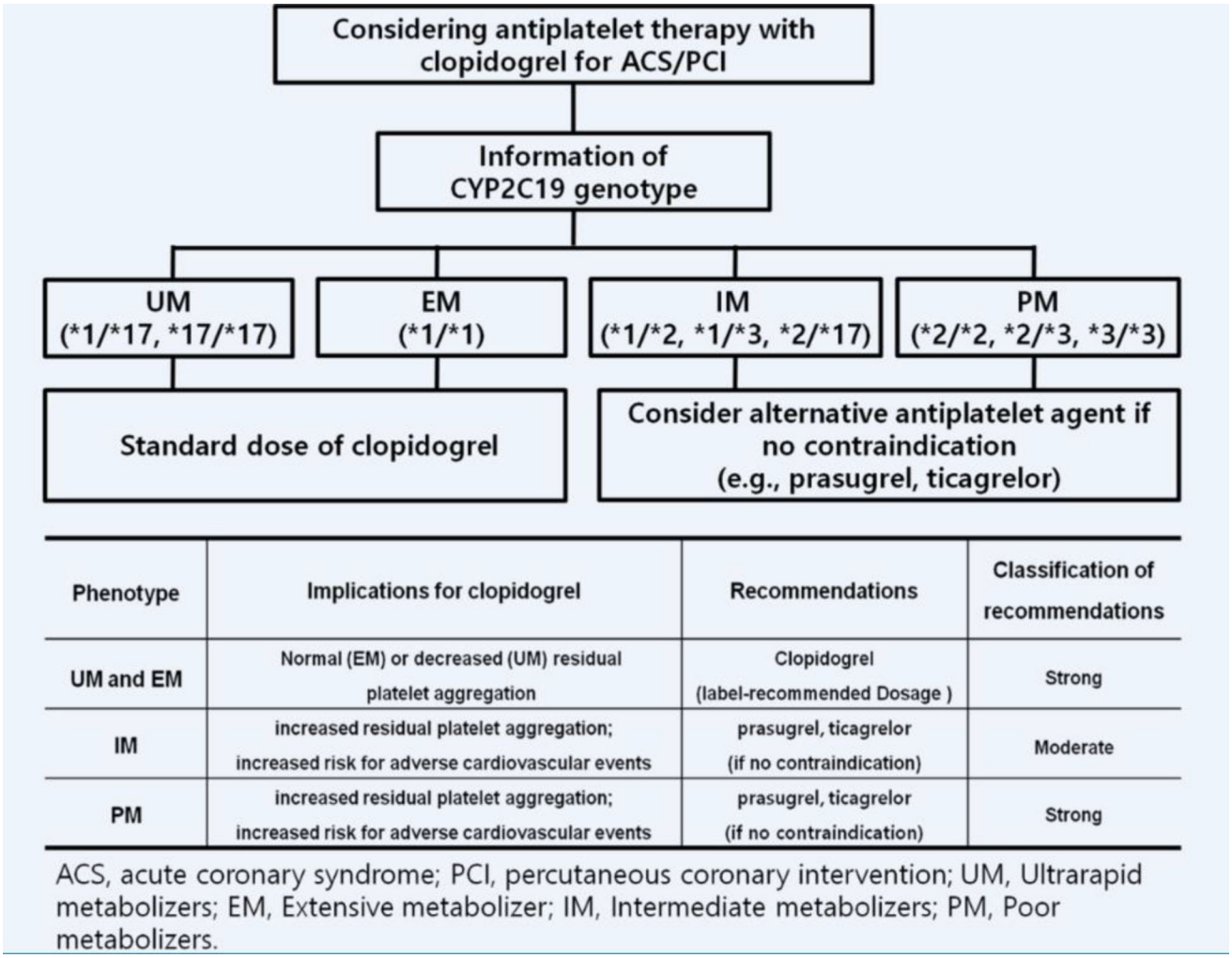


Figure 1. Metabolic profiles of three major $P2Y_{12}$ receptor inhibitors

Compounds with $P2Y_{12}$-receptor inhibiting properties are in red.

