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Personalizing antiplatelet prescribing using genetics for patients undergoing percutaneous coronary intervention

Larisa H. Cavallari

Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida College of Pharmacy, Gainesville, FL, USA

Abstract

Introduction—Clopidogrel is commonly prescribed with aspirin to reduce the risk for adverse cardiovascular events after percutaneous coronary intervention (PCI). However, there is significant inter-patient variability in clopidogrel response. The *CYP2C19* enzyme is involved in the biotransformation of clopidogrel to its pharmacologically active form, and variation in the *CYP2C19* gene contributes to clopidogrel response variability.

Areas covered—This article describes the impact of *CYP2C19* genotype on clopidogrel pharmacokinetics, pharmacodynamics, and effectiveness. Examples of clinical implementation of *CYP2C19* genotype-guided antiplatelet therapy for patients undergoing PCI are also described as are emerging outcomes data with this treatment approach.

Expert commentary—A large clinical trial evaluating outcomes with *CYP2C19* genotype-guided anti-platelet therapy after PCI is on-going. In the meantime, data from pragmatic and observational studies and smaller trials support improved outcomes with genotyping after PCI and use of alternative antiplatelet therapy in patients with a *CYP2C19* genotype associated with reduced clopidogrel effectiveness.

Keywords

Percutaneous coronary intervention; genotype; *CYP2C19*; clopidogrel; prasugrel; ticagrelor; polymorphism; cardiovascular events

1. Introduction

Clopidogrel is a thienopyridine prodrug that is converted in the liver to its pharmacologically active metabolite, which irreversibly binds to the P2Y₁₂ receptor on the surface of the platelet to inhibit adenosine diphosphate (ADP)-mediated platelet activation and aggregation. Clopidogrel is indicated in combination with aspirin for patients undergoing percutaneous coronary intervention (PCI) to reduce the risk for adverse cardiovascular

CONTACT: Larisa H. Cavallari, lcavallari@cop.ufl.edu, Center for Pharmacogenomics, Department of Pharmacotherapy and Translational Research, University of Florida, Gainesville, FL 32610-0486, USA.

Declaration of interest

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events and coronary artery stent thrombosis [1–4]. However, there is significant inter-patient variability in clopidogrel pharmacokinetics and pharmacodynamics, which translates into variation in clopidogrel effectiveness after PCI [5]. The gene encoding cytochrome P450 *CYP2C19* is a major contributor to the inter-patient variability in clopidogrel response [6]. This review describes variation in the *CYP2C19* gene and its impact on clopidogrel pharmacokinetics, pharmacodynamics, and clinical effectiveness, and emerging outcomes data with *CYP2C19* genotype-guided anti-platelet therapy after PCI. A discussion of platelet function testing is beyond the scope of this review, and the reader is referred to a recent review on this subject [7].

2. Clopidogrel metabolism

Once absorbed, approximately 85% of the clopidogrel dose is inactivated by esterases (Figure 1) [8]. The remaining 15% undergoes biotransformation via a two-step process to an active thiol metabolite. The *CYP2C19* enzyme is involved in both biotransformation steps. Approximately 30% of Whites and Blacks and over 50% of Asians inherit a deficiency in the *CYP2C19* enzyme [9]. In these individuals, clopidogrel bioactivation is impaired, resulting in reduced formation of the active thiol metabolite.

3. *CYP2C19* genotype

3.1. *CYP2C19* gene alleles

Genetic polymorphisms leading to either impaired or increased *CYP2C19* enzyme activity are common. *CYP2C19* alleles are referred to by the star allele nomenclature. The **1* allele is associated with normal enzyme activity. It is considered the default allele when polymorphisms associated with altered enzyme activity are absent. The *CYP2C19*2* (rs4244285, c.681G>A) and **3* (rs4986893, c.636G>A) alleles result from an aberrant splice site and premature stop codon, respectively. In both cases, this leads to loss of enzyme activity. The **2* allele is by far the most common of the two, with an allele frequency of approximately 15% in Whites and Blacks and 30–35% in Asians. Thus, approximately 25–30% of Whites and Blacks and over 50% of Asians have a **2* allele [9,10]. Other less common nonfunctional alleles are **4*, **5*, **6*, **7*, and **8*. The **17* allele (rs12248560, c. –806C>T) occurs in the 5' flanking region of the gene in a transcription factor binding site and results in increased transcriptional activity.

