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Clopidogrel Pharmacogenetics: State of the Art Review and the TAILOR-PCI Study

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Abstract

Common genetic variation in *CYP2C19* (**2* and **3* alleles) leads to a loss of functional protein and carriers of these loss-of-function alleles when treated with clopidogrel have significantly reduced clopidogrel-active metabolite levels and high on-treatment platelet reactivity resulting in increased risk of major adverse cardiovascular events, especially after PCI. The Food and Drug Administration has issued a black box warning advising practitioners to "consider alternative treatment in CYP2C19 poor metabolizers" who might receive clopidogrel and to identify such patients by genotyping. However, routine clinical use of genotyping for *CYP2C19* loss-of-function alleles in patients undergoing PCI is not recommended by clinical guidelines due to lack of prospective evidence. To address this critical gap, TAILOR-PCI is a large, pragmatic, randomized trial comparing point-of-care genotype-guided anti-platelet therapy with routine care to determine whether identifying *CYP2C19* loss-of-function allele patients prospectively and prescribing alternative anti-platelet therapy is beneficial.

Keywords

Clinical Studies; Genetics; Antiplatelet therapy; clinical implementation; clinical trial; *CYP2C19*; coronary stents

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Introduction

Clopidogrel remains the most widely prescribed anti-platelet drug in the US and Canada.[1,2] In an analysis of 64,600 patients who underwent PCI at 47 Michigan Hospitals, the proportion of patients receiving clopidogrel, prasugrel and ticagrelor was 72%, 20% and 8%, respectively. Clopidogrel is a prodrug requiring the cytochrome P450 (CYP) enzymes for biotransformation into its active thiol metabolite. Initial clopidogrel pharmacogenetic studies examined genetic variation in the CYP enzymes, primarily *CYP2C19*, that metabolize clopidogrel to its active form and the association of these genetic variants with active metabolite levels.[3] Subsequently a genome wide association study (GWAS) was performed to study the association of genomic variation with its effect on platelet reactivity among clopidogrel treated subjects[4] that confirmed the important role of *CYP2C19*. GWAS have not been performed to assess the association of genomic variation with clopidogrel drug levels or major adverse cardiovascular events (MACE) related to clopidogrel resistance. By adopting a candidate gene approach most studies have assessed the association of genetic variation in *CYP2C19*, on platelet reactivity and clinical outcomes in subjects treated with clopidogrel.

Despite the initial promise of clopidogrel pharmacogenetics and a Food and Drug Administration (FDA) black box warning that encourages the practice of routine genotyping to guide P2Y12 inhibitor anti-platelet therapy, the cardiovascular community has not adopted this approach.[5] The purpose of this manuscript is to describe the present state of knowledge on clopidogrel pharmacogenetics, reasons why a pharmacogenomic strategy has not been incorporated in routine clinical practice and the design of the TAILOR-PCI trial to address this issue. We will provide a rationale for the need of performing a *CYP2C19* genotype-based individualized anti-platelet drug therapy clinical trial by providing an overview of the genetic variation that occurs in *CYP2C19*, its impact on clopidogrel pharmacokinetics, pharmacodynamics, and clinical outcomes; and results of an updated meta-analysis of the association of clinical outcomes in clopidogrel treated post PCI patients with *CYP2C19* genotyping.

Genetic Variation in *CYP2C19*: Rationale for Screening for *CYP2C19*2* and *3*

The *CYP2C19* gene is highly polymorphic with over 2000 described genetic variants, of which the majority are intronic and the minority are coding region variants. The most common loss-of-function (LOF) variant alleles are *CYP2C19*2* and *3* alleles that result in degraded or nonfunctional proteins. The haplotype *CYP2C19*2* contains a variant (c. 681G>A) that leads to a premature stop codon that produces a non-functional truncated protein.[6] The minor allele frequency (MAF) of this single nucleotide polymorphism (SNP) varies with ethnicity, with it being most prevalent in South Asians (32.5%) and East Asians (31%), followed by individuals of African (18%,) Non-Finnish European (15%), and Latino (10%) descent.[7] The *CYP2C19*3* haplotype contains the a variant that also results in a premature stop codon producing a non-functional truncated protein.[8] This haplotype is rare in subjects of European and African ancestry (MAF 0.025% and 0.037%, respectively) but is

more common in East Asians (6.3%) and less common in South Asians (0.4%).[9] Although there are other *CYP2C19* LOF (loss of function) alleles reported, *CYP2C19*2* and **3* account for 99% or more of these in a multi-ethnic population and are the most commonly studied *CYP2C19* alleles. Hence, the recent advent of targeted point-of-care genotyping platforms[10] that provide a turnaround time of less than an hour, a feature that is essential for a cardiac catheterization laboratory based practice, are focused on the *CYP2C19*2* and **3* alleles.

