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Potential Usefulness of Clopidogrel Pharmacogenetics in Cerebral Endovascular Procedures and Carotid Artery Stenting

Jorge Duconge, PhD¹ and Dagmar F. Hernandez-Suarez, MD²

¹Pharmaceutical Sciences Department, School of Pharmacy, University of Puerto Rico Medical Sciences Campus (UPR-MSC), San Juan, PR, USA

²Department of Medicine, School of Medicine, University of Puerto Rico Medical Sciences Campus (UPR-MSC), San Juan, PR, USA

Abstract

Background—Previous reports have shown inadequate response to dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in 5–30% of patients undergoing percutaneous coronary interventions (PCI), due mostly to clopidogrel resistance. This prevalence increases up to 66% in patients undergoing neurointerventional procedures. However, clinical significance of *CYP2C19* genotypes in neurointerventional procedures or carotid artery stenting (CAS) is unknown.

Objective—The purpose of this review is to update our current knowledge and understanding of the pharmacogenetic basis for poor clopidogrel responsiveness in patients undergoing CAS and endovascular interventions as well as to explore usefulness of genotyping to reduce the rate of procedure-related thrombosis that results in ischemic complications.

Method—A literature search for pharmacogenetic studies in cerebral endovascular interventions and CAS was conducted on three databases using a list of the most relevant pharmacogenetic biomarkers.

Results—The review included 7 papers involving 3 genetic polymorphisms on *CYP2C19* and 442 subjects. Patients harboring at least one loss-of-function *CYP2C19* polymorphism (e.g., *CYP2C19**2 and *3) are at an increased risk of thromboembolic complications such as stent thrombosis following neurointerventional procedures. Notably, patients who carry the gain-of-function *CYP2C19**17 allele may have increased risk of ischemic events following endovascular treatment, independent of clopidogrel responsiveness.

Conclusion—Studies assessing the influence of *CYP2C19* polymorphisms on high on-treatment platelet reactivity in CAS and cerebrovascular disease patients are still limited and need further

Corresponding Author: Jorge Duconge, PhD, MSc, BSc Pharm, University of Puerto Rico Medical Sciences Campus, School of Pharmacy, Dept. of Pharmaceutical Sciences, Room 325-14, PO Box 365067; San Juan, PR 00936-5067, Tel. (787) 758 2525 ext. 5312, 3006, Fax (787) 767 2796; jorge.duconge@upr.edu.

Competing Interests

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validation in large multicenter studies. This review covers an important topic in the field of antiplatelet therapy for cerebral endovascular procedures and CAS.

Keywords

Clopidogrel; Pharmacogenetics; *CYP2C19*; Ischemic Stroke; Cerebral Endovascular Procedures; Carotid Artery Stenting

Introduction

The use of dual antiplatelet therapy (DAPT) with aspirin and an ADP receptor blocker (e.g., clopidogrel) has been well validated in peripheral vascular and coronary intervention to reduce periprocedural thromboembolic events by approximately 80%. Clopidogrel is an antiplatelet drug commonly used to reduce the rate of procedure-related thrombotic ischemic complications. Clopidogrel is the most widely used selective P2Y₁₂ receptor antagonist, mainly due to its lower cost as a generic drug [1–2]. Particularly, it is often prescribed to prevent secondary ischemia for patients undergoing carotid artery stenting (CAS) or with cerebrovascular conditions (e.g., intracranial aneurysms, large artery stenosis) treated by endovascular techniques (e.g., transluminal placement of thrombogenic metallic coils, flow diverting devices or stents). Endovascular intervention has emerged as a successful alternative for open surgical procedures in cerebrovascular disease. Up to 9% of patients undergoing neurointerventional procedures develop thromboembolic complications, while carotid angioplasty has been linked to ischemic complications in 3–13% of patients [3]. Besides that, American Heart Association (AHA)/American Stroke Association guidelines recommend monotherapy with clopidogrel as a reasonable option for secondary prevention of ischemic stroke [4]. DAPT with aspirin and clopidogrel might also be considered for initiation within 24 hours of a minor ischemic stroke or transient ischemic attack (TIA) [4].

