**A PHARMACOGENOMIC APPROACH TO ANTIPLATELET THERAPY FOLLOWING PERCUTANEOUS CORONARY INTERVENTION: A REVIEW**

by

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Submitted to the Graduate Faculty of

the Multidisciplinary Master of Public Health

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2018

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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**ABSTRACT**

Coronary artery disease is a substantial public health concern in the United States. Clopidogrel, an oral, antiplatelet medication, is a mainstay of medical therapy, but its activity is dependent on the CYP2C19 enzyme. Enzyme activity varies across the population based on variability in CYP2C19 alleles that can lead to loss of enzyme activity. Prasugrel and ticagrelor are newer alternatives to clopidogrel that avoid pharmacogenomic concerns but are more expensive and may be associated with more bleeding. This review aims to evaluate the existing literature surrounding the role of pharmacogenomics in the management of patients who require oral P2Y12 inhibitor therapy, discuss the implementation of clinical programs to promote a personalized medicine-based approach utilizing pharmacogenomics, and describe challenges and future directions for pharmacogenomics-based practice models.

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TABLE OF CONTENTS

[1.0 BACKGROUND 1](#_Toc512258739)

[2.0 Effects of CYP2C19 on clopidogrel activation, safety, and effectiveness 4](#_Toc512258740)

[3.0 Management of Intermediate and Poor Metabolizers 8](#_Toc512258741)

[3.1 High-Dose Clopidogrel 8](#_Toc512258742)

[3.2 Alternative Agents 9](#_Toc512258743)

[3.2.1 Prasugrel 9](#_Toc512258744)

[3.2.2 Ticagrelor 10](#_Toc512258745)

[4.0 Clinical Pharmacogenomics Implementation 12](#_Toc512258746)

[5.0 Personal Experience and Public Health Impact 15](#_Toc512258747)

[6.0 Conclusion 17](#_Toc512258748)

[bibliography 18](#_Toc512258749)

List of tables

[Table 1: Compiled frequencies of CYP2C19 alleles in selected populations 2](#_Toc512258750)

[Table 2: Summary of clinical trials examining the relationship between clopidogrel and CYP2C19 genetic polymorphisms 6](#_Toc512258751)

# BACKGROUND

Myocardial infarction (MI) is a leading cause of morbidity and mortality in the United States. Approximately 790,000 Americans experience an MI annually, the majority of which are first-time MIs.1 MI is a manifestation of coronary artery disease (CAD), plaque build-up in coronary arteries which can result in insufficient blood flow to the heart muscle tissue. CAD is subdivided into stable angina and acute coronary syndrome (ACS).1 ACS is a medical emergency that includes MI as well as unstable angina (UA). CAD is commonly managed either with medication alone or by percutaneous coronary intervention (PCI) with or without stenting which opens up plaque-occluded vessels to restore blood flow.1,2 Oral P2Y12 inhibitors are recommended in combination with aspirin as the first-line therapy for patients following stent-placement after UA or MI.2 Three oral P2Y12 inhibitors are currently available in the United States: clopidogrel, prasugrel, and ticagrelor.3–5 Clopidogrel was the first oral P2Y12 inhibitor approved by the FDA.3 It is labeled for secondary prevention of MI and stroke in patients who experience MI or UA managed with or without PCI and stenting. Prasugrel and ticagrelor are newer, more potent P2Y12 inhibitors which are more expensive than clopidogrel.4,5

Clopiogrel must be converted to its active metabolite to exhibit an antiplatelet effect. The primary enzyme that converts clopidogrel to its active form is cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP2C19).3,6 Consequently, clopidogrel carries a Food and Drug Administration (FDA) black box warning for diminished antiplatelet effect in patients with two loss of function (LOF) alleles for the CYP2C19 gene.3 The CYP2C19 gene is most commonly expressed in the liver, but the enzyme can also be found in the small intestine.6 At least 25 different variant alleles of the gene exist with varying frequency in the population.6 These variants result in dramatically different enzyme functionality, of which only the most common alleles are well understood.6 The most-common, wildtype allele is CYP2C19\*1, which codes for normal enzyme function. Two common variants, CYP2C19\*2 and \*3 result in reduced enzyme function. Finally, the CYP2C19\*17 variant results in enhanced enzyme function.