CES, human carboxylesterase; CYP, cytochrome P450; P-GP, P-glycoprotein. Reproduced with permission from British Journal of Clinical Pharmacology (2014) [16]



Phenotype	Implications for clopidogrel	Recommendations	Classification of recommendations
UM and EM	Normal (EM) or decreased (UM) residual platelet aggregation	Clopidogrel (label-recommended Dosage)	Strong
IM	increased residual platelet aggregation; increased risk for adverse cardiovascular events	prasugrel, ticagrelor (if no contraindication)	Moderate
PM	increased residual platelet aggregation; increased risk for adverse cardiovascular events	prasugrel, ticagrelor (if no contraindication)	Strong

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; UM, Ultrarapid metabolizers; EM, Extensive metabolizer; IM, Intermediate metabolizers; PM, Poor metabolizers.

Figure 2. Algorithm for suggested clinical actions based on *CYP2C19* genotype when considering treatment with clopidogrel for ACS patients undergoing PCI

Recommendations from Clinical Pharmacogenetics Implementation Consortium [47]

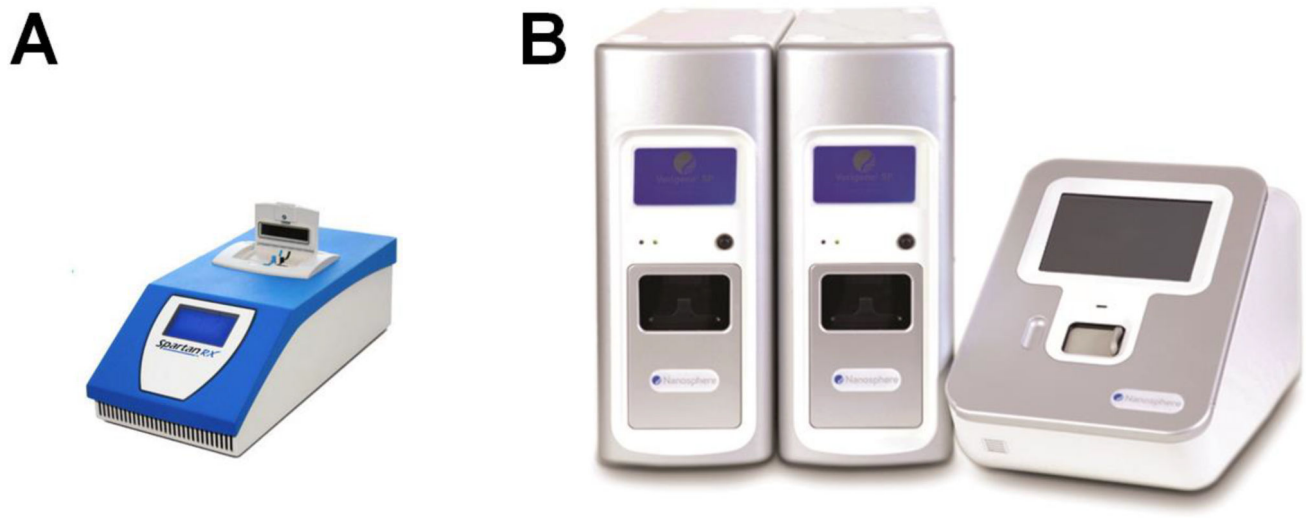


