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Pharmacogenomics of Anti-platelet Therapy: How much evidence is enough for clinical implementation?

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Abstract

Pharmacogenomics, the study of the genomics of drug response and adverse effects, holds great promise for more effective individualized (personalized) medicine. Recent evidence supports a role of loss-of-function variants in the cytochrome P450 enzyme *CYP2C19* as a determinant of clopidogrel response. Those who carry loss-of-function variants do not metabolize clopidogrel, a prodrug, into its active form resulting in decreased inhibition of platelet function and a higher likelihood of recurrent cardiovascular events. Despite a large body of evidence supporting clinical utility, adoption of anti-platelet pharmacogenetics into clinical practice has been slow. In this review, we summarize the pharmacokinetic, pharmacodynamics, and clinical evidence, identify gaps in knowledge and other barriers that appear to be slowing adoption, and describe *CYP2C19* pharmacogenetics implementation projects currently underway. Only when we surmount these barriers will the astute clinician be able to use pharmacogenetic information in conjunction with the history, physical exam, and other medical tests and information to choose the most efficacious anti-platelet therapy for each individual patient.

Keywords

pharmacogenomics; personalized medicine; anti-platelet therapy; clopidogrel; Plavix; platelet function; cardiovascular disease; thrombosis; coronary artery disease; percutaneous coronary intervention

Introduction

Anti-platelet medications are a widely prescribed drug class used in the primary and secondary prevention of thrombotic events associated with cardiovascular disease. The

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adenosine diphosphate (ADP) receptor inhibitors are a subclass of anti-platelet medications which include clopidogrel, prasugrel, ticagrelor and ticlopidine. Clopidogrel is currently one of the most commonly prescribed medications in the United States and world-wide, indicated in patients with acute coronary syndrome (ACS) and in patients undergoing percutaneous coronary intervention (PCI) ^{1,2}. Although effective in most patients, clopidogrel exhibits large inter-individual variability, which has prompted a large amount of research to better characterize its absorption, metabolism, excretion, and action toward a better understanding of the mechanisms underlying its variable response. Recent findings show that common genetic variation can explain an appreciable portion of inter-individual variation in clopidogrel response. With the addition of new anti-platelet therapy alternatives for those with a genetic predisposition toward inadequate response, the promise of translating these pharmacogenetic insights into more effective individualized anti-platelet therapy has sparked much excitement and optimism for the future of personalized medicine.

Clopidogrel (Plavix)

Clopidogrel is an oral thienopyridine prodrug often prescribed in combination with aspirin as standard of care dual anti-platelet therapy for patients with ACS undergoing PCI. Upon ingestion, absorption from the gastrointestinal tract into the bloodstream is regulated by ATP-binding cassette, sub-family B, member 1 (ABCB1) transporters located on the cell surface of intestinal epithelial cells, which transport clopidogrel back into the intestinal lumen inhibiting absorption^{3,4}. Once absorbed, approximately 85% of clopidogrel is hydrolyzed in the liver during first-pass metabolism by esterases, primarily carboxylesterase 1 (CES1), to create inactive metabolites⁵. Conversion of the remaining 15% of clopidogrel from prodrug to its active metabolite also occurs in the liver by two sequential oxidation steps that involve several cytochrome P450 (CYP450) enzymes (e.g., CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP2A4/5)⁶. Upon activation, clopidogrel acts to decrease platelet aggregation by selectively and irreversibly inhibiting the P2Y₁₂ receptor located on the surface of platelets. The inability of ADP to activate P2Y₁₂ receptors prevents the associated G_i proteins from inhibiting adenylyl cyclase resulting in an increase in cAMP which prevents the activation of phosphoinositide 3- kinase (PI3K) and subsequently decreases expression of glycoprotein IIb/IIIa (GpIIb/IIIa)⁷. The expression of GpIIb/IIIa on the surface of platelets mediates fibrinogen binding leading to platelet aggregation, endothelial adherence and thrombus formation. Thus, prevention of this pathway by clopidogrel and other ADP receptor inhibitors results in decreased platelet aggregation.