3.2. Inferred phenotypes

CYP2C19 genotype confers five drug metabolism phenotypes (Table 1): poor metabolism (PM), intermediate metabolism (IM), normal metabolism (NM), rapid metabolism (RM), and ultra-rapid metabolism (UM) [13]. Individuals who inherit two copies of the normal functioning **1* allele are deemed NMs with normal enzyme activity. Individuals with a single nonfunctional allele (e.g. **2* or **3*) are IMs, with reduced *CYP2C19* activity. Poor metabolizers have two nonfunctional alleles and complete absence of enzyme activity. Individuals with one normal functioning allele and one increased function allele (i.e. **17*) are called RMs, whereas those with two copies of an increased function allele are UM. The combination of a nonfunctional allele and the **17* allele is provisionally classified as the IM

phenotype, based on data that increased activity with the *17 allele is not sufficient to overcome reduced enzyme activity with a nonfunctional allele [14]. Examples of genotypes conferring each phenotype are shown in Table 1. There are ethnic differences in the distribution of CYP2C19 phenotypes (Table 1). Asians have a higher prevalence of the PM and IM phenotypes compared to Whites and Blacks. On the other hand, the prevalence of the RM or UM phenotype is much lower in Asians compared to other ethnic groups.

4. Implications of *CYP2C19* genotype for clopidogrel response

4.1. Pharmacokinetics and pharmacodynamics

Following clopidogrel administration, PMs and IMs have significantly lower concentrations of the active thiol metabolite of clopidogrel compared to patients with other phenotypes [15]. Among healthy volunteers given a 300 mg dose of clopidogrel, the plasma concentrations of the active metabolite were approximately 30% lower in carriers of a nonfunctional allele compared to those without a nonfunctional allele [15]. Similar reductions in plasma concentrations were observed following a 75 mg dose. Consistent with the pharmacokinetic data, the IM and PM phenotypes have been associated with significantly lesser reductions in platelet aggregation with clopidogrel compared to other phenotypes [15].

In contrast to data with the PM and IM phenotypes, clopidogrel exposure and antiplatelet effects are greatest among individuals with the RM and UM phenotypes. In a study of 1524 patients who underwent PCI and stent placement after pre-treatment with clopidogrel 600 mg, ADP-induced platelet aggregation, measured immediately before PCI, was found to be significantly lower in RMs and UMs compared to NMs [16]. A gene-dose effect was observed, with the lowest values for platelet aggregation in UMs and intermediate values in RMs compared to NMs.

A genome-wide association study further demonstrated the impact of the *CYP2C19* genotype on antiplatelet effects of clopidogrel and ruled out other genes with major effects on clopidogrel response [6]. This study was conducted in over 400 healthy Amish volunteers, who were administered a 300 mg loading dose of clopidogrel, followed by a maintenance dose of 75 mg/day for 6 days, after which platelet aggregation was assessed through *ex vivo* studies. Of over 400,000 polymorphisms genotyped, only those within the *CYP2C* cluster (containing the *CYP2C18*, *CYP2C19*, *CYP2C9*, and *CYP2C8* genes) were associated with antiplatelet response to clopidogrel. A variant in strong linkage disequilibrium with the *CYP2C19**2 allele was most strongly associated with anti-platelet effects. No other gene region was associated with clopidogrel response on a genome-wide significance level. Indeed, while other genes encoding proteins in the clopidogrel pathway have been examined for their effect on clopidogrel response, the data are largely negative or inconsistent [15,17–19]. Thus, only *CYP2C19* genotype is considered ‘clinically actionable’ with regard to prescribing decisions related to antiplatelet therapy.

Several studies have examined the impact of dose escalation on platelet response to clopidogrel in CYP2C19 PMs and IMs [20–22]. Investigators compared *ex vivo* platelet aggregation following 75, 150, 225, and 300 mg/day doses of clopidogrel in patients with

cardiovascular disease and a nonfunctional allele [20,22]. Doubling of the clopidogrel dose to 150 mg/day was found to be insufficient for achieving desired antiplatelet effects in IMs or PMs. A dose of 225 mg/day in IMs yielded similar inhibitory effects on platelet aggregation as a 75 mg dose in NMs. However, in PMs, even quadrupling the dose to 300 mg resulted in insufficient inhibition of platelet aggregation. A subsequent study further compared the effects of dose escalation in patients with and without diabetes [22]. Among IMs without diabetes, a 225 mg/day dose was sufficient for reducing platelet aggregation to acceptable levels. However, a dose of 300 mg/day was needed in IMs with diabetes to produce a similar inhibitory effects on platelet aggregation as a 75 mg dose in NMs. Thus, while tripling or quadrupling the clopidogrel maintenance dose may be sufficient to overcome the effects of the IM phenotype, dose escalation does not appear to be a viable option for improving response to clopidogrel in PMs.

