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Pharmacogenomics of Oral $P2Y_{12}$ Receptor Blockers

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Abstract

Dual antiplatelet therapy of aspirin and a $P2Y_{12}$ receptor antagonist is the cornerstone of therapy for patients. Thienopyridines (ticlopidine, clopidogrel and prasugrel) are prodrugs that need cytochrome–mediated conversion to active metabolites to block $P2Y_{12}$ receptors and subsequent ADP-induced platelet aggregation. Clopidogrel response variability has been attributed to a variable generation of its active metabolite which is in turn influenced by single nucleotide polymorphisms of genes associated with intestinal absorption protein, *ABCB1* and hepatic cytochrome isoenzymes particularly *CYP2C19*. Moreover, presence of loss-of-function allele of *CYP2C19* gene has been associated with poor active metabolite generation, poor antiplatelet response and increased risk for cardiovascular event occurrences particularly stent thrombosis in patients treated with clopidogrel. Recent studies suggest that genetic variations in *CYP2C19* and *CYP2B6* may affect response to the drug; however its clinical significance is unknown at this time. Although, ticagrelor (a cyclopentyl-triazolo-pyrimidine), is a prodrug, it is metabolized by *CYP3A4* and its active metabolite is as potent as parent drug. To date there are no reports of significant influence of genotype variations on ticagrelor metabolism, its antiplatelet response or clinical outcome. The optimal strategy to overcome the influence of *LoF* carriage in patients treated with clopidogrel is probably to switch therapy to either prasugrel or ticagrelor, although large-scale studies assessing this approach have not been performed.

Keywords: $P2Y_{12}$ receptor; Clopidogrel; CYP2C19; Ticagrelor

Introduction

Multiple lines of evidence from basic research support the pivotal role of $P2Y_{12}$ mediated signaling in the pathophysiologic events that affect the development of atherothrombosis. Although ADP-$P2Y_{12}$ receptor interaction plays a central role in sustaining the activation of glycoprotein (GP) IIb/IIIa receptors by amplifying the response to agonists leading to stable platelet-rich thrombus generation at the site of vessel wall injury [1,2]. $P2Y_{12}$ blockade: 1) attenuates platelet aggregation induced by multiple agonists [3], 2) modulates platelet procoagulant activity and thrombin generation [4,5], and 3) modulates P-selectin expression, and soluble CD40L and inflammation markers release (C-reactive protein and tumour necrosis factor-α) [6-8]. In *ex-vivo* experimental models of arterial thrombogenesis using human blood samples, combined therapy of a $P2Y_{12}$ receptor blocker, either ticlopidine or clopidogrel, with aspirin dramatically potentiated the antithrombotic effect of each drug alone [9,10]. Therefore, dual antiplatelet therapy of aspirin and a $P2Y_{12}$ receptor antagonist is the cornerstone of therapy for patients presenting with acute coronary syndromes (ACS) and in those treated with percutaneous coronary intervention (PCI) and a coronary stent [11]. Ticlopidine, a first-generation thienopyridine, added to aspirin was more effective than aspirin therapy alone or aspirin plus an oral anticoagulant (warfarin) in reducing stent thrombosis [12]. However, primarily due to unfavorable side effects, ticlopidine was largely replaced by the second-generation thienopyridine clopidogrel [11]. The most widely used $P2Y_{12}$ receptor blocker, clopidogrel, is associated with numerous limitations including; i) resistance and response variability, ii) high on-treatment platelet reactivity that has been associated with increased risk for ischemic event occurrence, iii) irreversible binding, and iv) slow onset and offset [13]. Prasugrel, a third-generation thienopyridine prasugrel, is associated with faster onset of action, greater platelet inhibition with less response variability and reduced ischemic event occurrence and stent thrombosis compared with clopidogrel therapy in patients with acute coronary artery syndrome (ACS) undergoing percutaneous coronary intervention (PCI) [14]. In the TRITON-TIMI-38 trial, prasugrel was associated with better protection against ischemic event occurrence compared with clopidogrel, but more bleeding occurred [15]. Thienopyridines are prodrugs that need cytochrome–mediated conversion to active metabolites to block $P2Y_{12}$ receptors. Ticagrelor (previously known as AZD 6140) belongs to the cyclopentyl-triazolo-pyrimidine (CPTP) class of antiplatelet agents and is structurally different to thienopyridines and ATP analogs. Ticagrelor is a direct-acting, reversibly binding orally administered and noncompetitive $P2Y_{12}$ receptor blocker that is associated with faster onset of action and greater inhibition [16]. In the PLATO trial, ticagrelor therapy was associated with reduced ischemic event occurrence than clopidogrel in acute coronary syndrome patients. Lower mortality and similar coronary artery bypass graft-related bleeding compared to clopidogrel are major advantages with ticagrelor therapy [17]. Although ticagrelor is direct-acting, it is metabolized by cytochromes and the active metabolite is as potent as parent compound [16]. In this review article, we discuss the pharmacogenomics of these orally administered $P2Y_{12}$ receptor blockers.