Statement of the Problem

The response to clopidogrel varies widely among these patients. Although clinical trials have shown the benefit of DAPT in different settings, a considerable number of patients still experience recurrent atherothrombotic events [5–8]. Previous reports in literature suggest that between 5 and 30% patients undergoing percutaneous coronary intervention (PCI) are non-responders to clopidogrel, but as much as 66% of patients with cerebrovascular disease show a suboptimal response to clopidogrel, placing them at higher risk of thrombosis [9–10]. Furthermore, about 15%–38% of patients are hyper-responsive to this drug.

Genome-wide association study (GWAS) revealed that the loss-of-function (LOF) *CYP2C19**2 polymorphism [11] accounted for about 12% of the observed variation in platelet responsiveness [12]. Most recently, epigenetics has been suggested as an important factor that may significantly contribute to the variability of clopidogrel responsiveness and recurrence of ischemic events in patients with stroke [13]. Current literature and the Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines suggest the use of an alternative agent (e.g. prasugrel, ticagrelor), provided it is not contraindicated clinically, for those patients identified by genotyping as *CYP2C19* intermediate or poor metabolizers (IM/PM) [14–16]. However, prasugrel is contraindicated in patients with previous stroke or

transient ischemic attack (TIA) due to bleeding risk compared with clopidogrel [17,18]. Noteworthy, both prasugrel and ticagrelor are yet to be validated as superior therapies in CYP2C19 IM/PMs.

On the other hand, it has not been proved that testing for *CYP2C19* genotypes have any clinical significance in neurointerventional procedures or CAS, in part because studies assessing the impact of common *CYP2C19* polymorphisms on high on-treatment platelet reactivity (HTPR) and related clinical outcome in clopidogrel-treated patients who are either suffering from cerebrovascular disease or undergoing CAS are scarce. Accordingly, their role in both situations is based only on that indirect experience but has never been specifically tested. As a matter of fact, the 2013 update to the CPIC guidelines contains actionable recommendations for the *CYP2C19*-clopidogrel pair based on clinical evidences gathered from studies conducted mostly in acute coronary syndrome (ACS) patients, almost all of whom underwent PCI [19]. Therefore, these recommendations that consider alternative antiplatelet medications in CYP2C19 intermediate- and poor-metabolizers are only directed to ACS/PCI patients, but do not apply to other medical indications for clopidogrel use such as medical management of ischemic strokes and endovascular neurointerventional procedures due to lack of enough clinical data on this matter [19]. Moreover, clopidogrel treatment failure in these particular groups of patients could also be magnified because they are at additional risk of a non-atherothrombotic recurrent cerebral infarct due to, for instance, a cardio-embolism with paroxysmal atrial fibrillation [20] or a lacunar stroke caused by hypohyalinosis or microatheromatosis related to hypertension or diabetes [21].

Methods

A literature search for pharmacogenetics studies of clopidogrel in cerebral endovascular procedures and CAS was conducted from October 2016 to December 2016 on three bibliographic databases (i.e., US National Library of Medicine MEDLINE, Scopus and SciELO) following a methodology used in previous studies [22] for peer-reviewed scientific literature. Additionally, the collaboration of practicing clinicians at our institution was required in order to enrich the review with updated information. The following list of terms was used as key words/phrases: ‘clopidogrel AND pharmacogenetics AND cerebral endovascular procedures AND/OR neuro-interventions AND/OR platelet reactivity AND genetic polymorphism AND CYP2C19 (or each of the gene names listed in Table 1)’, which were properly combined each other for better results. The quality of retrieved papers was appraised using standard tools. A qualitative content analysis was applied to assess the interventions and findings of included studies using a conceptual framework.