4.2. Clinical outcomes

Post-hoc analyses of randomized controlled trials and patient registries have shown a higher risk for cardiovascular events following PCI in clopidogrel-treated patients with the PM or IM phenotype compared to similarly treated patients with other phenotypes [15,23–27]. In a highly cited meta-analysis of nine trials and 9685 patients treated with clopidogrel, Mega et al. [28], showed a higher risk for major adverse cardiovascular events (MACE, defined as the composite of cardiovascular death, myocardial infarction, or stroke) in patients with the IM or PM phenotype compared to those with other phenotypes. This meta-analysis included studies of high-risk patients, with over 50% of patients having an acute coronary syndrome (ACS) and 90% undergoing PCI. The hazard ratio for MACE was 1.55 (95% confidence interval, 1.11–2.17) in IMs and 1.76 (95% confidence interval, 1.24–2.50) in PMs compared to patients without a nonfunctional allele. The hazard ratio for stent thrombosis was 2.67 (95% confidence interval, 1.69–4.22) in IMs and 3.97 (95% confidence interval, 1.75–9.02) in PMs compared to patients with other phenotypes.

Subsequent meta-analyses have also shown a higher risk for stent thrombosis among clopidogrel-treated patients with the PM or IM phenotype compared to those with other phenotypes, with hazard ratios ranging from 1.8 to 3.5 (Table 2) [29–35]. However, the point estimates for MACE were more variable, ranging from 1.1 to 1.6, and the association between genotype and MACE was inconsistent across studies. This heterogeneity is likely explained by variability in patient risk for adverse cardiovascular events across studies included in the meta-analyses. In particular, consistent associations between *CYP2C19* genotype and outcomes during clopidogrel treatment are observed in studies of high-risk patients, and particularly in those undergoing PCI [27,28]. However, negative associations have been observed in studies of lower-risk patients, such as those with atrial fibrillation, stable coronary disease, or ACS managed medically [36,37]. The variability in the association between genotype and clopidogrel effectiveness according to patient risk is probably best demonstrated in a meta-analysis by Sorich et al. [35], in which the risk for MACE based on genotype was examined separately in patients who underwent PCI and those who did not. Among patients undergoing PCI (i.e. high risk patients) treated with clopidogrel, there was significantly higher risk for MACE among PMs and IMs compared to those with other phenotypes (Table 2). However, among clopidogrel-treated patients with

non-PCI indications (i.e. lower risk patients), there was no increase in the risk for MACE by genotype.

The impact of the *CYP2C19*17* allele on clinical outcomes with clopidogrel has also been examined, and some, but not all, studies have reported an increased bleeding risk with clopidogrel in RMs and UMs [16,27,34,38]. In an examination of over 1500 patients who underwent PCI and received a clopidogrel 600 mg loading dose, followed by a maintenance dose of 75 mg/day, an increased bleeding risk was observed among RMs and UMs compared to NMs [16]. The highest risk was in UMs, who had over threefold increase in bleeding risk compared to NMs. A subsequent study observed an increased bleeding risk with the *CYP2C19*17* allele among Blacks, but not Whites [38]. Some investigators have also reported greater clopidogrel efficacy with the *CYP2C19*17* allele [34,39], but this has not been demonstrated by others [16,25]. Overall, the clinical outcomes data with the **17* allele are inconsistent and insufficient to support its role in antiplatelet therapy decisions.

5. Alternative antiplatelet therapy

5.1. Prasugrel and ticagrelor efficacy

Prasugrel and ticagrelor are newer P2Y₁₂ inhibitors that have been shown to be superior to clopidogrel at preventing MACE in the TRITON-TIMI 38 and PLATO trials, respectively [40,41]. The TRITON-TIMI 38 trial included 13,608 patients with an ACS and scheduled PCI and showed a lower risk for the primary efficacy endpoint of death from cardiovascular causes, non-fatal MI, or nonfatal stroke with prasugrel versus clopidogrel (hazard ratio 0.81, 95% confidence interval, 0.73–0.90) [41]. The PLATO trial included 18,624 patients with an ACS (over 60% underwent PCI) and showed a lower risk for the primary composite endpoint of death from vascular causes, myocardial infarction, or stroke with ticagrelor versus clopidogrel at 12 months (hazard ratio 0.84, 95% confidence interval, 0.77–0.92) [40]. Based on these data, current PCI guidelines recommend the use of prasugrel or ticagrelor over clopidogrel in patients who undergo PCI after an ACS (Class IIa recommendation, based on a moderate quality of evidence) [1].