Clopidogrel

Metabolism: Clopidogrel is a prodrug that is dependent on hepatic conversion to its active metabolite. Almost 85% of absorbed clopidogrel is subjected to hydrolysis catalyzed by human hepatic carboxylesterase-1, resulting in the formation of the inactive carboxylic acid of clopidogrel

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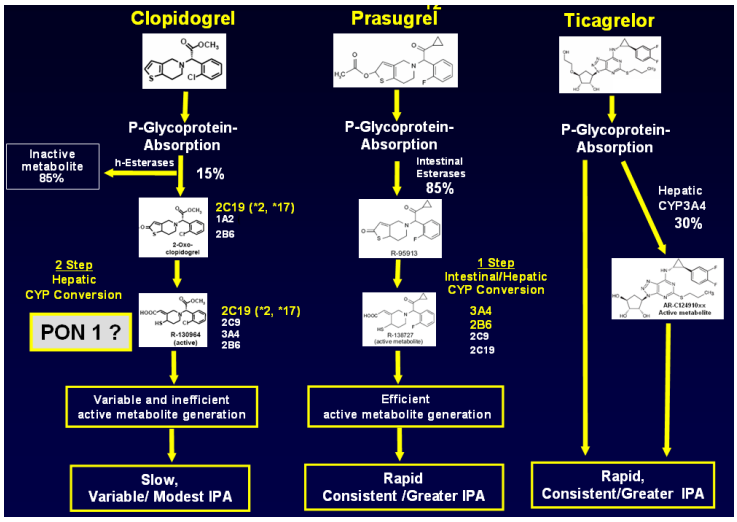

Figure 1: Metabolism of $P2Y_{12}$ receptor blockers.

(SR26334). The remaining clopidogrel (~15%) is oxidized into inactive 2-oxo-clopidogrel by the hepatic CYP system (*CYP2C19, CYP1A2* and *CYP2B6*). The 2-oxo-clopidogrel is further oxidized by CYP enzymes (*CYP3A4/5*, *CYP2B6, CYP2C9* and *CYP2C19*) to form the clopidogrel active metabolite (CL-AM; R-130964) responsible for exerting the antiplatelet activity [18] (Figure 1). The *CYP2C19* enzyme is the main contributor, followed by the *CYP3A4/5* enzyme [19]. The highly unstable CL-AM binds covalently to cysteine residues within the $P2Y_{12}$ receptor and thereby inhibits the receptor for the lifespan of platelets (~10 days) [18]. Clopidogrel response variability has been attributed to a variable generation of its active metabolite which is in turn influenced by: variable absorption influenced by *ABCB1* gene polymorphism; functional variability in CYP isoenzymes activity that is influenced by drug–drug interactions as well as other clinical factors; and SNPs of specific genes encoding hepatic CYP isoenzymes [13,20].

P-glycoprotein (*ABCB1*)

P-glycoprotein is an ATP-dependent efflux pump encoded by the *ABCB1* gene. It is expressed in intestinal epithelial cells and an increased expression or function can influence the bioavailability of drugs that are its substrate. Three categories of gene expression can be predicted based upon allele carriage of the *ABCB1* 3435C→T SNP: high (C/C), intermediate (C/T), and low (T/T) [21]. It was demonstrated by in vitro studies that exposure to a high concentration of clopidogrel may downregulate the efflux transporter, p-glycoprotein mRNA expression and limits its absorption [21]. Moreover, following a 300 or 600 mg clopidogrel loading dose, the p-glycoprotein encoding *ABCB1* 3435T gene variant was associated with decreased clopidogrel active metabolite generation in 60 patients undergoing PCI [22]. In the French Registry of Acute ST elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) study, clopidogrel-treated patients with low *ABCB1* expression (T/T) had a significantly higher rate of death, MI, or stroke than high expression *ABCB1* expression (C/C) (15.5% vs 10.7%, HR 1.72, 95% CI, 1.2-2.47; *P=0* .007) (26). Patients with 2 *CYP2C19 LoF* alleles and at least one *ABCB1* 3435C→T allele had the highest risk of CV events (HR 5.31, 95% CI, 2.13-13.20; *P* =0 .009) [23]. Similarly, in the TRITON-TIMI 38 genetic sub-study, clopidogrel-treated patients with low *ABCB1* expression (T/T) had a 72% increased risk of CV death, MI, or stroke compared with patients with intermediate (C/T) and high (C/C) expression (12.9% vs 7.8%, HR 1.72, 95% CI, 1.22-2.44; *P=0* .002) [21]. *ABCB1* genotype had no effect on CV events in prasugrel treated patients. In contrast to the findings of the FAST-MI and TRITON TIMI 38 studies, in the large genetic sub-study of PLATO, CV event rates in clopidogrel-treated patients were highest in patients with the high *ABCB1* expression (C/C) [24]. Given these conflicting findings, the impact of *ABCB1* polymorphisms on clinical outcomes in clopidogrel-treated patients remains uncertain.

CYP2C19 Single Nucleotide Polymorphisms

Several single nucleotide polymorphisms (SNPs) can influence the catalytic activity of the cytochrome p450 (CYP) 219 isoenzymes in a co-dominant (i.e., dose-dependent) manner. There are at least 25 SNPs of the gene encoding the *CYP2C19* isoenzyme [25]. The two most frequent gene variants associated with loss of function (*LoF* SNPs) are the *CYP2C19*2,* a G681A mutation in exon 5, resulting in an aberrant splice site, leading to the production of a truncated, non-functioning protein and the *CYP2C19*3*, a G636A mutation in exon 4 resulting in a premature stop codon [26,27]. Various independent studies have demonstrated the link between genetic polymorphisms, suboptimal active metabolite generation (pharmacokinetic measurement), decreased clopidogrel responsiveness as measured by platelet function assays (pharmacodynamic measurement) and clinical outcomes [28]. Less common *LoF* alleles include **4,*5,*6,*7* and **8*. *CYP2C19*1* allele denotes the lack of known polymorphisms, and therefore is considered to be wild-type (i.e., normal function). The frequency of these alleles differs amongst ethnicity (Figure 2) [29]. Approximately 2% of Caucasian, 4% of black, and 15% of Asian subjects are *CYP2C19*-poor metabolizers.