CYP2C19 Genetic Variants and their Effect on Clopidogrel Active Metabolite Levels

Approximately 50% of clopidogrel is absorbed and 15% of the absorbed prodrug undergoes a 2-step oxidative biotransformation.[11] CYP2C19 is the only CYP450 enzyme that plays an important role in both steps of this oxidative process and contributes 45% and 21%, respectively, to the formation of the two metabolites.[12] Enzyme kinetic parameters have demonstrated that *CYP2C19*2* allele heterozygotes and homozygotes have a lower area under the plasma concentration curve (AUC) and maximum plasma concentration (Cmax) for the active metabolite of clopidogrel for as compared to *CYP2C19* wild type (WT) subjects.[13] In a pharmacokinetic study involving 106 post myocardial infarction subjects, after adjusting for confounders like weight, diabetes, use of proton pump inhibitors and genetic variation in *PON1*, *CYP2C19*2* genotype remained the only significant predictor of clopidogrel active metabolite C_{max} and AUC for a 300 mg and 900 mg loading dose of clopidogrel.[14] In a linear mixed-effects model using the AUC as a primary outcome based on active metabolite measurements in 162 normal subjects compiled from 6 separate studies, carrying either *CYP2C19*2* or **3* was associated with the most significant reduction (−32%, $p<0.001$) in $AUC_{0–24}$ as compared to genetic variation in the other cytochrome P450 enzymes involved in clopidogrel metabolism (Figure 1).[15] In summary, *CYP2C19* LOF allele carriers have significantly reduced active clopidogrel metabolite levels when treated with clopidogrel as compared to WT subjects or the overall population. Whether these reduced active metabolite levels translate to adverse clinical outcomes and whether treatment with alternative platelet therapy will improve outcomes remain unanswered questions.

CYP2C19 Genetic Variants and High Residual Platelet Reactivity (HPR): Effects of Altering Anti-platelet Therapy in Carriers Using Platelet Aggregation as an Endpoint

The presence of LOF *CYP2C19* alleles has been associated with HPR on clopidogrel therapy.[15] In a meta-analysis of 4 studies involving 4341 subjects who received a 600 mg loading dose of clopidogrel, there was significant residual HPR that appeared to reflect a gene-dose effect in carriers of *CYP2C19*2* as compared to non-carriers (Figure 2).[16] HPR has been recommended as a surrogate marker of adverse cardiovascular outcomes and has been used to individualize anti-platelet therapy.[17] There have been several prospective randomized studies that have used platelet function tests as an intermediate endpoint to

assess the response of altering DAPT based on genotype.[10,18] Increasing the maintenance dose of clopidogrel may increase the bioavailability of the drug and may be useful in overcoming reduced active clopidogrel metabolite concentrations[19] observed in reduced function or LOF *CYP2C19* carriers. However, an increased clopidogrel maintenance dose of 150 mg daily as compared to 75 mg did not seem to overcome the risk of HPR in *CYP2C19* LOF carriers.[3]

The ELEVATE-TIMI 56 trial demonstrated that a higher clopidogrel dose of 225 or 300 mg significantly reduced the number of *CYP2C19*2* heterozygotes who had HPR from 52% to 10% ($p<0.001$) but homozygotes remained resistant at a dose as high as 300 mg.[18] Approved alternatives to clopidogrel include the newer P2Y12 inhibitors such as prasugrel and ticagrelor. Common genetic variation in *CYP2C19* does not seem to affect prasugrel or ticagrelor drug action and hence they may be useful as alternatives to clopidogrel in the carriers of *CYP2C19* LOF genetic variants.[20–22] The RAPID GENE study randomized 200 patients with acute coronary syndrome (ACS) or stable coronary artery disease (CAD) to a point of care rapid genotyping arm in which *CYP2C19*2* carriers received prasugrel and those in the other standard treatment arm received clopidogrel.[10] There were no *CYP2C19*2* carriers on prasugrel who had HPR while 30% of subjects with that genotype treated with clopidogrel had persistent HPR. This study in addition to the other studies demonstrate the efficacy of alternative DAPT like prasugrel or ticagrelor as opposed to high dose clopidogrel in *CYP2C19* LOF carriers in order to overcome the intermediate phenotype of platelet resistance.

Platelet Resistance as a Surrogate Endpoint of Drug Efficacy: Does Altering Anti-platelet Therapy Based on Platelet Resistance Affect Clinical Outcomes?

The concept of altering HPR with intensification or modification of conventional DAPT, to potentially affect clinical outcomes, remains controversial.[17,23,24] The predictive and discriminatory power of the various platelet function tests for development of MACE on clopidogrel, such as light transmittance aggregometry (AUC 0.63, positive predictive value [PPV] 12%) and VerifyNow (AUC 0.62, PPV 13%), is modest.[25] Furthermore, studies investigating the potential role of HPR-guided optimization or alterations in anti-platelet therapy have not demonstrated improved clinical outcomes.[26,27] In the GRAVITAS trial, despite a 22% absolute reduction ($p<0.001$) in the rate of HPR with high dose clopidogrel (150 mg/day) as compared to standard dose (75 mg/day) there was no significant difference in the primary outcome of MACE at 6 months ($p=0.97$).[27] The ARCTIC trial randomized patients to an anti-platelet therapy modifying strategy based on HPR prior to PCI which resulted in a reduction in the rate of HPR from 35% at randomization to 16% during a follow up visit between days 14 and 30. Similar to GRAVITAS, despite the significant improvement in HPR in the prospective platelet function test monitoring group there were no significant differences in the composite primary outcome of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization 1 year after stent implantation as compared to the standard therapy group without platelet function monitoring (34.6% versus 31.1%, $p=0.10$).[26] These studies have been criticized for being underpowered, using varying