Like clopidogrel, prasugrel is a prodrug that must be bio-transformed to its active metabolite that irreversibly binds to the platelet P2Y₁₂ receptor. The CYP2C19 enzyme is one of a number of CYP450 enzymes involved in prasugrel biotransformation. Ticagrelor is administered in its active form and reversibly binds the P2Y₁₂ receptor. Unlike clopidogrel, neither prasugrel nor ticagrelor is affected by *CYP2C19* genotype [27,42].

5.2. Limitations with prasugrel and ticagrelor therapy

Compared to clopidogrel, prasugrel is associated with a higher risk for major bleeding, and ticagrelor is associated with a higher risk for non-coronary artery bypass-related bleeding [40,41]. Because of its increased bleeding risk, prasugrel is contraindicated in patients with a history of stroke or transient ischemic attack or with pathologic bleeding. In addition, lower doses (i.e. 5 mg/day vs. 10 mg/day) are recommended for patients aged 75 years or older or weighing 60 kg or less to minimize bleeding risk. Ticagrelor is contraindicated in patients with active bleeding, hepatic impairment, or a history of intracranial bleeding.

In addition to their increased bleeding risk compared to clopidogrel, both ticagrelor and prasugrel are more expensive than clopidogrel, which is available generically. In contrast to clopidogrel and prasugrel, ticagrelor requires twice daily dosing, which may potentially impact adherence. Ticagrelor is also associated with higher discontinuation rate secondary to adverse effects such as dyspnea [43]. Thus, while ticagrelor and prasugrel are more effective than clopidogrel and not impacted by *CYP2C19* genotype, their higher cost and bleeding risk prevents their routine use over clopidogrel.

5.3. P2Y₁₂ inhibitor efficacy in *CYP2C19* subgroups

While prasugrel and ticagrelor were shown to be superior to clopidogrel in clinical trial populations overall, approximately 30% of trial participants were *CYP2C19* PMs or IMs, who have since been shown to have lower production of the active clopidogrel metabolite, reduced inhibition of platelet aggregation, and lesser reduction in cardiovascular events with clopidogrel compared to those without a loss-of-function allele, as discussed above [15,28]. Subsequent genetic substudies of the TRITON-TIMI 38 and PLATO trials have examined the efficacy of prasugrel and ticagrelor compared to clopidogrel according to *CYP2C19* genotype [27,44]. Genotype data were available for 2914 patients in the TRITON-TIMI 38 trial [44]. Using these data, investigators reported a relative risk of 0.57 (95% confidence interval, 0.39–0.83) for MACE with prasugrel versus clopidogrel in patients with a nonfunctional allele (e.g. PMs and IMs), suggesting greater efficacy of prasugrel versus clopidogrel in this genetic subgroup. However, among patients without a nonfunctional allele, the relative risk for MACE with prasugrel compared to clopidogrel was 0.98 (95% confidence interval, 0.80–1.20), suggesting similar efficacy with the two drugs. Similarly, in a genetic substudy of 10,285 patients from the PLATO trial, the hazard ratio for MACE was 0.77 (95% confidence interval, 0.60–0.99) for ticagrelor versus clopidogrel among patients with a *CYP2C19* nonfunctional allele (e.g. PMs and IMs), but 0.86 (0.74–1.01) among patients without a nonfunctional allele [27].

6. Guidance for *CYP2C19* genotyping

6.1. Clopidogrel labeling

In 2010, the US FDA approved revision of the clopidogrel label to include a boxed warning regarding the *CYP2C19* genotype, the most serious kind of warning on drug labeling [45]. The label warns of reduced clopidogrel effectiveness in PMs, with two nonfunctional alleles. The label advises that genetic testing is available to determine genotype and that alternative therapy should be considered in PMs. Since this label revision in 2010, additional data have shown that the risk for reduced effectiveness also extends to IMs [28]. The European Medicines Agency's Public Assessment Report for clopidogrel also includes information regarding reduced response in *CYP2C19* PMs.