Influence of *CYP2C19* polymorphisms on clopidogrel metabolism in healthy subjects

Hulot and colleagues first examined the influence of several *CYP450* polymorphisms on ADP induced platelet aggregation and vasodilator stimulated phosphoprotein (VASP) phosphorylation phosphorylation after 75 mg/d clopidogrel administration in 28 healthy volunteers. In his study, the mean on-treatment reactivity and the VASP platelet reactivity index was significantly higher in 28% of the subjects who were heterozygous for the *CYP2C19*2* allele (*1/*2) compared with

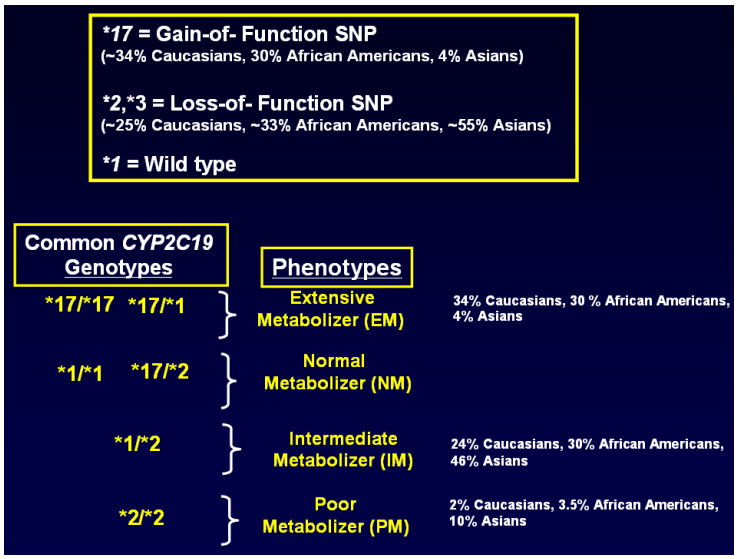

Figure 2: Common Single nucleotide polymorphisms of cytochrome *(CYP)2C19* gene.

the 72% of the subjects who were homozygous for *CYP2C19**1 (*1/*1) [29,30]. In another analysis of 162 healthy clopidogrel-treated subjects, carriage of at least one *CYP2C19 LoF* allele led to a 32% decrease in the active metabolite measured as area under the curve (AUC) and a 9% reduction in the change in maximal ADP-induced platelet aggregation [30,31]. Poor metabolizers (*2/*2) are not well represented in these studies due to their low genotypic frequency in Caucasian population.

In an East Asian Population where the frequency of poor metabolizers are high, Kim and colleagues found a codominant, or gene-dose, effect of *CYP2C19* genotype on clopidogrel pharmacokinetics and pharmacodynamics: the mean peak plasma concentration of clopidogrel prodrug in the poor metabolizers was 1.8- and 4.7-fold higher than that of intermediate and extensive metabolizers, respectively, and poor metabolizers exhibited a significantly lower antiplatelet effect than either the intermediate or extensive metabolizers [32]. Similar studies involving healthy individuals have shown consistent findings across ethnic groups [13].

Genome-wide association studies examine the genetic variation across the entire human genome to identify associations between 500,000 or more SNPs and a particular trait (such as blood pressure, diabetes, or platelet reactivity). The strong association of *CYP2C19*2* on clopidogrel response variability was confirmed in a Genome Wide association study conducted in healthy subjects administered with 75mg/day clopidogrel for 7 days. A cluster of 13 SNPs within and flanking the *CYP2C18-2C19-2C9-2C8* cluster on chromosome 10q24 (out of about 400,000 SNPs analyzed genome-wide) was strongly associated with diminished clopidogrel response. A genetic component was associated with ~70% of clopidogrel response variability. The association increased in a gene–dose-dependent manner, suggesting a linear relationship between the number of *CYP2C19*2* alleles and on-treatment platelet reactivity [33]. In this study, contribution of *CYP2C19 locus* to clopidogrel response variability as measured by ADP-induced platelet aggregation was only ~12% and non-SNPs (eg, copy number variants, insertions/deletions), rare variants, or an SNP not included in the analyses may also contribute to platelet response variability [34].

Influence of *CYP2C19* polymorphisms on clopidogrel metabolism in patients with coronary artery disease

In several studies carriers of the *CYP2C19 LoF* variant with coronary artery disease (CAD) during clopidogrel administration had lower levels of the active metabolite exposure ($p<0.0015$) and higher platelet reactivity measured by multiple platelet function assays ($p<0.05$) than non-carriers [34]. The association between *CYP2C19*2* genotype and antiplatelet response to clopidogrel in a wide spectrum of patients with CAD has been demonstrated in various candidate gene studies [13].