definitions of platelet resistance, the alternative anti-platelet therapy utilized (e.g., predominantly augmented clopidogrel dosing) as a means to overcome HPR and the type of endpoints assessed.[28] However, both trials were pragmatic, included a broad range of patients and resulted in significant improvement in the rate of HPR, previously defined to be associated with adverse outcomes. Furthermore, increasing sample size to demonstrate smaller reductions in relative risk may preclude clinical applicability and relevance to this strategy. For example, with a relative risk reduction of 15% in the platelet-monitoring group in ARCTIC, it is estimated that investigators would have needed to enroll a total of approximately 35,000 patients.[26] None of these clinical trials prospectively evaluated genotype with platelet function testing to determine differences in clinical outcomes. Thus, the concept that platelet function tests alone can serve as a surrogate for anti-platelet drug clinical efficacy is questionable. Currently, as a consequence of this knowledge gap, the consensus guidelines issued by the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) do not recommend routine platelet function testing to guide anti-platelet therapy.[29–32] Although HPR has been associated with MACE, intensifying anti-platelet therapy based on HPR has not yet proven to be of clinical value. However, recently the TROPICAL-ACS trial demonstrated a net clinical benefit of platelet function testing in guiding de-escalation of anti-platelet therapy from prasugrel to clopidogrel after PCI as opposed to continuing prasugrel in all patients.[33] Such an approach that identified HPR with platelet function testing after 7 days of clopidogrel therapy resulted in the continued subsequent use of clopidogrel in at least 60% of patients and prasugrel use in the rest without increased risk of MACE as compared to patients who did not undergo platelet function testing and were all treated with prasugrel. Whether in addition to platelet function testing, *CYP2C19* genotyping to identify high risk patients would have resulted in superiority of this approach is unknown at this time.

Should Genotyping Be Performed to Identify Potential Clopidogrel Treatment Failures? Association of *CYP2C19* Genetic Variants with Clinical Outcomes

There have been multiple studies describing the association of *CYP2C19* LOF alleles with clinical outcomes in clopidogrel treated patients.[4,14,15,34–44] Many of these studies have been summarized in two important meta-analyses that have differing conclusions.[16,45] In a meta-analysis that focused primarily on patients who underwent PCI (91% of subjects), involving 9685 study participants (55% with ACS) receiving clopidogrel, carriers of 1 (HR, 1.55; 95% CI, 1.11–2.17) or 2 (HR, 1.76; 95% CI, 1.24 – 2.50, p=0.002) *CYP2C19* LOF alleles had a significantly increased risk of MACE.[45] Furthermore, a significantly increased risk in stent thrombosis was observed with carriers of one (HR, 2.67; 95% CI, 1.69–4.22, p<0.0001) or two (HR, 3.97; 95% CI, 1.75–9.02, p=0.001) *CYP2C19* LOF alleles. Subsequently, a meta-analysis by Holmes et al, evaluating 42,016 patients revealed that carriers of one or two *CYP2C19* LOF alleles were at a higher risk for cardiovascular events (relative risk 1.18, absolute risk increase of 8–12 events per 1000 individuals) in a treatment only analysis that included studies in which all patients were treated with clopidogrel as compared to a clinical trial in which patients were randomized to either placebo or other

anti-platelet therapy. When this analysis was restricted to studies with 200 or more events, and when confined to genetic studies nested within randomized trials, *CYP2C19* genotype was not significantly associated with cardiovascular events. A limitation of this meta-analysis was the lack of a specific analysis for patients undergoing stenting compared with other medical treatments, and inclusion of a large number of patients who were treated for reasons other than stenting (e.g. atrial fibrillation, STEMI, stable coronary and atherosclerotic vascular disease).

The limitation of these studies, despite showing that *CYP2C19* LOF patients treated with clopidogrel are at an increased risk for MACE, was that genotyping was not performed prospectively and decision to treat was not based on genotyping results and hence conclusions were prone to bias. Furthermore, pharmacogenetic analysis was performed only in a sub-group of patients who had DNA collected and not in the entire cohort of patients. Therefore routine clinical use of genotyping for *CYP2C19* in patients who undergo PCI is not recommended as per recent guidelines published by the ACC/AHA and Society for Cardiovascular Angiography and Interventions (SCAI) due to lack of prospective clinical evidence demonstrating that changing anti-platelet therapy based on *CYP2C19* genotype will change outcomes.[29,46]

Recent Prospective Studies Addressing Modification of Antiplatelet Therapy Based on Genotyping

An observational study of 1,815 stable coronary artery disease and ACS post PCI patients in which the decision to perform *CYP2C19* genotyping and choice of anti-platelet therapy was left to the discretion of the clinician demonstrated that patients with *CYP2C19* LOF alleles receiving clopidogrel had greater number of MACE as compared to those on ticagrelor or prasugrel.[47] Due to lack of randomization, the clopidogrel treated *CYP2C19* LOF allele group had a greater proportion of patients with diabetes, prior strokes, and peripheral vascular disease and were older compared to the alternative anti-platelet drug treated *CYP2C19* LOF allele group which may have biased the outcomes. In addition clinical events were not adjudicated and were based on review of medical records. Recently, a trial randomizing ACS patients to standard of care versus pharmacogenomic plus clinical variables directed anti-platelet therapy stopped prematurely after enrolling 888 of the target 3,612 patients because of the lack of certification for the genotyping platform used in the study. The primary composite endpoint of cardiovascular death, myocardial infarction, stroke and major bleeding was significantly reduced (HR 0.58, [0.43, 0.78], $p<0.001$) in the personalized therapy arm. Although this trial may seem promising for precision medicine, conclusions from this trial must be considered with caution as it was prematurely discontinued with only 25% of targeted enrollment.[48,49] In addition, the suggested algorithm in the study incorporated the presence of *CYP2C19*17*, a gain-in-function allele and variation in *ABC1* (rs1045642) in addition to *CYP2C19*2* LOF allele; the influence of these additional genetic variants which in attenuating clopidogrel drug response is not as well established.