6.2. AHA/ACC guidelines

The American College of Cardiology Foundation and the American Heart Association published a response to the FDA-approved clopidogrel-labeling revision [45]. Their position is summarized in the current guidelines for management of patients undergoing PCI [1,2]. In brief, they state that routine use of genotyping to identify poor responders to clopidogrel is

not recommended, citing a lack of data from large randomized controlled trials demonstrating the clinical utility of genotype-guided antiplatelet therapy. However, guidelines state that genotyping might be considered in high-risk patients, such as those with diabetes or complicated coronary lesions (Class IIb recommendation, usefulness less well established). In these patients, if genotyping reveals a nonfunctional allele, consideration of alternative therapy is recommended.

6.3. CPIC guidelines

The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides guidelines for prescribing decisions based on genotype. The guidelines do not make recommendations on whether or not to order genetic testing. Instead, they provide guidance on appropriate therapy based on genotype results. In the case of *CYP2C19* genotype data for clopidogrel, the guidelines focus on patients with an ACS who undergo PCI, given that the evidence is strongest in this high-risk population [9]. For these patients, if genotyping reveals a nonfunctional allele, alternative therapy with either prasugrel or ticagrelor is recommended in the absence of contraindications. For patients without a nonfunctional allele (i.e. those with the NM, RM, or UM phenotype), clopidogrel is expected to be effective.

7. Clinical implementation of *CYP2C19* genotyping

A number of institutions have started offering *CYP2C19* genotyping as part of clinical care to guide antiplatelet therapy after PCI [11,46–49]. In fact, it is one of the most common examples of pharmacogenetic implementation in clinical practice [50]. The approach to genotyping varies across institutions, with some taking a preemptive approach and genotyping high-risk patients or those undergoing left heart catheterization, in the event that they later proceed to PCI and require dual antiplatelet therapy [46,47]. Other sites take a reactive approach, with genotyping ordered around the time of PCI [11,48]. The availability of rapid genotyping platforms allows for efficient turnaround of genotype results, so that results may be available before the patient leaves the cardiac catheterization laboratory, as has been recently demonstrated [49].

The University of Florida launched its Personalized Medicine Program in 2012 with implementation of *CYP2C19* testing to guide clopidogrel use [51]. Initially, the test was done preemptively for patients undergoing left heart catheterization, and testing was paid for by research and institutional support. After the first year, the clinical pathology laboratory began clinically billing for testing. From that point on, the test was only offered for patients proceeding to PCI since there is no reimbursement mechanism currently for preemptive testing. Genotyping is done in the UF Health Pathology Laboratory, with results available in 2 to 3 days and placed in the electronic health record along with the inferred phenotype. A clinical pharmacist receives an electronic in-basket alert for all genotype orders and follows up with the physician treating patients found to have a nonfunctional allele (PMs and IMs) to recommend alternative therapy in the absence of contraindications. Clinical decision support was also built into the electronic health record so that if a physician orders clopidogrel for a patient with a PM or IM phenotype on record, an alert will appear to warn the physician about reduced clopidogrel effectiveness and recommend alternative therapy.

Examples of other institutions that have implemented *CYP2C19* testing are Vanderbilt University Medical Center; University of Maryland, Baltimore; University of North Carolina, Chapel Hill; University of Pittsburgh; University of Alabama, Birmingham; and Sanford Health [49,50]. Details of implementation at several of these sites have been described [46–49].

8. Data with *cyp2c19*-guided antiplatelet therapy after PCI

8.1. Randomized controlled trial data

In an early proof-of-concept trial, investigators randomized 200 patients undergoing PCI to either treatment with clopidogrel 75 mg/day or a genotype-guided strategy [52]. For the genotype group, a rapid genotyping platform was used, with patients genotyped at the time of randomization. Patients with one or two *CYP2C19**2 alleles were treated with prasugrel, whereas those without a *2 allele received clopidogrel 75 mg/day. The primary endpoint of the trial was on-treatment platelet reactivity at 1 week. Significantly more patients with a *CYP2C19**2 allele in the clopidogrel treatment group versus the genotype group had high on-treatment platelet reactivity. This trial demonstrated the feasibility of rapid *CYP2C19* genotyping and tailoring antiplatelet therapy according to genotype results.

The Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR-PCI) trial is an ongoing, multi-site investigation of clinical outcomes with genotype-guided antiplatelet therapy among patients undergoing elective or emergent PCI (ClinicalTrials.gov Identifier: NCT01742117). The trial is targeting 5270 patients, who are being randomized to clopidogrel 75 mg/day, without genotyping, or *CYP2C19* genotyping with ticagrelor prescribed to IMs and PMs and clopidogrel prescribed to other patients. The primary outcome is MACE, defined as the composite of nonfatal myocardial infarction, nonfatal stroke, cardiovascular mortality, severe recurrent ischemia, or stent thrombosis, within 12 months of PCI. Trial results are much anticipated; however, they are not expected until 2020.