The inter-individual variability of the platelet inhibitory response from clopidogrel is well established⁸⁻¹². Clinical predictors of response have been documented and include high pretreatment platelet reactivity, use of proton pump inhibitors (PPIs), lipophilic statins, calcium channel blockers, or St. John's Wort, and smoking - all of which are associated with a decreased clopidogrel response^{8,13-16}. Combined, these factors only account for a small fraction of the variation of response to clopidogrel while the majority of variability remains unexplained. Clinically, increased on-treatment platelet aggregation is associated with a greater frequency of recurrent thrombotic events while low on-treatment platelet aggregation is associated with increased bleeding risk¹⁷⁻²⁴. Platelet function testing may be used to

identify patients with high on-treatment platelet aggregation; however, for logistic and other reasons, use of platelet function testing in clinical care remains controversial^{18,25-27}.

Cytochrome P450, family 2 C, polypeptide 19 (CYP2C19) and Clopidogrel Response

As described above, hepatic biotransformation of clopidogrel prodrug to its active metabolite requires CYP450 enzymes, particularly CYP2C19. In addition to clopidogrel, the CYP2C19 enzyme takes part in the metabolism of numerous drugs used in clinical practice such as antidepressants, benzodiazepines, mephenytoin and some PPIs⁶. The gene *CYP2C19*, which encodes the CYP2C19 enzyme, has over 25 known variant alleles with the wild-type allele, *CYP2C19*1*, being associated with functional CYP2C19-mediated metabolism^{28,29}. Common loss-of-function (LOF) variants in *CYP2C19* are the most well-established genetic determinants of clopidogrel responsiveness⁴. The most common *CYP2C19* LOF allele is *2 (c.681G>A; rs4244285) with allele frequencies of ~15% in Caucasians and Africans, and 29-35% in Asians. Additional *CYP2C19* reduced-function alleles have been identified (e.g., *3-*8), all of which have allele frequencies below 1%, with the exception of *3 (c.636G>A; rs4986893) with an allele frequency of 2-9% in Asians. At the molecular level, *2 and *7 alleles cause a splicing defect, the *3 allele results in the addition of a premature stop codon, the *4 allele causes a mutation in the initiation codon, and *5 and *6 alleles contain deleterious missense mutations^{30,31}, each resulting in an inactive CYP2C19 protein product. Conversely, *CYP2C19*17* (c.-806C>T; rs12248560) is associated with increased CYP2C19 transcription resulting in a modest gain of function. The *17 allele is relatively common with an average multi-ethnic allele frequency of ~3-21%. Due to linkage disequilibrium, the *17 allele is carried almost exclusively on the common *1 haplotype, i.e., an allele containing both *2 and *17 variants is very rare or non-existent^{30,32}.

CYP2C19 alleles are inherited as autosomal co-dominant traits allowing individuals to be assigned to likely CYP2C19 metabolizer phenotypes based on their *CYP2C19* genotype. The metabolizer phenotypes and associated genotypes include ultra-rapid metabolizers (UM; *1/*17, *17/*17), extensive metabolizers (EM; *1/*1), intermediate metabolizers (IM; *1/*2, *1/*3) and poor metabolizer (PM; *2/*2, *2/*3, *3/*3)⁶. A small percentage of individuals will carry one LOF and one *17 allele, which are usually classified as IMs. The frequency of IMs and PMs is ~18-45% and ~2-15% respectively, with populations of Caucasian and African background at the lower end of these ranges and populations of Asian background at the higher end of these ranges. Based on knowledge of CYP2C19 metabolizer phenotype and its role in the activation of clopidogrel, one would predict UMs and EMs to have adequate concentrations of the active metabolite for effective platelet inhibition and cardioprotection while PMs would be expected to have decreased concentrations of active metabolite, increased on-treatment platelet aggregation, and inadequate cardioprotection, with IMs response to clopidogrel falling somewhere in between.

Evidence for Association of *CYP2C19* Genotype with Clopidogrel Pharmacokinetics, Pharmacodynamics and Clinical Outcomes

Early evidence for a role of pharmacogenetics in clopidogrel response came from small pharmacokinetic and pharmacodynamics studies³³⁻³⁷. In an effort to determine if functional variants in genes coding for candidate CYP450 enzymes influence platelet responsiveness to clopidogrel, Hulot et al. performed a prospective pharmacogenetic study consisting of 28 healthy white male volunteers treated for 7 days with 75 mg/d of clopidogrel³³. Of the 4 *CYP450* variant alleles tested, only the *CYP2C19**2 LOF allele was significantly associated with a marked decrease in platelet responsiveness to clopidogrel compared to *1/*1 homozygotes; no association was found between *CYP2C19* genotype and baseline platelet activity, consistent with a true pharmacogenetic effect. Umemura et al. performed a similar study using 47 healthy Asian subjects to demonstrate that the *CYP2C19* pharmacogenomic status is a determining factor for the formation of the active metabolite of clopidogrel³⁴.