Table : Compiled frequencies of CYP2C19 alleles in selected populations

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Function | CYP2C19 Allele | Population Frequency | | |
|  |  | American | European | East Asian |
| Wild-type (normal) | \*1 | 69% | 63% | 60% |
| Loss of function | \*2 | 12% | 12% | 29% |
|  | \*3 | <1% | <1% | 9% |
|  | \*4, \*5, \*6, \*7, \*8 | <1% | <1% | <1% |
| Increased function | \*17 | 18% | 21% | 3% |

Adapted from Scott et al.7

Rate of variant allele expression vary across regional and ethnic groups.7 Compiled rates by ethnicity provided by the Clinical Pharmacogenetics Implementation Consortium (CPIC) indicate that for Americans, the frequency of the \*1, \*2, \*3, and \*17 alleles are 69%, 12%, <1%, and 18% respectively (see Table 1).7 While these proportions are reasonably consistent with European (63%, 15%, <1%, 21%) and African (68%, 15%, <1%, 16%) populations, they are dramatically different from Asian populations. East Asian allele frequencies are 60%, 29%, 9%, and 3% respectively, while South/Central Asian frequencies are 62%, 35%, 2.4%, and unknown. In Oceanian populations, the \*2 allele is the most common with a frequency of 61% (\*1 = 24%, \*3 = 15%, \*17 = unknown).

Individuals can be classified into different categories of predicted phenotypes according to their alleles.6,7 Extensive metabolizers (EM) have two wildtype alleles (\*1/\*1). Individuals with one wildtype and one loss-of-function (LOF) allele (\*1/\*2 or \*1/\*3) are called intermediate metabolizers (IM). Poor metabolizers (PM) have a combination of any two LOF alleles (\*2/\*2, \*2/\*3, or \*3/\*3). Ultrarapid metabolizers (UM) have at least one gain-of-function allele without any LOF allele (\*1/\*17 or \*17/\*17). No clear categorization exists for individuals with a combination of LOF and enhanced function alleles (\*2/\*17 or \*3/\*17), but because the effect of the LOF allele cannot be completely overcome by the \*17 allele, these patients are often grouped with the IMs.7

Because of the variability seen in the CYP2C19 gene and the dependence of clopidogrel on the CYP2C19 enzyme for activation, clopidogrel has been targeted for pharmacogenomic intervention.7 Pharmacogenomics is the application of individual genetic information to medication related decision making. The purpose of this review is to examine the existing literature surrounding the role of pharmacogenomics in the management of patients who require oral P2Y12 inhibitor therapy, discuss the implementation of clinical programs to promote a personalized medicine based approach utilizing pharmacogenomics in these patients, and describe challenges and future directions for pharmacogenomics-based practice models.

# Effects of CYP2C19 on clopidogrel activation, safety, and effectiveness

Numerous studies have been conducted investigating the relationship between CYP2C19 genotype and predicted phenotype with platelet activity and clinical outcomes. Most commonly, clinical outcomes are assessed using the composite endpoint of major adverse cardiovascular events (MACE) for effectiveness and bleeding for safety.8 While the exact definition varies slightly from study to study, MACE generally includes MI, stroke, stent thrombosis, and death or cardiovascular death. Typical MACE rates from large clinical trials range from 9.3% - 12.1% for ACS patients.9–11 Because MACE is not a commonly observed outcome, platelet function is often used as a surrogate for effectiveness. Clopidogrel and other P2Y12 inhibitors reduce platelet activity, so high on-treatment platelet reactivity (HTPR) could indicate that the drug is not having sufficient clinical effect.7,12 Platelet function can be measured after the initial loading dose or later in the treatment course for large numbers of patients, making it simpler to assess compared to MACE.