Why Use Clopidogrel? Adopting the Universal Use of the Newer P2Y12 Inhibitors Versus a Genotyping Driven Anti-Platelet Therapy Strategy

Although ticagrelor has been shown to be superior to clopidogrel in a large trial involving 18,624 patients with acute coronary syndrome in reducing MACE (HR 0.84, [0.77, 0.92]),[50] its use results in an increased risk of non-CABG-related TIMI bleeding (HR 1.25, [1.03, 1.20]). Whether the difference seen in the overall trial was largely driven by genetic differences is possible but unknown. The PLATO genetic substudy examined the DNA of 10,285 subjects from a total of 18,624 subjects for *CYP2C19* LOF alleles. The composite endpoint of CV death, MI and stroke was significantly reduced in *CYP2C19* LOF carriers receiving ticagrelor compared to clopidogrel (n=1384, p=0.038) and was not significantly different in those subjects with no *CYP2C19* LOF alleles (n=3554, p=0.06). However the interaction p value was not significant (p=0.46) that led to the authors suggesting that ticagrelor was more efficacious than clopidogrel irrespective of *CYP2C19* status. If the null hypothesis is that the benefits are equal in the two genotype subsets, then this null hypothesis cannot be rejected. However, if the null hypothesis is that there is no benefit in wild type individuals, then this null hypothesis also cannot be rejected. There are 2 important limitations of this genetic sub-study: 1. The analysis was performed in only a sub-group of patients with available DNA (55% of the total sample size) 2. The interaction test is fraught with problems with power, such that the only way the test could have achieved significance would have been for the point estimate for ticagrelor effect in WT to be 1.01. In order to have 80% power to discriminate the two effects, the HR would have to be 0.77 and 1.12, i.e. opposite directions. In fact the authors clearly state that the “sub-study was not prospectively powered and had to be based on the maximum number of patients consenting to provide a blood sample for genetic analysis,” hence the results of the PLATO genetic study are difficult to interpret. The TRITON-TIMI 38 trial demonstrated a benefit of prasugrel compared to clopidogrel (HR 0.81,[0.73, 0.09]) using a composite endpoint of CV death, non-fatal MI or non-fatal stroke.[51] Bleeding events including major or minor bleeding (HR 1.31, [1.11, 1.56]), life threatening bleeding (HR 1.52, [1.08, 2.13]) and CABG-related major bleeding (HR 4.73, [1.90, 11.82]) was significantly increased with prasugrel use.[51] Genetic analyses from TRITON-TIMI 38 suggested that, in contrast to clopidogrel,[15] *CYP2C19* LOF allele status did not affect active drug metabolite levels, inhibition of platelet aggregation, or CV event rates in persons treated with prasugrel.[20] The data on the use, efficacy and adverse effects of the newer P2Y12 inhibitors in Asians is limited despite the importance of whether these drugs should be universally used in this population given the high prevalence of the *CYP2C19* LOF alleles. The PHILO study evaluated treatment with ticagrelor as compared to clopidogrel in 801 Japanese, Taiwanese and South Korean ACS patients and found that both major bleeding events and MACE were higher but not significantly so in the ticagrelor group.[52]

The findings from these trials has likely contributed to the in inconsistent adoption of the newer P2Y12 inhibitors into routine use post-PCI, especially with the recent availability of generic clopidogrel, which is approximately one-sixth the cost of ticagrelor or prasugrel in the United States. The 2011 ACC/ AHA/SCAI guidelines for PCI continue to recommend clopidogrel as Class I antiplatelet therapy after PCI.[29,30] The 2013 ACC/AHA guidelines for

ST-elevation myocardial infarction (STEMI) recommend all 3 anti-platelet drugs (clopidogrel, ticagrelor and prasugrel) as Class I therapeutic choices after PCI.[31] The 2014 ACC/AHA guidelines for patients with unstable angina and non-ST elevation myocardial infarction (NSTEMI) also recommend all 3 drugs, clopidogrel, prasugrel and ticagrelor as Class I therapy[53] and this has been reiterated in the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease for PCI patients.[48] The 2017 ESC guidelines for DAPT similar to ACC/AHA guidelines recommend clopidogrel for patients with stable CAD post-PCI however differ in their recommendation for post-PCI ACS patients by recommending clopidogrel only if patients are ineligible for treatment with prasugrel or ticagrelor.[54]

The multiple clinical trials demonstrating the efficacy of clopidogrel and relatively lower bleeding risk with its use, together with its considerably reduced costs compared to the newer P2Y12 inhibitors, has led to its common continued use post-PCI. The continued prescription of clopidogrel in the United States is highlighted by the data from hospitals based in Michigan (Figure 3).[2] In Canada, despite provincial governments offering coverage for the newer and more expensive P2Y12 inhibitor ticagrelor, clopidogrel remains the most commonly prescribed drug on discharge (70% of patients) for the spectrum of ACS patients, including those with ST-elevation myocardial infarction.[1] Internationally, clopidogrel has also been the dominant P2Y12 inhibitor used in the post-MI (with or without PCI) setting.[55] As an alternative to the universal use of the newer P2Y12 inhibitors, there are two ongoing clinical trials (TAILOR-PCI and the POPular Genetics study) that are examining the role of a genotyping strategy in prescribing anti-platelet therapy after PCI to potentially optimize clinical outcomes.[56,57]

POPular Genetics Study

POPular Genetics (NCT01761786)[56] is a randomized, open-label, multicenter trial of 2,700 STEMI patients undergoing primary PCI. Patients are randomized to *CYP2C19* genotyping or routine ticagrelor or prasugrel treatment. In the genotyping group, **1/*1* (wild-type) patients receive clopidogrel whereas those carrying 1 or 2 **2* or **3* LOF alleles receive ticagrelor or prasugrel. The primary net clinical benefit end point is the composite of MACE and major bleeding at 1 year.