In the EXCELSIOR study of 797 patients under elective coronary stenting, no significant differences in the platelet reactivity at the baseline during aspirin therapy between genotypes was observed and the average platelet reactivity was significantly higher in *2 homozygytes followed by *2 heterozygotes and wild type carriers before PCI (after 600 mg loading) and also at the pre-discharge time (post-PCI) ($p< 0.001$ for trend for both time points) [35]. In another report from the same EXCELISOR study, *CYP2C19*2* was accountable for 4.6% of on-treatment platelet aggregation in a linear regression model. In a combined model, age, body mass index and presence or absence of diabetes accounted for 1% each of platelet aggregation variability. *CYP2C19*2* carrier status alone accounted for 5.2% of platelet aggregation variability and *CYP2C19*2* plus clinical variables was accounted for 11.5% of platelet aggregation [36]. In the POPULAR study, *CYP2C19*2* genotype was associated with approximately 4-6% and clinical variables with 9-17% variability in on-treatment platelet reactivity as assessed by ADP-induced platelet aggregation and VerifyNow P2Y12 assay. In the latter study both *CYP2C19*2* and clinical variables were together associated with 13-21% on-treatment platelet reactivity [37].

The association of *CYP2C19 LoF* and *GoF* status with platelet reactivity in 118 stented patients on dual antiplatelet therapy (DAPT) for ≥2 weeks and in 143 patients with stable coronary artery disease on aspirin therapy alone was studied by Gurbel et al. [38]. There was no association of *2 or *17 allele alone with platelet reactivity in patients on aspirin therapy. During DAPT, platelet aggregation was higher in those carrying the *2 allele than noncarriers ($P \leq 0.01$), but did not

differ between those carrying the *17 allele and non-carriers. However, platelet function on DAPT was highly variable within genotype groups and platelet reactivity was consistently higher than the HPR threshold in the *2 homozygotes only [38].

Relation of genetic polymorphisms, clopidogrel response variability and the time of measurement

The antiplatelet response to clopidogrel is dependent on the time of measurement and clopidogrel dose. In a study by Campo et al. age, diabetes, creatinine clearance, and admission for NSTE-ACS were independent predictors of variability in on-treatment platelet reactivity whereas *CYP2C19*2,CYP2C19*17* and *ABCB1* genotype together were accountable for ~18% (6.6%, 5.2% and 6.7% respectively). The influence of *ABCB1* genotype was higher after clopidogrel loading dose (9%) and fell to 6% and 5% at 1 month and 6 months respectively. However, the influence of *CYP2C19*2* and *17* was constant over time [39].

Similarly, *CYP2C19*2* accounted for 6.5% of on-treatment platelet reactivity at baseline and 5.1% at 30 days In the GIFT (Genotype Information and Functional Testing) trial. The influence of *17* was only 0.5-1.2%, whereas *PON1* and *ABCB1* genotypes had a negligible influence. In a subanalysis of GIFT, poor metabolizers had the highest risk for HPR at 30 days (odds ratio ~11). Moreover, among patients with HPR, the change in PRU in patients carrying 2 *LoF* alleles at 30 days during standard and high-dose clopidogrel was lower (~ 10 PRU decrease between baseline and 30 days for both doses) compared to a greater decrease in patients carrying one *LoF* allele with standard dose (24 PRU decrease) and high dose (69 PRU decrease). These results indicate that high-dose clopidogrel is a poor strategy to overcome HPR in poor metabolizers [40].

Influence of *CYP2C19*17* allele on clopidogrel metabolism

The *CYP2C19*17* polymorphism is a promoter variant, causing increased transcription of *CYP2C19* messenger RNA and in turn increased *CYP2C19* activity. In patients presenting with non–ST-elevation ACS, *CYP2C19*17* carriage is associated with an increased inhibitory response to clopidogrel [41]. In an observational study of 1524 patients undergoing planned PCI and pretreated with clopidogrel, 600 mg, 25% of patients were identified as *CYP2C19*17* carriers; *CYP2C19*17* genotype had a significant association with platelet aggregation as measured by multiple electrode aggregometry, with carriers of two *17 alleles having the lowest, carriers of one *17 allele having intermediate, and carriers of no *17 alleles displaying the highest levels of on-treatment reactivity [42]. The *2 and *17 alleles appear to have an additive effect on clopidogrel response [43]. However, in a smaller, multicenter, randomized pharmacodynamic study that used a several different *ex vivo* platelet function tests, *CYP2C19*17* allele carriage was not associated with the level of on clopidogrel platelet reactivity [44].