A number of subsequent studies support a relationship between *CYP2C19* genotype and clopidogrel active metabolite levels and residual platelet reactivity³⁸⁻⁴⁰. In the Pharmacogenomics of Anti-Platelet Intervention (PAPI) Study, 420 healthy Amish subjects, all of whom are related through a complex 14-generation pedigree were exposed to clopidogrel for 1 week and ADP-stimulated platelet aggregation was measured before and after intervention⁴¹. As previously observed, there was large inter-individual variation in response (Figure 1). The estimated heritability of clopidogrel response as measured by residual ADP-stimulated platelet aggregation was 70%. A genome-wide association study (GWAS) identified the *CYP2C19* locus, specifically *CYP2C19**2 as a major determinant of post-clopidogrel ADP-stimulated platelet aggregation, explaining approximately 12% of the variation in response in healthy individuals.

Indications that associations of *CYP2C19* LOF alleles with decreased active metabolite and increased residual on-treatment platelet reactivity translated to poorer clinical outcomes came from large prospective clinical trials of clopidogrel in which stored samples were genotyped retrospectively such as the Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial³, a large French acute myocardial infarction cohort⁴², as well as others^{41,43-45}. Mega et al conducted a meta-analysis of 9685 patients from 9 previously published studies on the relationship between *CYP2C19* genotype and clinical outcomes⁴⁶. The two end points that were examined were a composite end point comprising cardiovascular death, myocardial infarction or stroke, and stent thrombosis, a rare but potentially fatal complication of PCI. Of the 9685 patients, 54.5% had ACS and 91.3% had undergone PCI. The results showed a significantly increased risk of the composite end point in both carriers of one (heterozygotes; HR 1.55, 95% CI 1.11-2.17, p=0.01), and two (homozygotes; HR 1.76, 95% CI 1.24-2.50, p=0.002) LOF *CYP2C19* alleles as compared to *1 homozygotes. Similarly, there was a significantly increased risk of stent thrombosis in both carriers of one (heterozygotes; HR 2.67, 95% CI 1.69-4.22, p<0.001) and two (homozygotes; HR 3.97, 95% CI 1.75-9.02, p=0.001) LOF *CYP2C19* alleles compared to *1 homozygotes. The authors concluded that, “among patients treated with clopidogrel for percutaneous coronary intervention, carriage of

even 1 reduced-function *CYP2C19* allele appears to be associated with a significantly increased risk of major adverse cardiovascular events, particularly stent thrombosis.”⁴⁶

The increasing consistent evidence linking *CYP2C19* LOF alleles to decreased clopidogrel active metabolite, increased residual on-treatment platelet reactivity, and poorer clinical outcomes provoked the U.S. Food and Drug Administration (FDA) in March 2010 to add a boxed warning to the Plavix (clopidogrel) label to alert health care professionals and patients to the potential decreased efficacy of the drug in *CYP2C19* poor metabolizers (i.e., individuals carrying 2 LOF *CYP2C19* alleles). The purpose of the FDA adding the boxed warning was, “to highlight this warning to make sure health care professionals use the best information possible to treat their patients”⁴⁷. The warning emphasizes the effect observed in *CYP2C19* PMs specifically in patients with ACS undergoing PCI, and suggests that clinicians consider other anti-platelet treatments in patients known to be *CYP2C19* PMs. The label does not require genetic testing before starting a patient on clopidogrel therapy and thus if the patient’s genotype is not known, the decision to perform genetic testing is left up to the individual clinician. Furthermore, the boxed warning is silent regarding recommendations for intermediate metabolizers (i.e., individuals carrying 1 *CYP2C19* LOF allele).