Existing literature surrounding CYP2C19 and clopidogrel is summarized in Table 2. Generally, these findings demonstrate that the \*2 and \*3 alleles are associated with increased risk for HTPR and MACE, though some failed to identify significant differences possibly related to insufficient power.13–33 The significant effects are most clearly observed in ACS trials where risk of MACE is relatively higher, and in East Asian populations, where a higher proportion of subjects with \*2 and \*3 alleles adds power to the assessments.17,21,22,24,26,27,31–34 Some studies have also suggested that the \*17 allele may be associated with a lower degree of platelet activity.30,35 Several meta-analyses of the existing literature have supported the findings that PM/IM have increased risk for MACE compared with EM.36–41

Table : Summary of clinical trials examining the relationship between clopidogrel and CYP2C19 genetic polymorphisms

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Population | Primary Region | Significant Outcome | Major conclusions |
| Geisler (2008)42 | Patients undergoing PCI (n=237) | Europe | Platelet function | CYP2C19\*2 allele significantly associated with increased odds of elevated on-treatment platelet reactivity after clopidogrel loading dose |
| Lee (2009)21 | Patients undergoing PCI with stent placement (n=387) | East Asian | Platelet function | CYP2C19\*3 allele independently associated with HTPR |
| Collet (2009)14 | Age <45 receiving clopidogrel after MI (n=259) | Europe | Clinical MACE | CYP2C19\*2 allele significantly associated with increased MACE and in-stent thrombosis |
| Hochholzer (2010)16 | Patients undergoing elective PCI with stent placement (n=760) | Europe | Platelet function | CYP2C19\*2 allele significantly associated with increased odds of elecated on-treatement platelet reactivity after clopidogrel loading dose |
| Pare (2010)29 | Patients with ACS who underwent PCI (n=5059) | International | Clinical MACE | Clopidogrel use in PM/IM associated with reduction in MACE compared to placebo |
| Rideg (2011)30 | Patients who underwent stent implantation for stable angina (n=189) | Europe | Platelet reactivity | CYP2C19\*17 associated with the lowest degree of platelet reactivity while \*2 and \*3 were associated with the highest degree of platelet reactivity |
| Bhatt (2012)28 | Patients with CAD or multiple risk factors prescribed clopidogrel (n=4819) | International | Clinical bleeding | Significantly less bleeding in carriers of LOF allele suggesting higher platelet activity |
| Namazi (2012)25 | Patients who underwent elective PCI (n=112) | Middle East | Platelet function | No significant difference in platelet reactivity |
| Nishio (2012)26 | Patients who underwent PCI with stent implantation (n=160) | East Asian | Clinical MACE | IM/PM associated with significantly more MACE compared to EM |
| Oh (2012)27 | Patients who underwent PCI with stent implantation (n=1011) | East Asian | Clinical MACE | CYP2C19\*2 allele associated with significant increase in MACE |
| Jeong (2013)17 | Patients undergoing PCI (n=155) | East Asian | Platelet function | CYP2C19\*2 and \*3 alleles significantly associated with increased odds of elecated on-treatement platelet reactivity after clopidogrel loading dose and at 14 day follow up |
| Kim (2013)34  **Table 2 Continued** | Patients with acute MI and stable angina undergoing PCI (n=2188) | East Asian | Clinical MACE | PM compared to EM associated with increased MACE in those with acute MI, but not stable angina |
| Liu (2013)22 | Patients undergoing PCI with stent placement (n=109) | East Asian | Clinical MACE | At least one LOF allele independently associated with increased risk of MACE |
| Nakata (2013)24 | Patients with stable coronary disease who underwent stent placement (n=155) | East Asian | Platelet function | CYP2C19 LOF genotype associated with more HTPR |
| Tang (2013)31 | Patients who underwent PCI (n=670) | East Asian | Clinical MACE | Increasing number of LOF alleles were associated with increased risk of MACE |
| Zou (2013)33 | Patients who underwent PCI (n=617) | East Asian | Clinical MACE | PM/IM associated with increased risk of stent thrombosis compared to EM/UM |
| Karanzniewicz-Lada (2014)18 | Patients undergoing elective coronarography, PCI, stenting, or peripheral artery intervention (n=44) | Europe | Platelet function | IM compared to EM had significantly higher platelet reactivity and significantly lower concentrations of clopidogrel active metabolite. |
| Kim (2104)19 | Health male volunteers (n=92) | East Asian | Platelet function | PM/IM had significantly delayed time to maximal platelet inhibition compared to EM |
| Pedersen (2014)35 | Healthy volunteers (n=31) | Europe | Platelet reactivity | CYP2C19\*17 associated with significantly lower platelet reactivity compared to \*1 homozygotes |
| Collet (2015)13 | Patients undergoing PCI with drug-eluting stent (n=1394) | Europe | Platelet function | IM/PM significantly more likely than EM to be poor responders after load and at 14 days post-PCI |
| McDonough (2015)23 | Patients receiving clopidogrel for secondary stroke prevention (n=522) | International | Clinical Stroke/ bleeding | PM had increased risk of recurrent stroke in the Caucasian subgroup only. No significant difference in bleeding was observed |
| Doll (2016)20 | Medically managed ACS patients (n=2236) | International | Clinical MACE | No significant association observed in MACE between PM and EM |
| Wang (2016)32 | Patients receiving clopidogrel for secondary prevention of stroke (n=2933) | East Asian | Clinical stroke | Clopidogrel and aspirin compared to aspirin alone was associated with fewer recurrent events in EM only. No difference was observed for PM/IM |