Two smaller trials, each including approximately 600 patients, were conducted in Chinese patients who underwent PCI following an ACS and were randomized to either clopidogrel (300 mg loading dose followed by a maintenance dose of 75 mg/day) or genotype-guided antiplatelet therapy [12,53]. For IMs in both trials, alternative therapy consisted of high-dose clopidogrel (600 mg loading dose, 150 mg/day maintenance dose). High-dose clopidogrel plus cilostazol was prescribed for PMs in one trial, and ticagrelor was prescribed for PMs in the other. In both studies, there was a significant reduction in MACE (defined as death, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization) in the genotype-guided arm.

8.2. Observational and pragmatic studies

A study conducted in The Netherlands examined cardiovascular outcomes among patients receiving *CYP2C19* genotyping at the time of elective PCI to guide post-PCI antiplatelet therapy [54]. The study included 3260 total patients who underwent genotyping, with the analysis focused on PMs. Patients were followed for up to 1.5 years after PCI for adverse

cardiovascular events, consisting of death from a cardiovascular cause, myocardial infarction, stent thrombosis, stroke, or repeat PCI in the same artery. The investigators found that over the follow-up period, significantly more PMs treated with clopidogrel experienced an adverse cardiovascular event (31%) compared to PMs prescribed prasugrel (5%, $p = 0.003$).

A pragmatic study of outcomes with *CYP2C19* genotyping was conducted in the United States as part of the NIH-funded Implementing Genomics in Practice (IGNITE) Network [50,55]. Preliminary results were presented at the 2016 Scientific Sessions of the American Heart Association [56]. The study included seven institutions that had implemented *CYP2C19* genotyping into clinical care for patients undergoing elective or emergent PCI. At each site, alternative antiplatelet therapy (e.g. prasugrel or ticagrelor) was recommended for IMs and PMs, with the ultimate prescribing decision left to the discretion of the treating physician. The primary endpoint was MACE, defined as death, myocardial infarction, or stroke within 12 months following PCI. The median time from PCI to genotype result being available was 1 day (interquartile range, 1–3 days). Of 1815 patients included, 31.5% were IMs or PMs. Alternative therapy was prescribed for 60.5% of IMs or PMs, with prasugrel being most common. In contrast, clopidogrel was the most common P2Y₁₂ inhibitor prescribed for patients without a nonfunctional allele, with 84.5% of these patients taking clopidogrel. There was a significantly higher risk for MACE in IMs/PMs treated with clopidogrel compared to IMs/PMs treated with alternative therapy (hazard ratio 2.3, 95% confidence interval, 1.2–4.5). Results remained significant after adjustment for clinical covariates. These data demonstrate the ability to efficiently provide genotype-guided antiplatelet therapy in the clinical setting. Moreover, they suggest improved outcomes when alternative therapy versus clopidogrel is prescribed in patients with a nonfunctional allele. An economic analysis based on these data is ongoing.

An additional study, conducted in Spain, also assessed outcomes with a personalized approach to antiplatelet therapy among high-risk PCI patients [57]. Cardiovascular outcomes were compared between 317 patients in the intervention group, who received genotype-guided therapy, and 402 historical controls who underwent PCI prior to genotype implementation. In addition to *CYP2C19*, patients in the intervention arm were genotyped for *ABCB1*, which encodes for p-glycoprotein, an intestinal efflux pump with implications for clopidogrel bioavailability [8]. The *ABCB1* 3435 TT genotype has been associated with lower plasma concentrations of clopidogrel [58]. Intervention patients with a *CYP2C19* nonfunctional allele or the *ABCB1* TT genotype were treated with prasugrel or ticagrelor, whereas clopidogrel was prescribed to all others. Forty-one percent of patients in the intervention group had an actionable genotype and were treated with alternative therapy. In contrast, nearly all patients in the control group received clopidogrel. Compared to the control group, there was a significantly lower occurrence of the primary composite endpoint of cardiovascular death, ACS, or stroke in the 12-month period following PCI in the intervention group (adjusted hazard ratio 0.61, 95% confidence interval, 0.39–0.94).