Despite overall consistency in the relationship between *CYP2C19* genotype and clinical outcomes in patients with ACS/PCI, studies of *CYP2C19* genotype in patients treated with clopidogrel for other indications such as atrial fibrillation⁴⁸ and stable angina⁴⁹ have been largely negative. In a recent meta-analysis by Holmes et al, which included 32 studies of 42,016 patients over a range of indications for anti-platelet therapy, only marginal association between *CYP2C19* genotype and composite cardiovascular outcomes was observed⁵⁰. The authors argued that small study bias might underlie previous positive associations. An alternative explanation is that the effect size of *CYP2C19* on clopidogrel efficacy appears to parallel the effect of clopidogrel for a given indication; high in patients at high risk for recurrent cardiovascular events in the absence of effective anti-platelet therapy, e.g., ACS/PCI, and low or non-existent for indications in which clopidogrel has a smaller effect on cardiovascular outcomes, e.g., stable angina, atrial fibrillation, peripheral vascular disease⁵¹⁻⁵³. Thus, *CYP2C19*/clopidogrel is an example of indication-specific pharmacogenetics⁵⁴.

Other Genetic Determinants of Clopidogrel Response

Besides *CYP2C19*, additional genetic factors may contribute to clopidogrel’s inter-individual variability. These variants are within genes that encode proteins involved in the absorption, metabolism, excretion, or action of clopidogrel. A common genetic variant (c. 3435C>T; rs1045642) in *ABCB1* results in overexpression of the ABCB1 protein and has been shown to be modestly associated with decreased clopidogrel active metabolite⁵⁵, increased on-treatment platelet reactivity⁵⁶ and increased cardiovascular events⁵⁷. Using participants of the PAPI study, an uncommon *CES1* variant (rs71647871) encoding a non-synonymous Gly143Gln substitution resulting in decreased catalytic function⁵⁸ was shown to be associated with significantly higher active metabolite levels and more effective inhibition of ADP-simulated platelet aggregation⁵⁹. Paraoxonase 1 (PON1) is expressed in

liver and was not previously recognized to be involved in clopidogrel bioactivation until Bauman et al. reported a significant association between a *PON1* variant (c575A>G; rs662) and active clopidogrel metabolite concentration, level of platelet inhibition, and stent thrombosis⁶⁰. Controversially, subsequent studies have failed to replicate these findings resulting in a substantial amount of evidence that does not support a role for *PON1* genotype in clopidogrel response⁶¹⁻⁶⁷. The gene *P2RY12* encodes the P2Y₁₂ receptor on platelets which binds ATP leading to downstream platelet activation. Two common haplotypes exist, H1 and H2, which consists of two common linked genetic variants in the *P2RY12* gene. The H2 allele is believed to be associated with increased expression of P2Y₁₂ receptors⁶⁸ and decreased clopidogrel response⁶⁹, however, inconsistent results from multiple studies have led to the conclusion that if *P2RY12* variants have an effect on clopidogrel response, the effects is small⁴.

Moving Anti-platelet Pharmacogenetics from Discovery to Clinical Practice

In 2009, the irreversible P2Y₁₂ inhibitor, prasugrel was approved by the FDA for use as an anti-platelet agent in patients with ACS. In the overall TIMI-38 Study, prasugrel was superior to clopidogrel in its ability to decrease cardiovascular events, but was also associated with increased major bleeding events⁷⁰. More recently, the reversible P2Y₁₂ inhibitor, ticagrelor was FDA approved, and similar to prasugrel, was associated with overall superior cardiovascular outcomes when compared to clopidogrel⁷¹. Prasugrel is a prodrug but does not require *CYP2C19* for bioactivation while ticagrelor does not require bioactivation. During this same time period, clopidogrel has come off patent and thus inexpensive generic formulations are available. This collusion of events suggests a “perfect storm” for the application of pharmacogenetics to individualized anti-platelet therapy in which *CYP2C19* UMs and EMs might receive clopidogrel, reserving the more expensive agents (also associated with more bleeding events) for *CYP2C19* IMs and PMs.