Influence of *CYP2C19 LoF* alleles on clinical outcomes

Among the clopidogrel-treated patients with ACS undergoing PCI in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38 study, *CYP2C19 LoF* allele carriers had a higher rate of recurrent ischemic events compared with non-carriers in clopidogrel treated patients (hazard ratio [HR] 1.53, 95% confidence interval [CI], 1.07-2.19; *P* =0 .01), including stent thrombosis (HR, 3.09, 95% CI, 1.19-8.00; *P* =0.02) [31]. Shuldiner et al. demonstrated that carriers of the *CYP2C19*2* allele undergoing PCI had higher cardiovascular (CV) event rates compared with non-carriers (HR 2.42, 95% CI 1.18-4.99; *P* =0 .02) [33]. In the FAST-MI (French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction) registry including 2208 AMI patients treated with clopidogrel, patients carrying any two *CYP2C19 LoF* alleles (*2, *3, *4, or *5) had a higher event rate than noncarriers (21.5% vs. 13.3%; HR, 1.98; 95% CI, 1.10 to 3.58). Among PCI-treated patients (n=1535), the rate of cardiovascular events among patients with two_*CYP2C19 LoF* alleles was 3.58 times compared to noncarriers (95% CI, 1.71 to 7.51) [23]. In another French multi-center registry of 259 young AMI patients (aged 18 to 45) receiving clopidogrel treatment for at least one month (median 1.07 years), *CYP2C19*2* carriers (28%) had a 3.7-fold increase in the composite of cardiovascular death, non-fatal MI, or urgent revascularization compared with non-carriers. The risk of stent thrombosis was also significantly increased by 6-fold in carriers [45].

In a meta-analysis involving 11,959 patients enrolled in 10 studies (4 of which reported stent thrombosis), *CYP2C19*2* carriers displayed a 30% increase in the risk of major CV adverse clinical events compared with non-carriers (odds ratio [OR] 1.29, 95% CI, 1.12-1.49; *P*=0.001). In addition, carriage of at least one *CYP2C19*2* was associated with increased mortality (OR 1.79, 95% CI, 1.10-2.91; *P*=0.019) and increased stent thrombosis (OR 3.45, 95% CI, 2.14-5.57; *P*=0.001) [46]. A collaborative meta-analysis of nine clinical studies involving 9684 patients (91% of whom underwent PCI and 55% of whom had ACS) demonstrated a significantly increased risk of the composite endpoint of CV death, MI, or stroke among carriers of one *CYP2C19 LoF* allele (HR 1.55, 95% CI, 1.11-2.17; *P*=0.01) and 2 *CYP2C19 LoF* alleles (HR, 1.76; 95% CI, 1.24-2.50; *P*=0.002) as compared with non-carriers. A significantly increased risk of stent thrombosis in carriers of one and two *CYP2C19 LOF* alleles was also observed (HR 2.67, 95% CI, 1.69-4.22, *P*=0.0001; and HR 3.97, 95% CI, 1.75-9.02; *P* <0.001, respectively) [47]. Thus, the results of these meta-analyses indicate an apparent gene-dose effect of *CYP2C19 LoF* allele carriage on CV events that is more pronounced among patients undergoing PCI and particularly evident with respect to the occurrence of stent thrombosis.

The influence of *CYP2C19* genotype on outcomes is less apparent in populations treated with clopidogrel for indications other than PCI. In the genetic substudy of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE)-A, which was a randomized comparison of aspirin and clopidogrel compared with aspirin alone for the prevention of thromboembolic events in atrial fibrillation, the primary outcome was similar in carriers and non-carriers of *CYP2C19*2* [48]. Similarly, in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial, in which only 14% of patients presenting with ACS underwent PCI, there was no difference in ischemic outcomes according to *CYP2C19* genotype [48]. A genetic analysis of Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial showed no apparent risk in clopidogrel-treated patients who were carriers of *CYP2C19 LOF* alleles; [22] however, because clopidogrel had no effect on ischemic outcomes in the overall study population, no pharmacogenetic interaction would be expected [49].

Previous observations showing an association between *CYP2C19* genotype and clinical outcomes during clopidogrel administration are mostly derived from platelet-oriented ischemic events: procedure- or stent-related MI or stent thrombosis. Therefore, the influence of *CYP2C19* genotype on ischemic event occurrence seems less prominent in cohorts other than PCI-treated patients. Among ACS patients in the PLATO trial, the *CYP2C19* genotype in the clopidogrel-treated patients did not show a definite association with the composite of ischemic

events at the end of the study duration (carriers vs non-carriers: 11.2 vs 10.0%; p=0.25). The PLATO genetic substudy was the largest genetic study ever conducted in a clinical trial (n>10,000). Only 66% of the total number of patients in the PLATO trial had a planned invasive strategy compared with TRITON where enrollment required the performance of PCI. Adverse outcomes were more frequent in clopidogrel-treated patients carrying the *CYP2C19 LoF* genotype (**2*, **3*, **4*, **5*, **6*, **7* and **8*) in PLATO at 30 days compared with ticagrelor-treated patients (HR: 1.37; 95% CI: 1.04–1.82; p = 0.028), but this difference did not persist at the end of the follow-up period [50].

Influence of *CYP2C19 GoF alleles* on clinical outcomes during clopidogrel therapy

