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Role of genetic polymorphisms in clopidogrel response variability: a systematic review

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ABSTRACT

Introduction Clopidogrel is a $P2Y_{12}$ inhibitor that has become a mainstay treatment following percutaneous intervention with drug-eluting stent placement to decrease restenosis and its potential complications, including sudden cardiac death and ischaemic strokes in patients with significant vascular disease.

Areas covered As a prodrug, the metabolism and efficacy of clopidogrel are contingent on the presence of wild-type CYP450 (CYP2C19) alleles. Genetic polymorphisms and variants are well known to impair its ability to prevent major adverse cardiovascular events in these patients, with inadequate response rates as high as 30% in previous publications. Patterns of allelic frequencies are expected to exhibit similarities between individuals of the same ancestry, ethnic group or geographic region. Accordingly, we seek to further elucidate worldwide prevalence rates for genetic polymorphisms in the CYP2C19-dependent metabolism of clopidogrel and review the potential of personalised CYP2C19 genotyping in clinical practice to mitigate this high treatment resistance and its associated burden on patients.

Experts' commentary Our findings support the consideration of genotyping before initiation of therapy to guide adequate dosage or substitutions of other $P2Y_{12}$ inhibitors to promote personalised, precision medicine and to prevent adverse events when these therapies may inevitably fail in patients with variants of the CYP450 (CYP2C19) system.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clopidogrel is a mainstay therapy following percutaneous coronary intervention to prevent major adverse cardiac events (MACEs). Despite its effectiveness, clopidogrel resistance or rapid metabolisation affects up to 30% of patients due to genetic polymorphisms in CYP2C19-dependent metabolism of the drug. However, less is known regarding worldwide prevalence rates for these polymorphisms across various ethnic and geographical strata.

WHAT THIS STUDY ADDS

⇒ Our systematic review reveals persistently elevated rates of genetic polymorphisms and resultant variation in CYP2C19-mediated response to clopidogrel. These findings are consistent across various ethnic groups, including Caucasians, African-Americans, Asians and Europeans.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings may support the consideration of genotyping before initiation of clopidogrel in combination with current guidelines from major societies that support the role of personalised, precision medicine to guide antiplatelet therapy. Mitigating potentially deadly MACE due to CYP2C19-dependent resistance or over metabolism may be more achievable with this approach.

INTRODUCTION

$P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor) are widely used alongside aspirin in patients who undergo percutaneous coronary intervention (PCI) or have an acute coronary syndrome (ACS) to prevent subsequent major adverse cardiovascular events (MACE).[1–3] These agents exert their effect by inhibiting the $P2Y_{12}$ receptors (ADP receptor) on platelets leading to reduced expression of GPIIb/IIIa on the surface and thus decrease platelet aggregation.[3]

Despite their relative effectiveness, clinical variability exists in the response to $P2Y_{12}$ inhibition. The newer agents prasugrel and ticagrelor seem to overcome this at the expense of increased bleeding rates, while clopidogrel resistance remains well-documented.[4] Clopidogrel resistance is usually defined by the presence of a high on-treatment platelet reactivity, indicative of persistent platelet aggregation despite being on optimised antiplatelet therapy.[5] Although clopidogrel response variability can be attributed to three main biochemical mechanisms including alterations in absorption, metabolism and drug–drug interactions, genotypic polymorphisms in the expression of the CYP2C19 allele is a critical factor

impacting the clinical response to $P2Y_{12}$ inhibitors.[6] In light of this evidence, in 2010, the Food and Drug Administration added a black-box warning noting the reduced efficacy and safety concerns in certain patients who may intermediately or poorly metabolise the drug,[7] thereby imploring the consideration of another P2Y12 inhibitor for treatment.[8]

Herein, this review focuses on the effect of genetic polymorphisms on clopidogrel response variability across the world stratified by patient ancestry, ethnicity, origin and geographic region. Although genetic testing may be a financial burden for some, we support the consideration of genotype testing for polymorphisms for optimal guidance of therapy. We support an individualised approach, as suggested by previous authors, to prevent thrombotic events while simultaneously mitigating bleeding and other adverse effects from other agents.[4]

OBJECTIVES

To evaluate and compare existing worldwide data regarding CYP2C19 genotypic variation in $P2Y_{12}$ inhibitor metabolism based on ancestry, ethnicity or geographical origin of the patient, to ultimately advocate for individualised testing to maximise clinical efficacy and response.