Figure 3. Rapid genetic assays for *CYP2C19*

A. SpartanRx™ (Spartan Bioscience, Ottawa, Canada) and **B**. the Verigene® System (Nanosphere, Northbrook, Illinois)

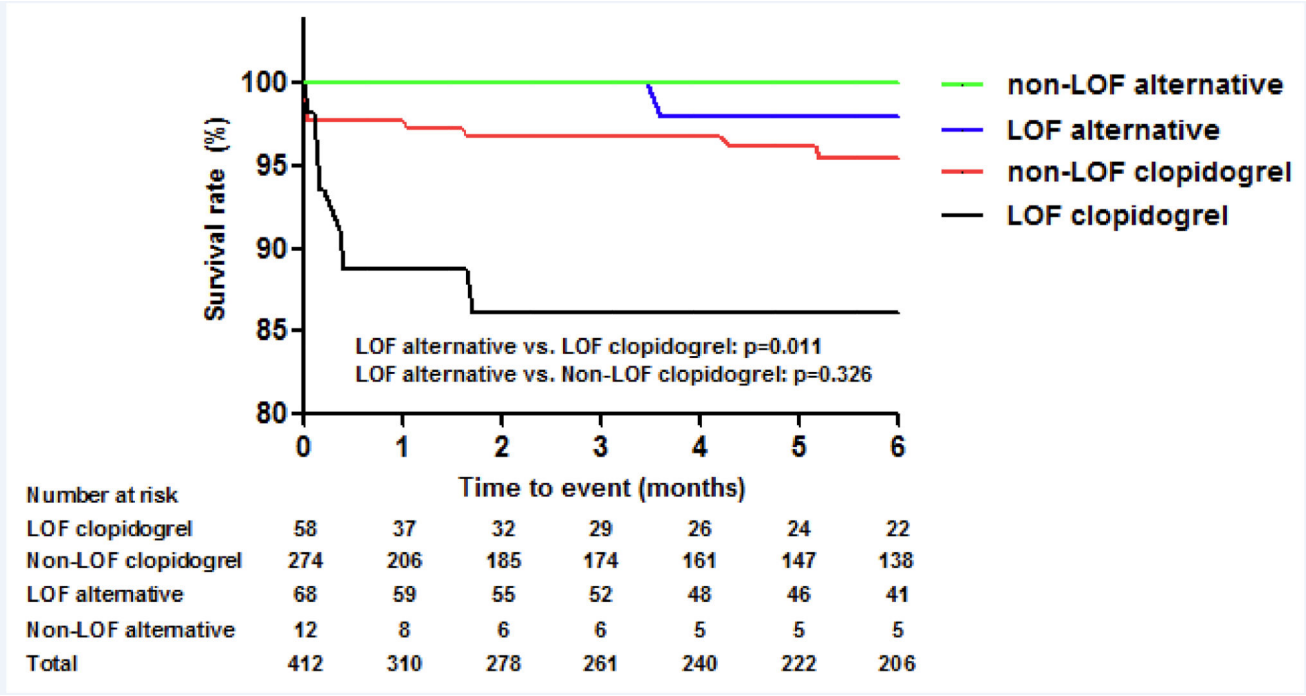


Figure 4. Clinical outcomes of *CYP2C19* LOF genotype-based antiplatelet therapy

MACE free survival curve from multivariable Cox regression analysis with propensity score adjustment. Patients with *CYP2C19* LOF alleles who were treated with alternative antiplatelet therapy (black line) had a significantly lower risk for MACE (major adverse cardiac events) compared to patients with LOF alleles who were treated with clopidogrel (blue line).

Table 1

Frequencies of *CYP2C19* alleles in major ethnic groups.

Allele	African	American	European	East Asian	South/Central Asian
1	0.68	0.69	0.63	0.60	0.62
2	0.15	0.12	0.15	0.29	0.35
3	0.0052	0.00028	0.0042	0.089	0.024
17	0.16	0.18	0.21	0.027	ND

ND: not determined.

Among various reports of allele frequency, we present the value from Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy [47]

Table 2

Five of *CYP2C19* phenotypes in clopidogrel metabolism based on genotypes.