Despite a compelling body of data supporting clinical relevance of *CYP2C19* genotype in clopidogrel-treated ACS/PCI patients, to date, there have been no randomized prospective clinical trials that have demonstrated that genotype-directed therapy is more effective than conventional approaches. This, combined with other factors (see below) has led to controversy with regard to the role of *CYP2C19* genetic testing in patient care. Recent guidelines issued by the American College of Cardiology Foundation/American Heart Association²⁷ suggest a Class IIb recommendation for *CYP2C19* genetic testing in patients with ACS. Class IIb indicates conditions for which usefulness/efficacy is less well established by evidence or opinion. The consensus guideline states, “On the basis of the current evidence, it is difficult to strongly recommend [*CYP2C19*] genotype testing routinely in patients with ACS, but it might be considered on a case-by-case basis, especially in patients who experience recurrent ACS events despite ongoing therapy with clopidogrel. The article goes on to state, “The Class IIb recommendation of these strategies suggests that a selective, limited approach to platelet [*CYP2C19*] genotype assessment and platelet function testing is the more prudent course until better clinical evidence exists for us to provide a more scientifically derived recommendation.”²⁷

A major challenge to establishing the evidence base for or against implementation of *CYP2C19* genetic testing, and indeed for the field of pharmacogenetics more generally, is that properly powered definitive prospective randomized clinical trials of genotype-directed therapy may not be feasible. Such clinical trials are expensive, time consuming and are unlikely to address the issues surrounding the standardization of pharmacogenetic test result storage, interpretation, and clinical action. Therefore, it may be necessary to resort to real-world pragmatic clinical trials in which early adopters develop evidence for or against clinical efficacy and cost effectiveness over time. It is in this light that the Clinical Pharmacogenetics Implementation Consortium (CPIC) provides recommendations and suggested genotype-directed treatment algorithms for drug-gene pairs for which there is reasonable evidence for clinical utility⁶. CPIC guidelines suggest initiating *CYP2C19* genotyping as early as possible in patients in the acute PCI setting if *CYP2C19* genotype is not already known. CPIC's 2013 update also stresses that these genotyping recommendations are applicable only to patients with ACS and/or those undergoing PCI, particularly in those with stent placements given the burden of evidence regarding increased risk of stent thrombosis in *CYP2C19* IMs and PMs. As described above, the use of *CYP2C19* genotyping in other non-ACS/PCI clopidogrel-treated patient populations is not supported by experimental data.

Genetic testing for *CYP2C19* *2, *3, *17 and other variants is currently offered by a number of commercial Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. However, the turn-around time is typically several days to more than a week, which is suboptimal in acute medical settings, particularly post PCI in which stent thrombosis is an early, and sometimes fatal, complication of ineffective anti-platelet therapy. In this situation, rapid and reliable point of care genotyping is desirable. Indeed a number of options are emerging for this purpose (e.g., Spartan Bioscience RX *CYP2C19*; Nanosphere Verigene *CYP2C19*; GeneMark Dx eSensor XT-8).

Recently, Roberts et al. performed a prospective, randomized proof-of-concept trial (RAPID GENE trial)⁷² to assess the ability of a rapid turn-around point-of-care *CYP2C19* genetic test to identify patients' *CYP2C19**2 carrier status as well as evaluate the possible benefits of genotype-directed personalization of anti-platelet treatment. Two hundred patients undergoing PCI for ACS or stable angina were randomly assigned to either the rapid genotyping arm of the study or the standard treatment arm and treated with an ADP receptor inhibitor anti-platelet medication for 7 days. Patients in the rapid genotyping arm were treated with 75 mg of clopidogrel daily if they did not carry any copies of the *CYP2C19**2 allele or 10 mg prasugrel daily if they carried one or more copies of the *CYP2C19**2 allele. All of the patients in the standard treatment arm of the study received 75 mg clopidogrel daily and were not genotyped until after the 7 day period. Platelet function measurements were obtained on all patients on day 7. None of the 23 *CYP2C19**2 carriers in the prasugrel-treated rapid genotyping arm had a P2Y₁₂ reactivity unit (PRU) value, a measurement of on-treatment platelet reactivity, of more than 234 at day 7, compared with 7 of 23 *CYP2C19**2 carriers (30%) given standard clopidogrel treatment (p=0.0092). There were no significant differences in the proportion of patients above this PRU threshold between genotype-directed and genotype-ignorant groups in patients homozygous for the wild type

*CYP2C19*1* allele. A post-hoc analysis using a lower residual platelet reactivity threshold (PRU<208) was performed based upon results of the GRAVITAS trial⁷³ suggesting that a PRU<208 was associated with improved clinical outcomes. Analysis using the lower threshold yielded results similar to the primary analysis with 11 of 23 carriers (48%) given standard treatment having PRU values >208 at day 7 compared with 1 of 23 carriers (4%) in the rapid genotyping group (p=0.0017). The authors' interpretations of these results were that, "point-of-care genetic testing after PCI can be done effectively at the bedside and treatment of identified *CYP2C19*2* carriers with prasugrel can reduce high on-treatment platelet reactivity."⁷² While these results are encouraging given that residual on-treatment platelet reactivity is associated with poorer clinical outcomes, the study was not powered nor were patients followed long enough to directly demonstrate improved clinical outcomes in the genotype-directed anti-platelet therapy group compared to the standard therapy group.