We conducted a systematic retrospective analysis utilising search terms "CYP2C19" and "P2Y12 inhibitors" in Levy Library (Icahn School of Medicine), Medscape, PubMed, and multiple journals including: *Journal of the American College of Cardiology*, *New England Journal of Medicine*, *Journal of the American Medical Association*, *American Heart Association*, *The Lancet*, *European Heart Journal*, *British Medical Association Journal*, *The Journal of Clinical Pharmacology*, *National Center for Biotechnology Information*, *Annals of Internal Medicine*, *International Journal of Molecular Sciences*, *Seminars in Thrombosis and Hemostasis*, *Biochemical Pharmacology Journal*, *International Journal of Clinical and Experimental Pathology*, *European Journal of Human Genetics*, *Expert Opinion on Drug Metabolism & Toxicology*, *European Journal of Clinical Pharmacology*, *Journal of Pharmacology and Experimental Therapeutics*, *Medical Science Monitor Journal*, *Circulation: Genomic and Precision Medicine*, *Cold Spring Harbor Molecular Case Studies*, *Medical Science Monitor*, *Circulation: Cardiovascular Quality and Outcomes*, *National Center for Biotechnology Information*, *Current Drug Metabolism*.

INCLUSION CRITERIA

The articles assessed CYP2C19 allele status in adult patients. Studies considered included the variants of the alleles, including but not limited to CYP2C19*2 (rs4244285), CYP2C19*3 (rs4986893), CYP2C19*4 (rs28399504), CYP2C19*5 (rs56337013), CYP2C19*6 (rs72552267), CYP2C19*7 (rs72558186), CYP2C19*8 (rs41291556) and the gain of function variant CYP2C19*17 (rs12248560). A total of 41 articles met the inclusion criteria and were selected for review.

DRUG METABOLISM

Clopidogrel, a thienopyridine prodrug, is absorbed in the small intestine.[9] Its clinical efficacy is dependent on its conversion in the liver via cytochrome P450 enzymes (CYP450) to its active metabolite which irreversibly inhibits the $P2Y_{12}$ receptor on platelets to impede fibrin cross-linking.[9–11] The cytochrome P450 2C19 (CYP2C19) system is responsible for the metabolism of other therapeutic agents, including anticonvulsant drugs, sedatives, antipsychotic medications, omeprazole, proguanil, propranolol, citalopram and imipramine, all of which may alter the metabolism of clopidogrel.[12–14] Thus, consideration of polypharmacy is essential to initiating proper dosing of clopidogrel.

However, underlying variation in the expression of CYP450 alleles has also been importantly implicated in the clinical efficacy of this drug. The CYP2C19 metabolism of clopidogrel varies depending on expression of alleles based on individual patient genotypes, thus affecting its clinical dosing.[15] Furthermore, patients can be characterised based on the function of their CYP2C19 alleles according to consensus terminology given by the Clinical Pharmacogenetics Implementation Consortium (CPIC).[16] For ultrarapid metabolisers who possess two alleles with increased function (eg, *17/*17), rapid metabolisers who possess one allele with increased function and one normal allele (eg, *1/*17), and normal metabolisers who possess two normal alleles (eg, *1/*1), dosing per label is recommended.[15 16] For intermediate metabolisers who possess one allele with normal function and one with reduced function or one allele with no function and one with increased function (eg, *1/*2, *1/*3, *2/*17, *3/*17), likely intermediate metabolisers (*1/*9, *9/*17, *9/*9), poor metabolisers who carry two alleles without function (eg, *2/*2, *2/*3, *3/*3) and likely poor metabolisers (*2/*2, *2/*3, *3/*3); alternative antiplatelet therapy with ticagrelor or prasugrel is recommended.[15 16] In response to this allelic and phenotypic heterogeneity, the Dutch Pharmacogenetics Working Group offers personalised recommendations to further guide prescription of clopidogrel (table 1).[17]