TAILOR-PCI: A Prospective Randomized Trial to Assess the Effect of Individualizing Anti-platelet Therapy after PCI Based on *CYP2C19* Genotype

Study Design.

TAILOR-PCI (Clinicaltrials.gov: NCT01742117) is a multi-center, open label, prospective, randomized trial testing the hypothesis that guiding the choice of post-PCI dual antiplatelet therapy (DAPT) according to *CYP2C19* LOF status will improve outcomes in *CYP2C19* LOF carriers versus prescribing clopidogrel for all. Subjects in the prospective genotyping arm undergo FDA-approved “point-of-care” genotyping (Spartan Biosciences, Ottawa, Canada). *CYP2C19* LOF carriers are prescribed ticagrelor 90 mg twice daily for 12 months; subjects determined to be wild type are prescribed clopidogrel 75 mg once daily. Subjects in

the conventional care arm are not prospectively genotyped and are prescribed clopidogrel 75 mg once daily. All subjects have a blood sample drawn for genotyping to be performed by using the ABI TaqMan assay after completion of the duration of anti-platelet therapy, i.e., after 12 months (Figure 4). The primary endpoint is a composite, defined as cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia, during the first year after PCI. The secondary endpoint is major or minor bleeding. The definitions of the primary and secondary endpoints are outlined in the Data Supplement. The primary analysis will be conducted on subjects determined to be *CYP2C19 *2* or **3* carriers according to the ABI TaqMan assay. TAILOR-PCI is an international trial with sites based in the United States, Canada, Mexico and the Republic of Korea. Patients with ACS and stable CAD who undergo PCI and require DAPT for at least 12 months are considered for recruitment with randomization taking place within 72 hours post PCI. Exclusion criteria have been created to ensure patient safety and feasibility of follow up. A detailed list of enrollment criteria is in Table. All randomized subjects are followed up by telephone at 30 days, 6 months, and 1 year after PCI. All endpoints relating to the primary and secondary endpoints are adjudicated by an independent adjudication committee.

Clopidogrel Therapy in the Era of Precision Medicine: Should We Adopt a Systems Biology Approach?

Although variability in *CYP2C19* affects concentration of plasma clopidogrel metabolites, impacts platelet reactivity and clinical outcomes, a systems wide approach may be required to adequately assess, predict and manage inter-individual variation and antiplatelet drug therapy response. The clinical endpoints used to assess antiplatelet drug therapy response such as myocardial infarction, stroke, stent thrombosis and cardiovascular death may be modulated by multiple factors. Systems biology studies include a multi-omics approach to understand individual variation on a broader scale using techniques such as transcriptomics, proteomics, metabolomics and the microbiome. For example as depicted in Figure 5 methylation of P2Y12 receptors, microRNAs103 and 107, transferrin and peroxsiredoxin-4, TMAO are “omic” factors in addition to clinical variables that have been implicated in recurrent major cardiovascular events.[58] The integration of these data in developing a computational model to predict high versus low risk patients to ultimately individualize therapy remains a challenge.

Conclusions

The role and clinical utility of pharmacogenomics for guiding the use of clopidogrel or alternative anti-platelet therapies in patients undergoing PCI remains one of the most important unresolved issues in interventional cardiology. Genetic variation in *CYP2C19*, the cytochrome P450 enzyme that metabolizes the pro-drug clopidogrel into an active metabolite, plays an important role in individual pharmacokinetic differences observed with standard clopidogrel dosing. The loss-of-function *CYP2C19* genotypes that result in significantly reduced active clopidogrel metabolite levels are associated with adverse clinical outcomes as demonstrated in our post-PCI only updated meta-analysis. Whether treatment of such patients with alternative anti-platelet therapy such as ticagrelor as recommended by

the FDA black box warning for clopidogrel will result in improved morbidity and mortality remains unproven. TAILOR-PCI, a large, pragmatic, prospective, randomized international multi-center trial is designed to specifically address that question to eventually help guide practitioners whether individualizing anti-platelet therapy using a cost effective genetic based approach by selective use of the newer P2Y12 receptor inhibitors is beneficial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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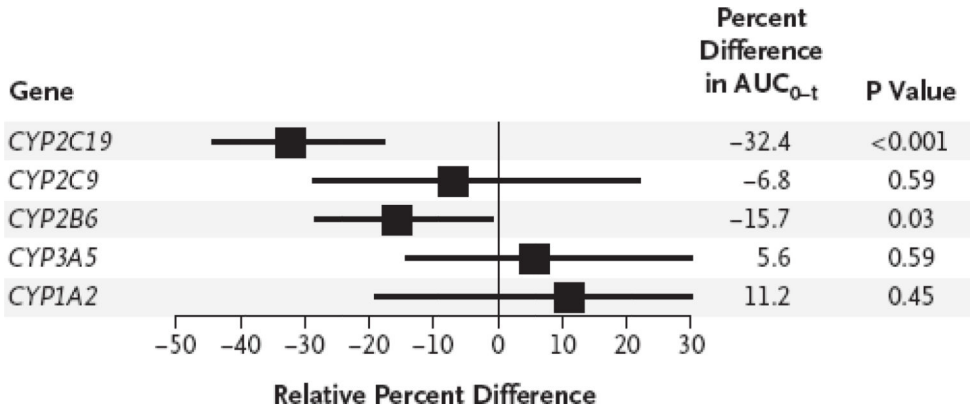

Figure 1.