Overcoming Barriers to Implementation of Anti-platelet Pharmacogenetics

A recent review by Manolio and colleagues⁷⁴ describes the challenges to implementation of genomic medicine. These include limited evidence and conflicting interpretation of benefit/value, often due to lack of prospective randomized clinical trials, lack of institutional and clinician acceptance, limited access to genomic medicine expertise and testing, lack of standards for genomic applications, electronic health record integration of genomic results and clinical decision support, follow-up of genotyped patients, consent, understanding by patients, clinicians and the public, and lack of research funding and reimbursement. All of these are applicable to the under-utilization of *CYP2C19* genetic testing in clinical practice today despite substantial evidence supporting clinical utility and the FDA label suggesting its use. Until these barriers to implementation are traversed, a futile cycle will persist in which clinicians remain confused about which actions to take if any, while professional associations await "high-quality" evidence from large prospective randomized trials before creating consensus guidelines, and third-party payers agree to reimbursement for testing⁷⁵

Furthermore, for *CYP2C19* genetic testing to be widely adopted, it must be shown to be cost effective. Besides the cost of the test itself, the alternative medication for patients identified as IMs and PMs (eg. prasugrel, ticagrelor) are considerably more expensive than the current standard-of-care anti-platelet medication, clopidogrel. These costs must be offset by potential cost-savings from decreased cardiovascular events for genotype-directed anti-platelet therapy and/or the cost of treating all patients with the newer alternative agents. Indeed, simulation models suggest that genotype-directed anti-platelet therapy is more effective and/or less costly when compared to selection of clopidogrel or prasugrel in all patients⁷⁶. As *CYP2C19* genotyping is implemented in various health care settings, it will be important to perform real-world cost and effectiveness analyses.

Another barrier to clinical implementation of *CYP2C19* pharmacogenetics is the return of genetic results into a patient's electronic health record, which currently has no standard format. For time and cost purposes, this is worth addressing to prevent repeat pharmacogenetic testing as well as increasing the quality of patient care. In addition, inexperience of many clinicians to interpret and act upon genetic information, a lack of clear recommendations for pharmacogenetic testing by professional associations, and a non-

existing information structure to provide decision support for genomic medicine all add to the complexity of clinicians utilizing pharmacogenetic testing as a tool to manage patients⁷⁷. In contrast to these barriers, a factor that favors adoption of pharmacogenetics into clinical care is that ethical, legal and social issues surrounding use of genomics for pharmacogenomics seem less daunting than use of genomics for prediction of disease risk since the test has health implications only when the drug is prescribed.

The Translational Pharmacogenomics Program (TPP) of the NIH Pharmacogenomics Research Network is a coordinated effort to identify and overcome the aforementioned barriers to implementation of evidence-based pharmacogenetics into real-world clinical practice⁷⁷. In this context, the University of Maryland Medical Center is among the early adopters of rapid turnaround *CYP2C19* testing, offering PCI patients testing for *CYP2C19* *2, *3 and *17 with a 4-hour turn-around time. This information, along with clinical and other information, is being used by the treating physician to optimize anti-platelet therapy for each patient.

With *CYP2C19* genotyping being relatively inexpensive and straightforward, another model for implementation into patient care is pre-emptive genotyping. With this approach, patients predicted to have a high likelihood of requiring anti-platelet therapy in the future are genotyped pre-emptively. When coupled with an electronic health record and clinical decision support, *CYP2C19* genotype information can be immediately available to guide anti-platelet therapy at the time it is indicated. The Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) Project initiated at Vanderbilt University Medical Center is one example of pre-emptive pharmacogenetics in which more than 3,000 patients have been genotyped on a multiplex platform that include *CYP2C19* variants⁷⁸. The genotype data is deposited in the electronic health record for point-of-care decision support at the time clopidogrel is ordered. In the future, the pre-emptive pharmacogenetic model may be further enabled by the increasing number of direct-to-consumer genetic testing and DNA sequencing services. Thus, the number of patients who know their *CYP2C19* genotype prior to requiring anti-platelet treatment may increase in the coming years.