Phenotype	Examples of diplotypes
Ultrarapid metabolizer (UM) Increased enzyme activity compared to RM	**17/*17*
Rapid metabolizer (RM) Increased enzyme activity compared to NM but less than UM	**1/*17*
Normal metabolizer (NM) Fully functional enzyme activity	**1/*1*
Intermediate metabolizer (IM)† Decreased enzyme activity	**1/*2, *1/*3, *2/*17*
Poor metabolizer (PM) Little to no enzyme activity	**2/*2, *2/*3, *3/*3* or other combination of two LOF alleles (**2–*8*)

†An individual carrying one functional allele (**1*) plus one LOF allele (**2–*8*) or one LOF allele (**2–*8*) plus one increased-activity allele (**17*). It seems that **17* allele is unable to completely compensate for reduced activity with the **2* allele, so **2/*17* is classified to IM.

Table 3

Large scale clinical outcome trials investigating genetic tests guided personalized antiplatelet therapy

NCT number	Title	Status	Indication (number)	Design	Test	Methods	Primary end point
NCT00995514	Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes Study (GeCCO)	Terminated	ACS (14,600)	Observational Cohort	*CYP2C19*2*	Prasugrel 10mg in LOF alleles vs. Clopidogrel 75mg control.	Composite of CV death, nonfatal MI, or non-fatal stroke at 6 months
NCT01452152	Pharmacogenomics of Anti-platelet Intervention-2(PAPI-2)	Terminated	PCI (7,200)	Randomized	*CYP2C19*2* or **3*	Genotype directed group: prasugrel 5–10 mg/day for IM and PM, Clopidogrel for other genotype. vs. Observational group: no Intervention and standard of care without genetic information	Composite of non-fatal MI, non-fatal stroke, ST and death secondary to any cardiovascular cause at 12 months
NCT01177592	Thrombocyte Activity Reassessment and GEnoTyping for PCI (TARGET-PCI)	Terminated	PCI (1,500)	Randomized	*CYP2C19*2*	*CYP2C19*2* carriers: Prasugrel 60mg,vs. Others: clopidogrel 75mg	Composite of cardiovascular death, ischemic stroke, non-fatal myocardial infarction, urgent target vessel revascularization at 6 months
NCT01761786	Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment (POPGenetics,)	Recruiting	Primary PCI (2,700)	Randomized	*CYP2C19*2* or **3*	Wild type *CYP2C19* allele: clopidogrel 75 mg. vs. *CYP2C19*2* and **3*: ticagrelor or prasugrel.	Composite of non-fatal MI, non-fatal stroke, CV death, and ST Pharmacoeconomics
NCT01134380	Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment (GIANT)	Completed	Primary PCI (1,500)	Observational Case Control	*CYP2C19*2*	Physician can change or adjust initial DAPT regimen after notification of result of genetic test (Increase of the clopidogrel dosage, Change drug to prasugrel or clopidogrel)	Composite of death, MI and ST at 12 months
NCT01742117	Tailored Antiplatelet Therapy Following PCI (TAILOR-PCI)	Recruiting	PCI (5,270)	Randomized	*CYP2C19*2* or **3*	Wild type *CYP2C19* allele: clopidogrel 75 mg. vs. *CYP2C19*2* and **3*: ticagrelor 90 mg.	Composite of non-fatal MI, non-fatal stroke, CV death, severe recurrent ischemia, and ST at 12 months
NCT02508116	Assessment of Prospective CYP2C19 Genotype Guided Dosing of Anti-Platelet Therapy in Percutaneous	Recruiting	PCI (700)	Randomized	*CYP2C19*2* or **3*	The genotype guided arm: prasugrel or ticagrelor in LOF carrier and clopidogrel in non-carrier. vs. Control	Cost of medical service utilization. MACEs at 12 months

NCT number	Title	Status	Indication (number)	Design	Test	Methods	Primary end point
	Coronary Intervention (ADAPT)					group: usual antiplatelet treatment.	

LOF, loss-of-function; CV, cardiovascular; MI, myocardial infarction; IM, intermediate metabolizer; PM, poor metabolizer; DAPT, dual antiplatelet treatment; ST, stent thrombosis; MACEs, major adverse cardiovascular events