Genetic effects and pharmacokinetic response to clopidogrel. [Reproduced with permission from Massachusetts Medical Society]

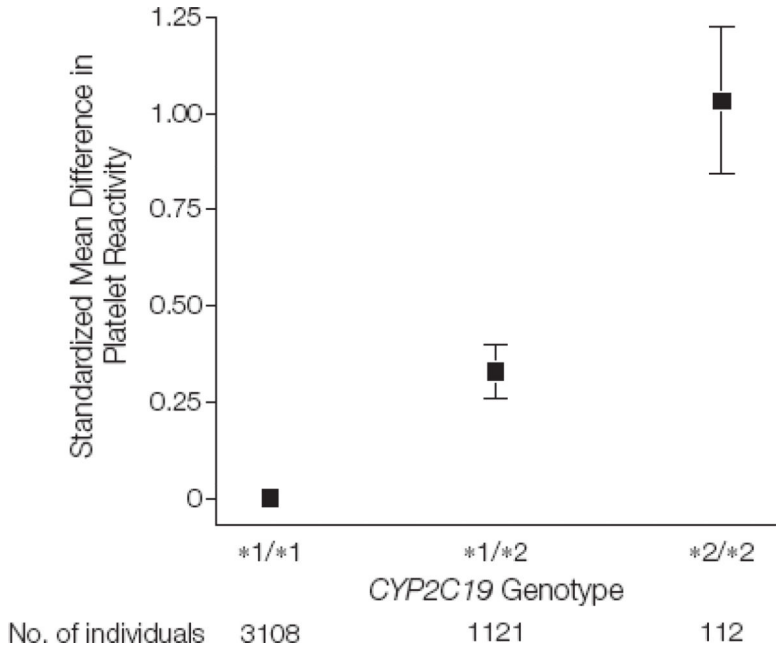

Figure 2.
Platelet reactivity by *CYP2C19* genotype after clopidogrel loading. [Reproduced with permission from American Medical Association]

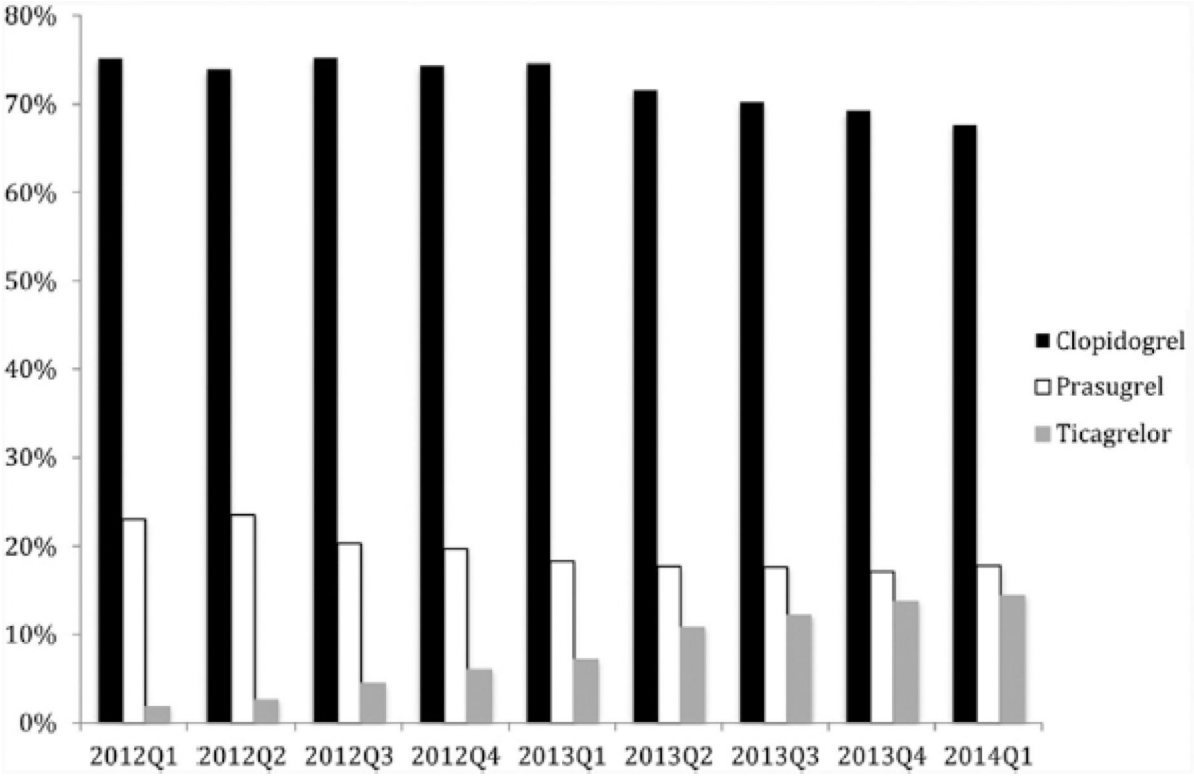

Figure 3.