# Management of Intermediate and Poor Metabolizers

Two types of strategies for treating patients PM and IM predicted phenotypes have been proposed: increasing the dosage of clopidogrel to overcome reduced levels of clopidogrel active metabolite and use of alternative oral P2Y12 inhibitors to avoid drug-gene interactions. This section discusses the existing evidence supporting these management options.

## High-Dose Clopidogrel

One strategy proposed for addressing reduced clopidogrel metabolite exposure due to LOF CYP2C19 variants. Horenstein and colleagues demonstrated in healthy volunteers that PMs compared to EMs required quadruple the standard maintenance dose to achieve similar concentrations of clopidogrel active metabolite.43 In a study by Gladding and colleagues involving 60 genotyped patients who underwent elective PCI, platelet inhibition was reduced in patients with CYP2C19\*2 and \*4 alleles compared to wildtype homozygotes (median 10% vs 23%, p=0.03) after a normal 600 mg loading dose of clopidogrel.44 Increasing the loading and maintenance dose in these patients resulted in similar platelet inhibition compared to standard dose clopidogrel in EMs.44 A prospective, randomized evaluation by Collet and colleagues found that subjects with the CYP2C19\*2 allele had significantly higher platelet activity that those without.45 For carriers of the \*2 allele, but not homozygotes, the difference in platelet activity could be overcome with triple-dose clopidogrel. Another prospective analysis in patients with stable coronary disease found that triple the clopidogrel standard maintenance dose was required for IMs to achieve similar platelet inhibition to EMs at normal dose.46

## Alternative Agents

### Prasugrel

Prasugrel is another oral P2Y12 inhibitor with an FDA labeled indication for the reduction of thrombotic cardiovascular events in ACS patients who undergo PCI.4 Similar to clopidogrel, it irreversibly binds to the P2Y12 receptor on platelets, resulting in platelet inhibition. While it is a prodrug, its metabolism to its active metabolite is not substantially dependent on CYP2C19 or any other known common genetic variation like clopidogrel is.47 Instead, prasugrel is activated primarily by CYP3A5 and CYP2B6, though genetic variations in these genes do not have a clinically relevant effect on efficacy.4 This finding was supported in a genetic subgroup analysis of the prasugrel approval trial which demonstrated superior effectiveness for prasugrel in preventing MACE compared to clopidogrel in IM and PM.48

Additionally, prasugrel has been shown to overcome HTPR better than high-dose clopidogrel in patients with LOF alleles.49–52 Dridi and colleagues demonstrated that prasugrel overcame HTPR better than double-dose clopidogrel in a population that was not genotyped.52 A possible, genetically-based explanation for the finding was demonstrated in a study by Sardella and colleagues, where prasugrel successfully overcame high-on clopidogrel platelet reactivity in 100% of patients with CYP2C19\*2 alleles compared to only 56.3% in the high-dose clopidogrel group (p=0.003).49 No significant difference between prasugrel and high-dose clopidogrel was observed in EM.49 Similar findings were observed by Alexopoulos and colleagues in a randomized, cross-over study in patients undergoing PCI with demonstrated HTPR.50 Rates of HTPR were lower for prasugrel compared to high-dose clopidogrel across all genotypes (7.5% vs 35.8%, p<0.01), however this difference was substantially larger when examining clopidogrel PMs/IMs (5.3% vs 47.4%, p<0.01).50