9. Conclusion

Post-hoc analyses of randomized controlled trials and patient registries have demonstrated an increased risk of cardiovascular events following PCI among clopidogrel-treated patients with a *CYP2C19* nonfunctional allele compared to similarly treated patients without a nonfunctional allele. In response to this, information about genotype is included in the FDA-approved clopidogrel labeling, and CPIC guidelines are available to assist with clinical use of genotype information. In recent years, a number of institutions have started clinically genotyping patients undergoing PCI to assist with selection of antiplatelet therapy. Data have recently emerged from small randomized controlled trials and observational and pragmatic studies that support improved outcomes when genotype is available after PCI and alternative therapy versus clopidogrel is prescribed for patients with a nonfunctional *CYP2C19* allele. A large randomized clinical trial is ongoing and will provide additional data on outcomes with genotype-guided antiplatelet therapy after PCI.

10. Expert commentary

The level of evidence needed to support pharmacogenetic implementation is controversial. Some argue that randomized controlled trials demonstrating the clinical utility of genotype-guided therapy are necessary. Others argue that genotype is yet another factor that may assist with optimizing drug therapy, much like serum creatinine, and need not to be held to such high standards [59]. In the case of *CYP2C19* genotyping for predicting clopidogrel response, there is a large clinical trial ongoing, though it is not expected to be completed for three more years. Many have felt that this is too long to wait and based on the substantial evidence base supporting associations between *CYP2C19* nonfunctional alleles and reduced clopidogrel effectiveness have proceeded with clinical implementation [50]. Data from these efforts are beginning to emerge and support improved outcomes in patients with a nonfunctional allele who are treated with alternative therapy over clopidogrel [54,56,57].

In addition to the evidence barrier, there are a number of other barriers to clinical implementation of *CYP2C19* testing, not the least of which is the need for timely return of *CYP2C19* genotype results in order to inform antiplatelet therapy early after PCI when risks for adverse cardiovascular events are highest [2]. While there is an FDA-cleared platform available for rapid *CYP2C19* genotyping, clinical pathology regulations in the United States somewhat limit its use. Specifically, all genetic testing in the United States is designated as high complexity and must be conducted in a Clinical Laboratory Improvement Amendments/College of American Pathologist-licensed laboratory, which may not be feasible in institutions with the clinical pathology laboratory is located some distance from the cardiac catheterization laboratory. Nonetheless, data demonstrating the feasibility of rapid genotyping in clinical practice are available [49]. The availability of pre-emptive genetic testing, done prior to the patient presenting to the cardiac catheterization laboratory, would negate the need for rapid genotyping. However, pre-emptive testing is not currently reimbursed by most third-party payers.

Changing practice patterns create an additional barrier to *CYP2C19*-clopidogrel implementation. Specifically, current PCI guidelines provide a Class IIa recommendation for

the use of alternative antiplatelet agents in preference to clopidogrel in patients undergoing PCI after an ACS [1]. This is based on superiority of newer P2Y₁₂ inhibitors over clopidogrel in clinical trials, although as noted earlier, approximately 30% of patients included in these trials were CYP2C19 PMs or IMs, and thus not expected to respond well to clopidogrel. In fact, the recently published EUCLID trial of clopidogrel versus ticagrelor in patients with symptomatic peripheral artery disease excluded PMs from participation for this reason [60].

For patients initially started on alternative P2Y₁₂ inhibitors per treatment guidelines, there is still a role for *CYP2C19* genotyping in informing chronic P2Y₁₂ therapy. Specifically, for patients without a nonfunctional allele (e.g. NMs, RMs, or UMs), data would suggest that clopidogrel would be effective [27,44] in the event that a patient has difficulty affording or tolerating prasugrel or ticagrelor or for patients at high bleeding risk (e.g. of older age, small body size, or with severe renal dysfunction), in whom the physician is wary of continuing more potent agents.

Other barriers include the need to educate clinicians about pharmacogenetics and how to optimally integrate genetic test results into clinical decision-making. This is addressed in part through the CPIC guidelines [9]. However, education is still important at the institutional level. Clinical decision support is a valuable tool to provide point-of-care assistance with interpretation of genotype results and translation into antiplatelet therapy recommendations. The NIH-funded IGNITE Network is working to address evidence, procedural, and education barriers to implementation of genomic medicine [55].