P2Y12 inhibitor use by quarter from January 2012 to January 2014 at 47 Michigan hospitals in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. [Reproduced with permission from Elsevier Publishing]

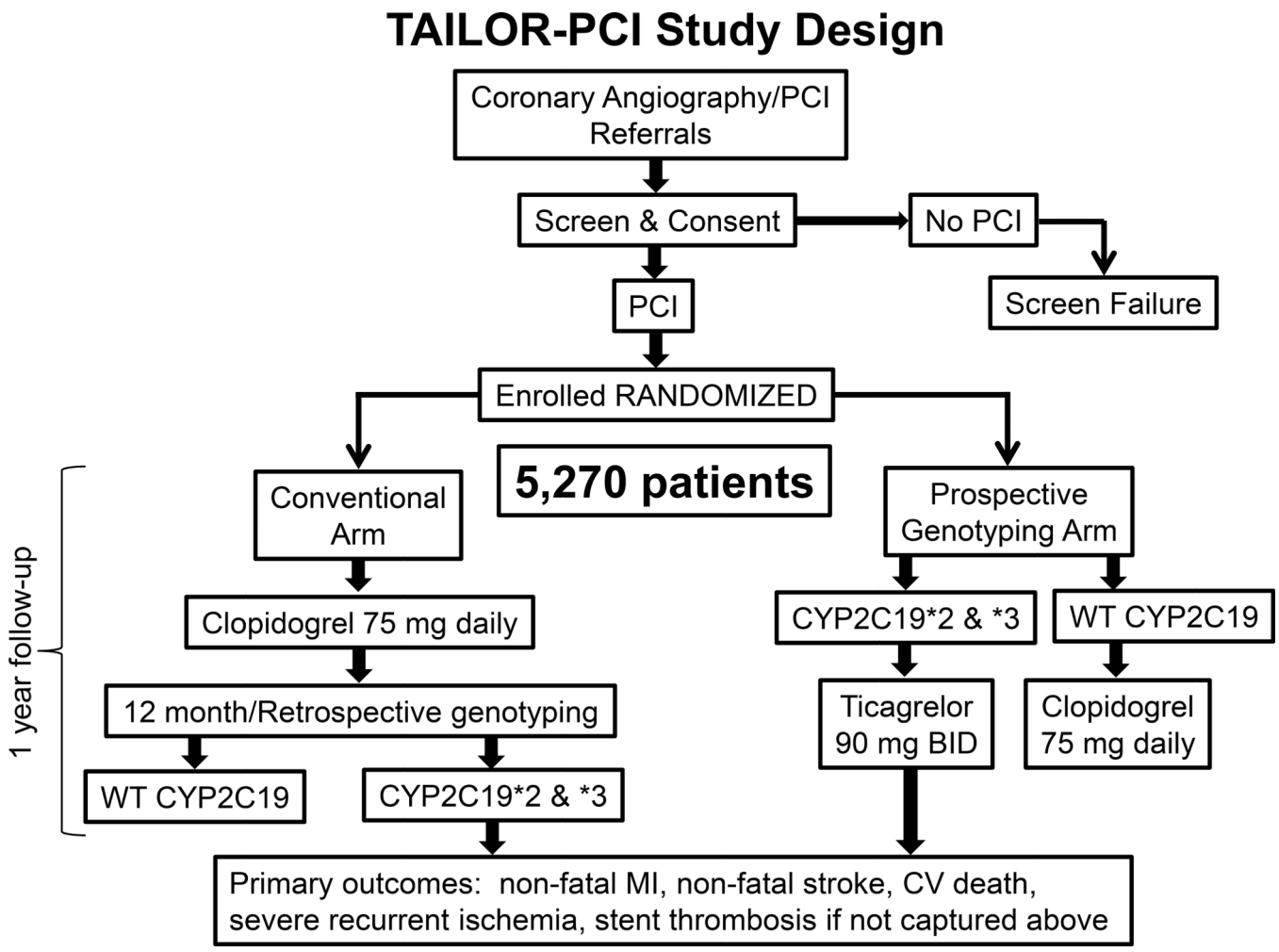

Figure 4.
TAILOR-PCI Study Design.