PHARMACOGENOMICS

Cytochrome P450 genes are located on chromosome number 10 arm q24.[18] Specifically, CYP2C19 metabolises clopidogrel in a two-step oxidative biotransformation process to its thiol metabolites, which target the P2Y12 receptor for ADP on the platelets.[19] The most common variant alleles are CYP2C19*2 and *3, which result in non-functional proteins,[20] and these genetic polymorphisms affect the ability to metabolise the drug. Even if the amino acid remains the same, it may create a non-functional protein, thus rendering the drug ineffective.[21 22]

Table 1 Dutch Pharmacogenetics Working Group recommendations for the prescription of clopidogrel depending on phenotype.[17]

Phenotype	Recommendation
Ultrarapid metaboliser	No action is required for this gene–drug interaction
Intermediate metaboliser	Percutaneous coronary intervention, stroke or TIA: Choose an alternative or double the dose to 150 mg/day (600 mg loading dose) Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent). Other indications: No action required
Poor metaboliser	Percutaneous coronary intervention, stroke or TIA: Avoid clopidogrel Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent). Other indications: 1. Determine the level of inhibition of platelet aggregation by clopidogrel. 2. Consider an alternative in poor responders. Prasugrel and ticagrelor are not metabolised by CYP2C19 (or to a lesser extent)

TIA, transient ischaemic attack.

MECHANISM-BASED INACTIVATION

For our review, studies reporting an association with a loss of function variant were eligible if they had genotyped at least the CYP2C19*2 alleles, as it accounted for more than 95% of the loss of function allele carrier status in white and black populations and more than 75% in Asian populations.[23] Previous data from Bauer *et al* suggested that antiplatelet therapy regimens should not be individually guided by the CYP2C19 genotype.[24] However, this contrasts the results and suggestions from other studies. In a meta-analysis by Mega *et al*, of the total 9685 patients (91.3% of whom underwent PCI, and 54.5% of whom had an ACS), 863 experienced cardiovascular death, myocardial infarction (MI), or stroke; 84 out of 5894 patients had stent thrombosis despite clopidogrel therapy.[25] A total of 71.5% were non-carriers, 26.3% had one and 2.2% had two CYP2C19 reduced-function alleles. Morbidity and mortality were significant in carriers of one (HR 1.55, 95% CI 1.11 to 2.27, p=0.01) and two (HR 1.76, 95% CI 1.24 to 2.50, p=0.002) CYP2C19 reduced-function alleles.[25] Increased risk of stent thrombosis was evident in both carriers of one (HR 2.67, 95% CI 1.69 to 4.22, p<0.0001) and two (HR 3.97, 95% CI 1.75 to 9.02, p=0.001) CYP2C19 reduced-function alleles.[25] The authors clearly reasoned that carriage of even one reduced-function CYP2C19 allele appeared to be associated with a significantly increased risk of MACE, particularly stent thrombosis, implicating the need for individualised testing and treatment protocols.[25]

In another meta-analysis of 15 studies with a total of 4762 patients with a stroke or a TIA on clopidogrel, genetic variants other than CYP2C19 did not have an impact on clinical outcomes, except those that were on any medications that impacted the P450.[6] Increased risk of stroke in comparison with non-carriers (12.0% vs 5.8%; risk ratio 1.92, 95% CI 1.57 to 2.35; p<0.001) and composite vascular events were also more frequent in carriers of CYP2C19 loss-of-function alleles than in non-carriers (13.7% vs 9.4%; risk ratio 1.51, 95% CI,1.10 to 2.06; p=0.01); whereas bleeding rates were similar (2.4% vs 3.1%; risk ratio 0.89, 95% CI 0.58 to 1.35; p=0.59).[6] Genetic variants other than CYP2C19 were not associated with clinical outcomes, with the exception of significant associations of PON1, $P2Y_{12}$ and COX-1.[6]