Unlike the *CYP2C19 LoF* alleles, the influence of the *gain-of-function (GoF) CYP2C19*17* allele on clinical outcome in patients treated with clopidogrel is less studied. Sibbing and co-workers studied the impact of *CYP2C19*17* on bleeding in 1524 patients undergoing PCI after pre-treatment with clopidogrel, 600 mg. In a multiple logistic regression model, a gene-dose effect of *CYP2C19*17* on 30-day TIMI bleeding was observed (compared with no *17 carriage, OR for one *17 allele 1.85, 95% CI, 1.19- 2.86; OR for 2 *17 alleles 3.41, 95% CI, 1.42-8.17; *P* =0.006) (49). An effect of *17 carriage on ischemic events was not observed [51]. However, in the genetic substudy of CURE, clopidogrel had a significantly more pronounced effect on ischemic events compared with placebo in carriers of at least one *CYP2C19*17* allele compared with non- carriers (HR with clopidogrel among carriers 0.55, 95% CI, 0.42-0.73; HR among non carriers 0.85, 95% CI, 0.68-1.05; *P* =0.02 for the interaction) [48]. A potential effect of *CYP2C19*17* carriage on bleeding events was detected in the Platelet Inhibition and Patient Outcomes (PLATO) genetic substudy. The rate of major bleeding was significantly greater in clopidogrel-treated patients with a *17 allele compared with patients without any *17 or *LoF* alleles (11.9% vs 9.5%; *P* =0 .02). However, there were no significant interactions of bleeding rates with any *CYP2C19*17* or *LOF* alleles within or between the treatment groups; that is, non-coronary artery bypass graft bleeding consistently increased with ticagrelor compared with clopidogrel, irrespective of *CYP2C19* polymorphisms [51].

The Asian population has a high prevalence of *CYP2C19 LoF* carriage (intermediate vs poor metabolizers: 45–50 vs 10–15%, respectively). However, multiple lines of evidence from registries and prospective studies have also demonstrated that the risk of stent thrombosis in east Asians (annually 0.2–0.6%) was not higher compared with Caucasians [52,53]. In a large Korean registry including 2146 patients undergoing drug-eluting stent implantation, carriers of the *CYP2C19*2 LoF* allele (47%) had a greater risk of 1-year ischemic event occurrence compared with non-carriers (2.0 vs 0.8%; p = 0.02) [54].

Alternative Dosing Regimens

Increasing the clopidogrel loading and maintenance dosages could potentially increase active metabolite generation in patients with decreased *CYP2C19* catalytic activity due to genetic polymorphisms by providing more substrate for clopidogrel bioactivation [55]. Higher clopidogrel loading dose (600mg) has been shown to provide higher circulating levels of active metabolite and more rapid and intense platelet inhibition than standard 300mg loading dose [56,57]. Furthermore, a maintenance dose regimen of 150 mg/d is associated with greater platelet inhibition than 75 mg per day therapy [57,58].

In the subanalysis of the GRAVITAS trial, the *CYP2C19 LoF* allele was significantly associated with the risk of HPR at 1 month during double-dose clopidogrel therapy (odds ratio: 1.62 for one *LoF* allele and 11.2 for two *LoF* alleles). *CYP2C19 LoF* homozygotes with HPR receiving double-dose clopidogrel exhibited a similar poor antiplatelet response as *CYP2C19 LoF* homozygotes with HPR receiving standard-dose clopidogrel [40]. These observations suggest that the earlier recommendation noted by the FDA to treat patients carrying *CYP2C19 LoF* with double-dose clopidogrel, which was based on a healthy volunteer study, is ineffective for patients treated with PCI [59].

Prasugrel

Prasugrel is a second-generation thienopyridine like clopidogrel, but its biotransformation into the active metabolite is different. In has been shown that, hydrolysis by intestinal human carboxylesterase-2 (and to a lesser extent, human carboxylesterase-1) rapidly generates a thiolactone precursor (*R*-95913) that is oxidized in a single CYP-dependent step to the active metabolite (*R*-138727) with *CYP3A4/5* and *CYP2B6* being major contributors and *CYP2C19* and *CYP2C9* play a minor role; oxidation by intestinal *CYP3A* also contributes to the bioactivation of prasugrel. The bioactivation of prasugrel is more efficient than that of clopidogrel because there is no competing metabolic pathway to an inactive metabolite. Moreover, the different CYP isoenzymes can compensate for one another. The more rapid and intense inhibition provided by prasugrel is primarily the result of this more efficient process, as the inhibitory potency of the prasugrel and clopidogrel active metabolites is similar [18,60].

Influence of *CYP2C19* SNPs on Prasugrel metabolism

It was reported that *CYP2C19* or *CYP2C9 LoF* carriage did not influence exposure to the active metabolite or antiplatelet effect of prasugrel in healthy volunteers treated with a 60mg loading dose [61]. Similarly, no significant attenuation of the pharmacokinetic or pharmacodynamic response to prasugrel was observed in *LoF* allele carriers versus non-carriers in a pooled analysis of studies in 238 healthy subjects comprising different ethnic populations treated with and without aspirin [62]. In a randomized study of patients with stable CAD, *CYP2C19* genotype did not affect prasugrel active metabolite formation or the magnitude of platelet inhibition during either the loading or maintenance phase after prasugrel, 60 mg followed by 10 mg daily. Moreover, the AUC of prasugrel active metabolite was greater than that of clopidogrel irrespective of *CYP2C19* genotype [63]. In a recent prospective study of 71 patients undergoing PCI treated with either prasugrel 10 mg/day versus high-dose 150 mg/day clopidogrel, prasugrel therapy was more effective in reducing platelet reactivity compared with high clopidogrel particularly in *CYP2C19*2* carriers [64]. In another study of 355 patients who underwent percutaneous coronary stenting and treated with either prasugrel (n=90; 60/10 mg: loading/daily maintenance dose) or 600/75 mg clopidogrel (n=265) in addition to 500/100 mg aspirin, although prasugrel therapy was associated with significantly lower on treatment platelet reactivity, 9.8% of patients had high platelet reactivity during prasugrel therapy compared to 35% of patients treated with clopidogrel. Moreover, 50% of patients with HPR during prasugrel therapy were carriers of the reduced-function allele *CYP2B6*6*, and 41.7% were carriers of CYP2C9*2 allele [65]. Cuisset et al. [66] demonstrated that, among 213 patients undergoing stenting for ACS and treated with prasugrel 10 mg daily, *CYP2C19* 2 carriers had significantly higher PRI VASP than noncarriers (33 ± 15% vs. 27 ± 14%, p = 0.03) and higher prevalence of HPR (16% vs. 4%, p = 0.01). Moreover, lower PRI VASP than non-carriers (25 ± 13% vs. 31 ± 15%, p = 0.03, p = 0.03), lower rate of HTPR (1% vs. 10%, p = 0.02), higher rate of hyper-response (34% vs. 21%, p =