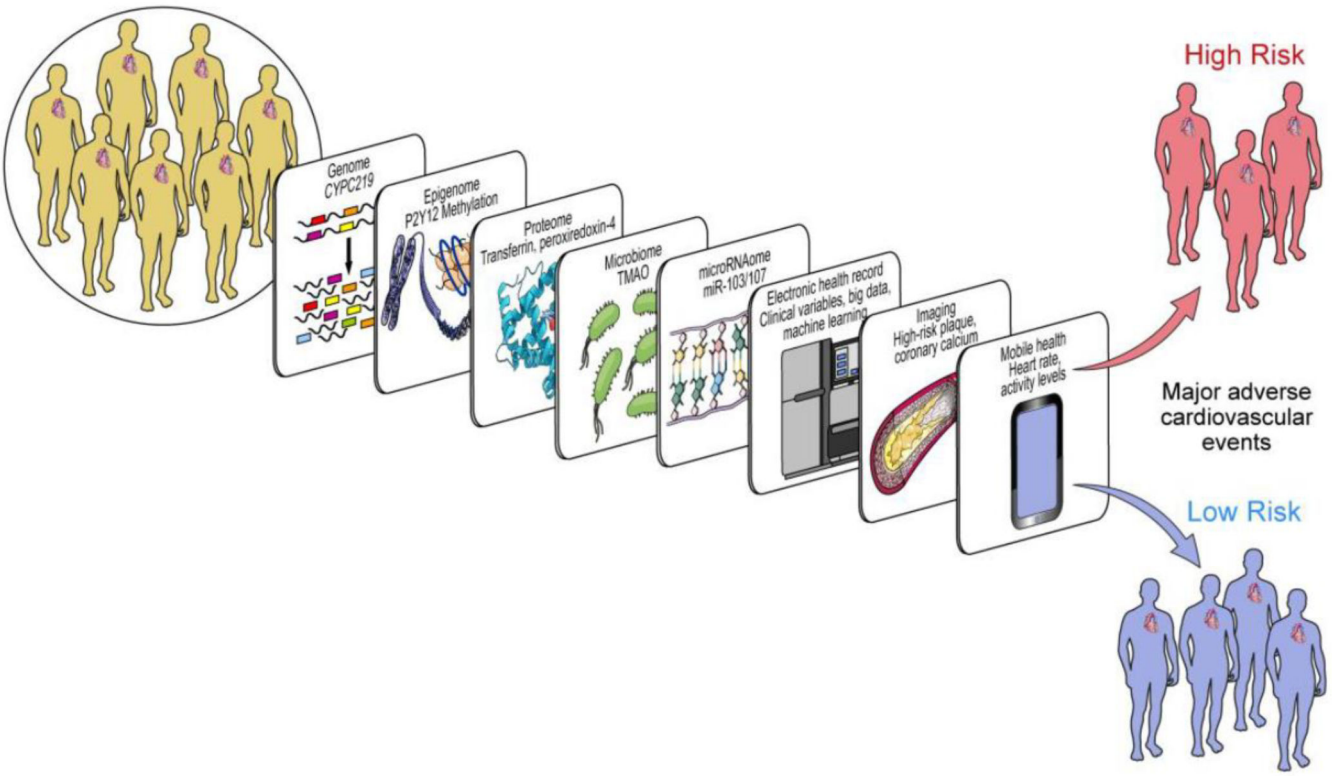

Figure 5.

Systems Medicine tools for CYP450 regulation in Precision Cardiovascular Medicine. Scheme attic representation of factors identified from various omic technologies that may regulate the pharmacogenomic impact of CYP450 variation on antiplatelet therapy. For example, in addition to *CYPC219* genomic variants identified in genome-wide association studies, methylation of P2Y12 receptor in epigenomics, the action of miR-103/107 on CYP2C19 in microRNAomics, transferrin and peroxiredoxin-4 identified by proteomics, TMAO in metabolomics and microbiomics can impact cardiovascular outcomes. Beyond omics, incorporation of 'big data' and clinical variables from the electronic health record with heart rate and activity levels from mobile health technology, along with findings from imaging (such as high risk plaque, coronary calcium), may help predict individuals who may be at high risk for clinical events. (Abbreviations: CYP450: cytochrome P450; CYP2C19: cytochrome P450, family 2, subfamily C, polypeptide 19; P2Y12: the adenosine diphosphate receptor on the surface of platelets, to which clopidogrel binds; miR-103/107: microRNA-103 and microRNA-107; TMAO: trimethylene N-oxide). [Reproduced with permission from MDPI]

Table.

Tailor PCI Inclusion and Exclusion Criteria

Inclusion Criteria
- Patient ≥18 years of age
- Patient presents with ACS or stable CAD
- Patient is eligible for PCI
- Patient is willing and able to provide informed written consent

Exclusion criteria
- Patient not able to receive 12 months of dual anti-platelet therapy
- Failure of index PCI
- Patient or physician refusal to enroll in the study
- Patient with known *CYP2C19* genotype prior to randomization
- Planned revascularization of any vessel within 30 days post-index procedure and/or of the target vessel(s) within 12 months post-procedure
- Anticipated discontinuation of clopidogrel or ticagrelor within the 12 month follow up period, example for elective surgery
- Serum creatinine >2.5 mg/dL within 7 days of index procedure
- Platelet count <80,000 or >700,000 cells/mm^3, or white blood cell count <3,000 cells/mm^3 if persistent (at least 2 abnormal values) within 7 days prior to index procedure.
- History of intracranial hemorrhage
- Known hypersensitivity to clopidogrel or ticagrelor or any of its components
- Inability to take aspirin at a dosage of 100 mg or less
- Patient is participating in an investigational drug or device clinical trial that has not reached its primary endpoint
- Patient previously enrolled in this study
- Patient is pregnant, lactating, or planning to become pregnant within 12 months
- Patient has received an organ transplant or is on a waiting list for an organ transplant
- Patient is receiving or scheduled to receive chemotherapy within 30 days before or after the procedure
- Patient is receiving immunosuppressive therapy or has known immunosuppressive or autoimmune disease (e.g., human immunodeficiency virus, systemic lupus erythematous, etc.)
- Patient is receiving chronic oral anticoagulation therapy (i.e., vitamin K antagonist, direct thrombin inhibitor, Factor Xa inhibitor)
- Concomitant use of simvastatin/lovastatin > 40 mg qd
- Concomitant use of potent CYP3A4 inhibitors (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) or inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, and rifapentine)
- Non-cardiac condition limiting life expectancy to less than one year, per physician judgment (e.g. cancer)
- Known history of severe hepatic impairment
- Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions
- Patient has an active pathological bleeding, such as active gastrointestinal (GI) bleeding
- Curent substance abuse (e.g., alcohol, cocaine, heroin, etc.)