11. Five-year view

Based on data that *CYP2C19* genotype influences the pharmacokinetics and pharmacodynamics of clopidogrel, an increasing number of institutions have implemented genotyping into the clinical care of patients undergoing PCI to assist in selection of P2Y₁₂ inhibitor therapy. Results of a large ongoing randomized controlled trial examining the clinical utility of *CYP2C19* genotype-guided antiplatelet therapy will likely influence guidelines for the management of patients undergoing PCI and may drive further institutions to incorporate an individual's *CYP2C19* genotype into P2Y₁₂ prescribing decisions. Ongoing economic analyses evaluating the cost-effectiveness of genotype versus nongenotype-guided approaches to antiplatelet therapy are expected to influence payer decisions regarding genotyping. While use of newer P2Y₁₂ inhibitors will likely increase, especially in the setting of ACS, genotype information will remain of value in selection of chronic anti-platelet therapy for those unable to continue treatment with newer agents due to high cost or adverse drug effects. Genotype information may also be useful for selection of antiplatelet therapy for other diseases such as ischemic stroke.

Genotyping to predict clopidogrel response is typically done reactively at the time of PCI. A challenge with reactive testing is the need to efficiently turn around genotype results so that they are available early after PCI, when risks for adverse events are highest, to guide antiplatelet therapy. Over the next five years, it is expected that a preemptive approach to genotyping will become more commonplace, with patients presenting with *CYP2C19*

genotype data at the time of PCI. This will negate the decision of whether or not genotyping should be done. Rather, the physician will have genotype data readily available to guide prescribing decisions for individual patients.

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Key issues

- Data consistently demonstrate an increased risk of cardiovascular events following PCI among clopidogrel-treated patients with a *CYP2C19* non-functional allele compared to similarly treated patients without a non-functional allele.
- A large randomized controlled trial assessing the clinical utility of genotype-guided antiplatelet therapy is ongoing, with an anticipated completion date of 2020.
- In recent years, a number of institutions have started clinically genotyping patients undergoing PCI to assist with selection of antiplatelet therapy.
- Data have recently emerged from small randomized controlled trials and observational and pragmatic studies that support improved outcomes with use of alternative therapy versus clopidogrel in patients genotyped after PCI and found to have a non-functional allele.

Figure 1.
Clopidogrel Metabolism.

Table 1

CYP2C19 phenotypes, genotype examples, and prevalence across race groups [9,11,12].

Phenotype	Example genotypes	Prevalence ^a		
		Whites (%)	Blacks (%)	Asians (%)
Poor metabolism (PM)	<i>*2/*2, *2/*3</i>	3	4	12
Intermediate metabolism (IM)	<i>*1/*2, *1/*3</i>	25	30	45
Normal metabolism (NM)	<i>*1/*1</i>	39	33–34	38
Rapid metabolism (RM)	<i>*1/*17</i>	28	29	4
Ultra-rapid metabolism (UM)	<i>*17/*17</i>	5	2–3	<1

^aPercentage of patients with each phenotype.

Table 2

Meta-analyses of studies assessing cardiovascular outcomes and stent thrombosis with clopidogrel by *CYP2C19* genotype.

Reference	No. studies	No. patients	Patient population	HR or RR (95% CI) for clopidogrel-treated patients with a nonfunctional allele (e.g. PMs or IMs) versus those without a nonfunctional allele (e.g. NMs, RMs, or UMs)	
				Cardiovascular events	Stent thrombosis
Mega et al. [20]	9	9685	Established CAD; most (91%) underwent PCI; 54.5% had an ACS	1.6 (1.1–2.2)	2.8 (1.8–4.4)
Hulot et al. [29]	10	11,959	Established CAD; most underwent PCI	1.3 (1.1–1.5)	3.5 (2.1–5.6)
Bauer et al. [30]	15	18,529	Established CAD; most underwent PCI, with the exception of patients in one study included	1.1 (0.9–1.4)	1.8 (1.3–2.4)
Liu et al. [31]	16	24,120	Established CAD	1.3 (1.1–1.5)	2.6 (1.8–3.8)
Holmes et al. [32]	22	26,251	Unselected	1.2 (1.1–1.3)	1.8 (1.5–2.0)
Jang et al. [33]	16	20,785	Established CAD	1.4 (1.1–1.8)	2.4 (1.8–3.3)
Zabalza et al. [34]	11	16,360	Established CAD	1.2 (1.0–1.6)	2.2 (1.5–3.3)
Sorich et al. [35]	17	26,059	Unselected with results analyzed separately in patients with and without PCI	No PCI: 1.0 (0.8–1.2) PCI: 1.2 (1.1–1.3)	2.0 (1.7–2.4)

HR: hazard ratio; RR: risk ratio; CI: confidence interval; PM: poor metabolizer; IM: intermediate metabolizer; NM: normal metabolizer; RM: rapid metabolizer; UM: ultra-rapid metabolizer; PCI: percutaneous coronary intervention.