### Ticagrelor

Ticagrelor is the third FDA approved oral P2Y12 inhibitor. Ticagrelor is not a prodrug, so it has antiplatelet activity without activation. Ticagrelor and its active metabolite reversibly inhibit platelet function.5 It does not require the activity of CYP2C19 for activation. In a study of 174 coronary artery disease patients, ticagrelor demonstrated superior platelet inhibition compared to clopidogrel regardless of genotype.53 The platelet inhibitory effect did not appear to differ for ticagrelor across any predicted phenotype group.53 Slight differences in ticagrelor pharmacokinetics were observed based on genetic factors affecting other, non-CYP2C19 cytochrome p450 enzymes and intracellular transporters, but these effects have not been shown to impact clinical outcomes.54

Prasugrel and ticagrelor have been studied together as clopidogrel alternatives for patients with IM or PM predicted phenotypes. A large, multi-center, open-label pragmatic clinical trial by Cavallari and colleagues found that for patients with a LOF allele, those prescribed clopidogrel were more likely to experience MACE than patients prescribed alternative therapy (23.4 vs 8.7 events per 100 patient-years; HR: 2.26, 95% CI: 1.18-4.32).55 No differences were observed in rate of MACE between those with an LOF allele on alternative therapy and those without LOF allele (HR:1.14, 95% CI: 0.69-1.8

# Clinical Pharmacogenomics Implementation

A 2018 publication by Empey and colleagues surveyed 12 existing clinical and research pharmacogenomics programs for clopidogrel use in the United States.56 While the majority (11) of programs utilized genetic testing in reactive manner, four programs used preemptive testing alone or in combination with reactive testing. Preemptive testing, or testing before the need for antiplatelet therapy, has potential advantages versus reactive testing because it allows for initial selection of the most appropriate agent based on the patients predicted phenotype. Reactive testing methods usually require initial selection of an agent without knowledge of the patient’s genetics, though rapid, point of care testing may help to ameliorate this concern.57,58 Without initial guidance, clinicians are forced into either a “step-up” or “step-down” approach. The step-up approach is to start all patients on clopidogrel and transition IM/PM to alternative agents once genetic results are available. This approach risks exposing patients suboptimal therapy until results are returned. The step-down approach starts patients on either ticagrelor or prasugrel, then switches EM/UM to clopidogrel once genetic results are available. This removes the risk of an initial poor response to clopidogrel but utilizes more expensive agents that may have a higher bleeding risk in patients who may not need them.10,11 Clinically, the feasibility of the step-down approach using prasugrel was demonstrated in the TROPICAL-ACS study, but importantly, no genetic component was included.59 The applicability of the step-down approach in a pharmacogenomic model has not been proven. Still, early selection of the appropriate agent is important. In-hospital switching has been associated with increased risk of bleeding in prior retrospective studies.60,61 For these reasons, preemptive testing may be preferred to a reactive approach, though challenges with insurance coverage and payment limit the use of this approach.56

Irrespective of the testing model used, implementation of clinical programs faces a number of challenges. Common challenges reported by Empey and colleagues were stakeholder buy-in, laboratory contracts with hospitals for new genetic testing, electronic health record (EHR) display of genetic results, development of clinical decision support, logistics, acceptance of clinical recommendations, and billing/reimbursement.56 These challenges are often connected. For instance, unclear formatting of results in the EHR combined with a lack of clinical support can lead to provider confusion about results and subsequent rejection of or indifference to clinical recommendations. Guidelines for standardization of terms for clinical pharmacogentic test results were published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) in 2017.62 While this has proved beneficial within the field of pharmacogenomics, difficulties can arise in interpreting results for prescribers unfamiliar with pharmacogenomics terminology. Programs are addressing these challenges through formal provider education through meetings or in-services, clinical note writing, direct communication with providers, EHR messaging and decision support (when available), and, most often, a combination of these methods.56 EHR clinical decision support in particular holds the promise of allowing genetic testing results to be applied to multiple medication, potentially leading to the expansion of the use of pharmacogenetics in clinical practice. Additionally, CPIC offers recommendations on the components of a successful pharmaogenomic program for clopidogrel use.7 Sufficiently meeting the challenges of result interpretation and implementation will determine the long-term success of new and existing clinical pharmacogenomics programs.