BIODIVERSITY

A secondary analysis of patients enrolled in TRIUMPH, a multicentre prospective trial that included 72 062 Caucasians and 670 African-Americans hospitalised with acute MI[26] sought to evaluate genetic mediators of racial disparities in outcomes among these patients treated with clopidogrel to assess whether cytochrome P450 polymorphisms were associated with morbidity and mortality. The results showed that African Americans with the CYP2C19*17 (ultra-rapid metaboliser) variant were more likely to experience bleeding.[27] The CYP2C19*2 variant was not associated with increased mortality, neither unadjusted (HR 0.66; 95% CI 0.29 to 1.47; p=0.30) or adjusted (HR 0.63; 95% CI 0.28 to 1.41; p=0.26). The CYP2C19*17 variant was associated with significantly increased mortality (33.3% 1-year mortality for CYP2C19*17/*17 homozygotes vs 9.8% for CYP2C19*17/*1 heterozygote vs 4.9% for *1/*1 homozygote; log-rank p=1e-05).[27] These data showed a statistically significant interaction between ethnicity and mortality for CYP2C19*2 (p=0.042) and CYP2C19*17 (p=0.011).[27] When compared with Caucasians, there was a trend of increased recurrent MI in carriers of the CYP2C19*2 variants in unadjusted (HR 2.08; 95% CI 0.95 to 4.59; p=0.0687) and adjusted (HR 2.10; 95% CI 0.95 to 4.63; p=0.0661) models, but these patients were not shown to have increased bleeding

events.[27] The CYP2C19*2 variant was associated with significantly increased all-cause mortality (5.4% 1-year mortality for CYP2C19*2 allele carriers vs 3% for *1/*1 homozygote).[27] The interaction between CYP2C19*2 SNP and clopidogrel treatment for mortality in Caucasian TRIUMPH patients discharged on clopidogrel was not significant (p=0.860).[27]

In an analysis of more than 82 000 patients in Europe, the frequency of CYP2C19*2 was highest in Northern and Western European countries, including Cyprus (21%) and Malta (20%), whereas the lowest was in the Czech Republic. CYP2C19*17 was more common in Central Europe while lower in Southern European countries.[28] Thus, these findings by Petrović *et al*[28] suggest the need to refine pharmacogenomic mapping to guide precision public health, especially in populations with a high incidence of these polymorphisms and an increased likelihood of experiencing MACE or other consequences of clopidogrel resistance.

In another study, Khalil *et al* assessed the prevalence of CYP2C19 variants in patients living in the Mediterranean region and its impact on MACE outcomes in those treated with clopidogrel. Carriers of CYP2C19 loss of function alleles were more likely to experience MACE (OR 2.52, 95% CI 1.23 to 5.15, p=0.011).[29] These authors also reported a statistically significant association between body mass index and MACE incidence, suggesting a possible role for lifestyle management to mitigate the impact of these variants.[29] Overall, replication of the association of genetic polymorphisms in CYP alleles and MACE reported in previous studies suggests the need for individualised genetic testing and optimisation of antiplatelet treatment to improve outcomes and potentially reduce the morbidity and mortality of MACE.