0.02) were observed in *CYP2C*17* carriers. *CYP2C19*17* carriers had a higher rate of bleeding complications than non-carriers [66].

Influence of *CYP2C19 LoF alleles* on clinical outcomes during prasugrel therapy

In an genetic analysis of the TRITON TIMI 38 trial, there was similar rates of cardiovascular death, myocardial infarction, or stroke among carriers and noncarriers of *CYP2C19 LoF* alleles during prasugrel treatment among ACS patients undergoing PCI (Hazard Ratio 0.89, 95% CI 0.60-1.31, p=0.27) which is in contrast to the results observed during clopidogrel therapy. This is in consistent with the pharmacokinetic and pharmacodynamic results observed during clopidogrel and prasugrel administration [31,62].

Ticagrelor

Ticagrelor (AZD6140) is a selective, reversible $P2Y_{12}$ inhibitor that belongs to a new class of antiplatelet agents, the cyclopentyl-triazolo-pyrimidines. In addition to antiplatelet effects, ticagrelor blocks ADP-mediated vasoconstriction and is thought to increase adenosine-induced coronary blood flow. Ticagrelor is primarily metabolized via the cytochrome *CYP3A4* enzyme resulting in the generation of an equally potent active metabolite, with plasma concentrations similar to one-third of the parent compound. Ticagrelor does not require activation, therefore drug-drug interactions are less likely to interfere with antiplatelet effects and outcomes compared with clopidogrel [16,67].

Influence of *CYP3A4* on ticagrelor metabolism

Ticagrelor has been shown to be a strong inhibitor of *CYP3A5*, a moderate inhibitor of *CYP2C9* and *CYP2D6*, and a weak inhibitor of *CYP3A4*. As a P-glycoprotein substrate and inhibitor, ticagrelor has been shown to significantly increase plasma digoxin concentrations, which would necessitate monitoring of plasma drug concentrations with co-administration. Multiple metabolites have been identified, with the major metabolites across all species being AR-C124910XX andAR-C133913XX; gormation of AR-C124910XX is thought to be via O-dealkylation, which leads to loss of the hydroxyethyl side chain [68]. *In vitro* experiments with human liver microsomes have shown that ticagrelor is primarily metabolized by cytochrome P450 (CYP) 3A enzymes. *CYP3A4* and *CYP3A5* appear to be primarily responsible for the formation of AR-C124910XX, whereas formation of ARC133913XX is most likely by *CYP3A4* with less contribution from *CYP3A5* [69].

Influence of P-glycoprotein on ticagrelor metabolism

Ticagrelor is a P-gp substrate and a weak P-gp inhibitor [70,71]. Concomitant use of ticagrelor and digoxin had no impact on ticagrelor exposure and led to an increased exposure to digoxin (Cmax by 75%, AUC by 28%). Although no data are currently available, concomitant use of ticagrelor with potent P-gp inhibitors (e.g. verapamil, quinidine) may lead to increased exposure to ticagrelor; caution is therefore advised [72,73].

Influence of *CYP2C9* and *CYP2C19* on ticagrelor metabolism

In vitro studies suggested that ticagrelor is a moderate inhibitor of CYP2C9, but it is unlikely to alter CYP2C9-mediated metabolism of products such as warfarin and tolbutamide [69].

In the PLATO trial, the effect of ticagrelor was compared to that of clopidogrel on platelet function as per genotype. Ticagrelor exhibited lower platelet reactivity than clopidogrel by all assays irrespective of *CYP2C19* genotype or metabolizer status (P<0.01) [17].

In the genetic analysis of Onset and Offset of Antiplatelet Effects of Ticagrelor versus Clopidogrel in Patients with Stable Coronary Artery Disease (ONSET/OFFSET) and Response to Ticagrelor in Clopidogrel Non-Responders and Effect of Switching Therapies (RESPOND) genotype studies, *CYP2C19* genotype influenced the antiplatelet effect of clopidogrel, whereas there was no effect of *CYP2C19* genotype during ticagrelor therapy. Ticagrelor therapy was associated with lower platelet reactivity than clopidogrel in all assays, irrespective of *CYP2C19* genotype or metabolizer status (p< 0.01) [74].