Conclusions

There is impressive and consistent evidence that *CYP2C19* LOF variants are determinants of clopidogrel pharmacokinetics and pharmacodynamics. *CYP2C19* LOF variants have been demonstrated to be clinically significant determinants of poor outcomes in ACS/PCI patients, particularly those in whom stents have been placed. It is this patient population in whom *CYP2C19* testing should be recommended or strongly considered.

Despite the promise of pharmacogenetics, implementation into clinical practice has been slow. Ongoing *CYP2C19* implementation efforts by early adopters are in progress using a number of models. Identification of barriers to implementation of pharmacogenetics and the development of real-world solutions is an important step forward and ultimately may enable pragmatic clinical trials to advance the evidence base and to evaluate the cost effectiveness of *CYP2C19* genetic testing. Only when we surmount these barriers will the astute clinician

be able to use this information in conjunction with the history, physical exam, and other medical tests and information to choose the most efficacious anti-platelet therapy for each individual patient.

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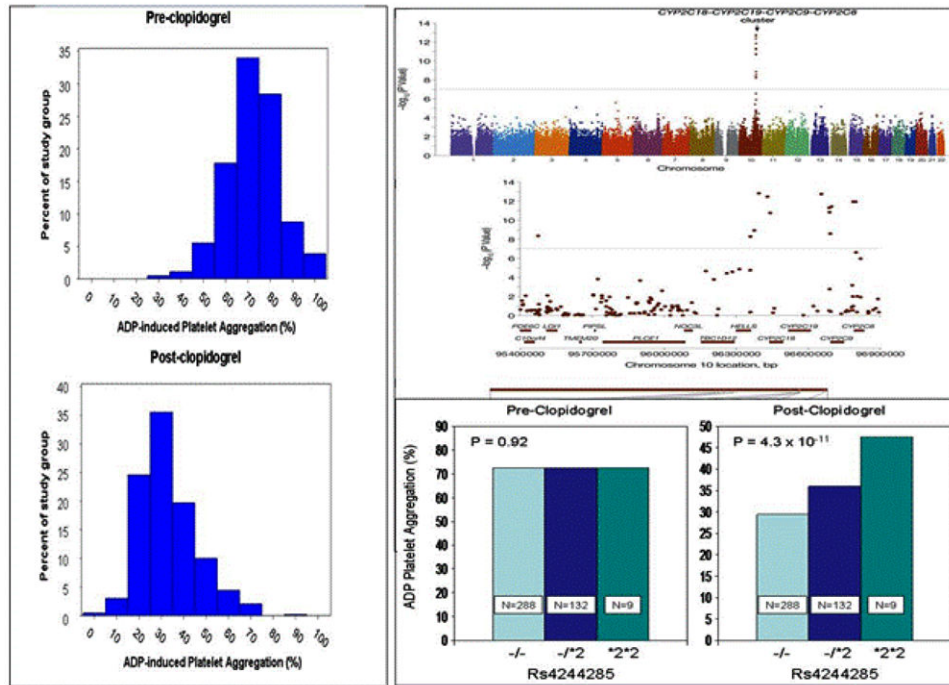


Figure 1. Summary of results from the Pharmacogenomics of Anti-platelet Intervention (PAPI) Study. Panel A. Distribution of ADP-stimulated platelet aggregation before (upper panel) and after (lower panel) 7-days of clopidogrel exposure in 420 PAPI Study participants. Panel B. Genome-wide association analysis of clopidogrel response in the PAPI Study (upper panel) revealing genome-wide significant associations in the region of the *CYP2C18-CYP2C19-CYP2C9-CYP2C8* cluster on chromosome 10 (lower panel). Panel C. Association of the loss of function *CYP2C19**2 variant (rs4244285) with ADP-stimulated platelet aggregation post-clopidogrel (lower panel) but not pre-clopidogrel (upper panel) in PAPI Study participants. Figure adapted from Shuldiner⁴¹