A recently completed randomized prospective trial investigated the effectiveness of a pharmacogenomic approach to therapy in Italy.63 Patients hospitalized for ACS were randomized to either standard of care or pharmacogenomic therapy selection. The study was stopped early after the enrollment of 888 patients for overwhelming efficacy of the pharmacogenomic approach. The primary endpoint, a composite of MACE as well as significant bleeding events, occurred in 15.9% of patients managed with the pharmacogenomic approach and 25.9% of patients in the standard of care arm (HR: 0.58, 95% CI: 0.43-0.71, p<0.001).63 Two randomized clinical trials are currently in progress to demonstrate the effects of clinical pharmacogenomics program implementation in patients undergoing PCI. The TAILOR-PCI trial will randomize a target 5000 PCI patients to either a conventional or pharmacogenomics approach to antiplatelet management.64,65 It will utilize a step-up approach of starting patients on clopidogrel and converting those with PM/IM phenotypes to ticagrelor in the pharmacogenomics management arm. The second in-progress study is the POPGenetics trial. Similar to the TAILOR-PCI trial, POPGenetics aims to randomize 2700 STEMI patients to conventional or pharmacogenomics management. POPGenetics applies a step-down approach, switching pharmacogenomically managed patients without an LOF allele from ticagrelor or prasugrel to clopidogrel treatment.64–67 Interestingly, POPGenetics also includes a cost-effectiveness component which could aid in future hospital and payer decision making surrounding pharmacogenetics testing for PCI patients.66,67

# Personal Experience and Public Health Impact

My experience with the pharmacogenomic consult service at the University of Pittsburgh Medical Center (UPMC) has provided me with firsthand experience utilizing a pharmacogenomic treatment approach for patients undergoing PCI. The clinical service is responsible for coordinating blood sample collection between the cardiac catheterization clinical unit and the laboratory that completes pharmacogenomic testing. Results are then interpreted and a pharmacist note is added to the electronic medical record that is viewable in both the inpatient and outpatient medical record. Absent clinical characteristics associated with high bleeding risk, patients with an IM/PM phenotype who are started on clopidogrel are targeted for step-up intervention. When these patients are identified, a recommendation for an alternative agent is made directly to the supervising provider.

In addition to the clinical component of the program, I am also involved with the ongoing research efforts of the group. The initial results of the program are being evaluated in a retrospective fashion to describe impact in terms of the proportion of patients on appropriate therapy based on their predicted phenotype and clinical outcomes of MACE and bleeding. Data are collected retrospectively and entered into a de-identified research database. Data collection and analysis remain ongoing.

The public health impact of pharmacogenomic management strategies in PCI therapy selection are substantial. Heart disease, particularly CAD is a leading cause of morbidity and mortality in the US.1 The nature of the genetic variability that affects clopidogrel response means that specific ethnic groups, most notably Asians, have disproportionally high rates of IM/PM phenotypes. Using a pharmacogenomic approach in this setting can help to reduce the risk of MACE in these populations.

Clinical pharmacogenomics programs also necessity a multidisciplinary approach to patient care and continued research. Expertise in interpretation of genotypic results is required in the form of trained health professionals with an understanding of both genetics and medication pharmacokinetics. In the UPMC model, pharmacists fill this role. The pharmacist must communicate information about the predicted phenotype to the supervising provider so that appropriate therapy can be chosen based on a combination of genetic and clinical factors specific to the individual patient. Research efforts should involve persons trained in public health disciplines such as epidemiology, human genetics, and biostatistics to appropriately design and execute future trials in this area. Future efforts to involve health information specialists in creating clinical decision support within electronic health records can further help with result communication as well as application of results to other pharmaceuticals.

# Conclusion

Pharmacogenomics offer significant promise to optimizing antiplatelet therapy in patients with CAD. The link between CYP2C19 LOF alleles, PM/IM phenotypes and increased risk of MACE has been well established through numerous trials and meta-analyses, and management strategies for these patients through the use of alternative agents are supported by existing literature. Clinical pharmacogenomics programs have been implemented to incorporate pharmacogenomics-based approaches to antiplatelet management. While substantial challenges exist for the widespread implementation of these programs, advances in EHR and clinical decision support technology offer opportunities to overcome some of these obstacles. On-going studies seek to establish pharmacogenomics programs as viable systems to improve patient outcomes and deliver care in a cost-effective manner. The results of these studies as well as the experiences of existing programs will guide the implementation of future pharmacogenomics programs both for clopidogrel and beyond.

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