Paraoxonase-1 (*PON-1*)

PON-1 is a calcium-dependent glycoprotein present in liver cells. PON-1 is also present in the circulation and is carried by high-density lipoproteins, causing prevention in peroxidation of low-density lipoproteins. Bouman et al. [75] identified *PON-1* as a key enzyme participating in the second step of clopidogrel bioactivation and found no evidence for the involvement of *CYP2C19* in either of the steps of clopidogrel bioactivation. Lower *PON1* plasma activity, lower plasma concentrations of active metabolite, lower platelet inhibition and a higher rate of stent thrombosis were observed in *PON1 QQ192* homozygous patients treated with clopidogrel following stenting than patients who were *RR192* homozygous [75]. However, several cohort studies [76-78] and a substudy of the GRAVITAS (Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety) trial showed no influence of the *PON-1* polymorphism on platelet function during clopidogrel therapy [78].

Assays for genotyping

Currently *CYP2C19* and *ABCB1* genotype cab be assessed by Taq-Man® assay (Applied Biosystems, CA, USA), the AmpliChip® CYP450 (Roche Diagnostics, IN, USA) and the INFINITI™ Analyzer assay (AutoGenomics, CA, USA). These standard genotyping assays require expensive laboratory infrastructure, batch processing and a separate DNA isolation step. Mostly these assays are performed by outside laboratory and therefore associated with substantial turnaround times for reporting results. Therefore many of these genotyping platforms are not practical for routine clinical use in the catheterization laboratories where immediate results are required to treat patients optimally and effectively.

The Verigene® System (Nanosphere, Inc., IL, USA) is a near point-of-care assay that is based on gold nanoparticle probe technology. It is a cartridge-based assay that requires 1 ml of whole blood and allows for rapid random access testing in the individual patient without the need for a separate DNA isolation step. This assay enables multi-target detection of SNPs, including SNPs of *CYP2C19*, within approximately 2–3 h. The Spartan DX-12™ (Spartan Bioscience Inc., ON, Canada) is another assay that is designed for nonbatched PCR applications. The *CYP2C19*2* variant is determined from the DNA obtained from a buccal swab. Results are available within one hour.

Clinical Trials and Future Direction

Currently, few published small studies are available that demonstrated the benefit of personalized antiplatelet therapy. Roberts et al. demonstrated the utility of pharmacogenetic strategies using a point of care genetic test to personalize post PCI antiplatelet therapy. In this study, 200 patients were treated with either standard dose clopidogrel, or prasugrel in patients carrying *CYP2C19*2* allele and the primary endpoint is the proportion of *CYP2C19*2* allele carriers with high on treatment platelet reactivity assessed by VerifyNow assay. The authors found that genetic testing performed at bedside can reduce high

on treatment platelet reactivity, but reported no clinical outcome data [79]. Ahn et al. [80] assessed both genotype and phenotype directed antiplatelet therapy in 65 patients and found that these testings may be effective in decreasing high on treatment platelet reactivity at 30 days. Xie et al. [81]. performed a study to compare personalized antiplatelet therapy according to *CYP2C19* phenotype and conventional antiplatelet therapy in 600 Chinese patients treated with PCI. In this study, personalized antiplatelet therapy according to *CYP2C19* genotype was associated with significantly decreased 180 days incidence of major adverse cardiovascular events (MACE) events. In this study double dose clopidogrel and cilostazol was used as an alternative in patients with *CYP2C19* genotype based intermediate or poor metabolizer status. AT this time, in the absence of strong evidence from a randomized trial proving the utility of the genetic testing, genetic testing alone may performed in clopidogrel naïve patients to assist physician to treat patient with a specific $P2Y_{12}$ receptor blocker. In clopidogrel-treated patients suffering from recurrent events, non-ACS patients carrying *LoF* allele (i.e. high risk patients) can be treated with prasugrel or ticagrelor. Currently the TAILOR-PCI trial (NCT01742117) is assessing personalized antiplatelet therapy (genetic testing) vs. standard of care after PCI in 6000 patients worldwide.

Conclusions

Extensive research has been performed to characterize the influence of genetic polymorphisms of enzymes associated with metabolic pathways on the pharmacokinetic and pharmacodynamic properties of clopidogrel, prasugrel and ticagrelor, as well as on clinical outcomes associated with treatment with these $P2Y_{12}$ blockers. Pharmacokinetic and pharmacodynamic responses to clopidogrel appear to be affected mainly by *CYP2C19*, which is the major cytochrome involved in the biotransformation of clopidogrel. Carriers of a *CYP2C19 LoF* allele carriage is associated with poorer pharmacodynamic responses to clopidogrel, and an increased risk of thrombotic events particularly in PCI-treated patients in a gene-dose fashion. In contrast, there is no conclusive evidence that genotype affects the pharmacokinetic, pharmacodynamic, or clinical responses to prasugrel or ticagrelor. Although initial genetic studies did not indicate any effects of genotype variations on response to prasugrel therapy, recent studies suggest that genetic variations in *CYP2C19* and *CYP2B6* may affect response to the drug. To date there are no reports of significant influence of genotype variations on ticagrelor metabolism, its antiplatelet response or clinical outcome. The optimal strategy to overcome the influence of *LoF* carriage in patients treated with clopidogrel is probably to switch therapy to either prasugrel or ticagrelor, although large-scale studies assessing this approach have not been performed. The role of genetic testing is now addressed in the ACCF/AHA and ESC guidelines where there is a Class IIb recommendation for testing if it will alter management [82]. Point-of-care genotyping is an emerging technique that may facilitate personalized antiplatelet therapy [83-86] but further research on how to incorporate such testing into clinical practice is warranted.

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