Further studies determined that when allelic frequency estimations were compared for CYP2C19*2 and CYP2C19*3 in other ethnic populations, the allelic frequency of CYP2C19*2 in Asian populations was up to 30.0%, and 15.0%–17.0% in European and black patients.[30 31] The allelic frequencies of the CYP2C19*2 in the west South American, Asian, Scandinavian, European and African-American populations were relatively low.[32] Compared with other ethnicities, the prevalence of CYP2C19 loss-of-function alleles was higher in Asiatic populations. Overall, the allelic frequency of CYP2C19*2 in the Hakka subjects (31.06%) was closer to that of Chinese-Dai (30%), but they were in between that of populations from Chinese Li (25%) and Chinese-Han ethnic groups (37%).[33–35]

The CYP2C19*3 allele was found with a frequency of 0.0461% in the Hakka population, which was consistent with findings within East Asian populations.[36] In contrast, other studies reported that CYP2C19*3 was present in lower frequency or nearly absent in Turkish, Swedish, Russian, Italian, Bolivian, Faroese, Tanzanian, Ethiopian and Zimbabwean populations.[32 37 38]

Zhong *et al* noted that the prevalence of CYP2C19*3 was consistent with previous reports on the Chinese population, but it was lower than in Japanese, Korean, Vietnamese and Thai populations.[36] These authors also implored that more attention should be paid to the populations that had a higher frequency of the loss-of-function of CYP2C19, especially in China, since people with the CYP2C19*2 or CYP2C19*3 variants were more likely to be predisposed to abnormal metabolism of clopidogrel.[36] A comprehensive tabular array of the multiethnic CYP2C19 allele frequencies and phenotypes are found in online supplemental tables 1 and 2, respectively.[39 40]

OUR RECOMMENDATIONS

As we have elucidated, given the high worldwide prevalence of CYP2C19 genetic polymorphisms and their association with increased MACE, our findings offer support for genetic testing before initiating therapy with clopidogrel to mitigate possible life-threatening outcomes following PCI. Our findings, supported by previous studies,[41–44] suggest the implementation of personalised genetic testing to support precision medicine and individualised care in prescribing clinically effective and safe $P2Y_{12}$ inhibitors. The IGNITE network, investigated the outcomes of CYP2C19 genotype-guided therapy after percutaneous intervention of the coronary arteries. Their observations demonstrated higher risk for cardiovascular events in the presence of CYP2C19 loss-of-function allele on clopidogrel versus alternative therapy.[45] Thus, the decision to initiate clopidogrel may be at least partially based on CYP2C19 genotypes as to prognosticate possible adverse events in ACS patients.[46 47] In contrast with other societies such as American Heart Association/American College of Cardiology, the CPIC guidelines for cytochrome P450-2C19 (CYP2C19) genotyping support these recommendations for personalised therapy when considering clopidogrel for ACS or PCI.[39 48] On the other hand, there is no evidence of cytochrome polymorphisms affecting prasugrel bioactivation, as the genetic variables that may affect the clinical outcomes of patients treated with ticagrelor or prasugrel have not been identified.[49] The results of the TRITON-TIMI 38 and PLATO trials showed a clinical benefit of prasugrel and ticagrelor, respectively, over clopidogrel and did not reveal evidence that CYP2C19 loss-of-function alleles carriage would affect these patients.[50 51] Thus, genetic testing may help facilitate the clinical decision to switch to one of these alternative P2Y12 inhibitors when genetically and clinically indicated.

CONCLUSION

We have reviewed multiple studies regarding worldwide rates of CYP2C19 genetic polymorphisms and their effect on clopidogrel resistance. Although these rates vary depending on ethnicity or geographic region, we contend that there is enough support to consider individualised genetic testing to guide the initiation of antiplatelet therapy.

Despite our findings of an abundance of worldwide data showing the high prevalence of CYP polymorphisms and their association with MACE, there is a lack of current medical guidelines that establish the role of genetic testing to direct antiplatelet therapy in ACS patients following PCI. Instituting testing to determine genotypes could potentially address the failure of $P2Y_{12}$ inhibitor therapy to warrant dosage augmentation or to direct clinicians to initiate alternative pharmacological therapies. As our review revealed varying rates of polymorphisms across different patient ethnicities, ancestries and geographical regions, a tailored approach may be warranted for all, though more randomised trials are needed to fully assess outcomes and cost-effectiveness.

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