The biomarkers (i.e., clopidogrel-related genetic polymorphisms) investigated were extracted from the list of 640 annotations for clopidogrel pharmacogenetics available at PharmGKB website [23], and also mentioned in the list proposed by the US FDA and CPIC guidelines for the pharmacogenetics of clopidogrel [14,19]. Articles were selected if the study: involved or described data from patients; analyzed one or more of the preselected biomarkers (Table 1); were written in English and published between 1975 and 2016. Papers were not excluded based on the country of origin, ethnicity/race of the study population and

number of participants. Co-authors of this review article served as reviewers for this purpose. One reviewer extracted the data from the original research papers. A second reviewer checked for accuracy. Disagreements were resolved with the aid of a third party.

Results

A nonspecific search strategy in three databases (see 'Methods' section) yielded 7 papers (both research articles and reviews) involving 3 genetic polymorphisms on only one biomarker or pharmacogene of interest (i.e., *CYP2C19*, as expected) and 442 subjects from two countries and describing data in two populations worldwide, with cerebral endovascular intervention (3 hits) and CAS (4 hits). No reports of clopidogrel pharmacogenetic studies, with significant clinical implications of the others biomarkers (i.e., *PON1*, *ABCB1*, *P2RY12*, *B4GALT2*, etc.) on patients with cerebral endovascular procedures and CAS were found. Accordingly, their role in clopidogrel responsiveness remains uncertain.

Role of CYP2C19

Several clinical studies have been conducted in multiple populations worldwide in order to ascertain the purported association between *CYP2C19* genetic variants and the observed variability in clinical outcomes and platelet inhibition. *CYP2C19* is a highly polymorphic human gene, having more than 25 known variant alleles [11]. It is located within a cluster of cytochrome P450 genes on chromosome 10q23.33 (National Center for Biotechnology Information [NCBI] Genome build 37.1, GenBank NG_008384; HGNC: 2621, mapped to this locus in the GRCh37 archive: ENSG00000165841) that encodes for a major liver drug-metabolizing enzyme gene product (UniProtKB identifiers: P33261), a member of the Cytochrome P450 superfamily (family 2 subfamily C member 19), involved in the bioactivation and breakdown of many xenobiotics, endogenous compounds and clinically relevant prescription drugs within the body (RefSeq Gene ID 1557: <https://www.ncbi.nlm.nih.gov/gene/1557>).

The *CYP2C19**2 [c.681G>A; rs4244285, with minor allele frequencies (MAF), of ~15% in Caucasians and Africans and 29–35% in Asians] and *CYP2C19**3 (c.636G>A; rs4986893, MAF of 2–9% in Asians, but <1% in other populations) loss-of-function (LOF) alleles have been previously associated with an increased incidence of stent thrombosis in coronary intervention studies [12, 14]. This is largely attributed to the fact that clopidogrel is an orally administrated prodrug requiring metabolic transformation to exert its effects, a process that is mainly catalyzed by the *CYP2C19*-mediated metabolic pathway. In contrast, *CYP2C19**17 (c.–806C>T; rs12248560, with average multi-ethnic MAF of ~3–21%) gain-of-function allele may increase hemorrhagic complications, but its impact on ischemic events and clinical outcome has not yet been definitively clarified.

Effect of Pharmacogenetics on the Platelet Response to Clopidogrel in CAS

Current guidelines recommend the use of DAPT in patients with carotid artery stenosis undergoing stenting to decrease further atherothrombotic events [24]. However, the length of DAPT therapy varies from no recommendations to at least one or 3 months [25,26]. The CARESS trial showed the superiority of DAPT over aspirin alone in reducing transcranial

detected cerebral asymptomatic embolization in cohort of 230 patients with significant carotid artery stenosis [27]. A carotid angiogram showing a patient with left cervical carotid artery severe stenosis treated with balloon angioplasty and stenting is depicted in Figure 1.

Gonzalez *et al.* (2016) reported the influence of common *CYP2C19* allelic variants (e.g., *2, *3, *17) on response to clopidogrel, as well as on the effect of dose adjustment (i.e., high versus standard dose), in 209 patients undergoing CAS with high on-treatment reactivity [28]. Notably, clopidogrel non-responders were significantly overrepresented among patients who showed an IM/PM status due to the presence of the *CYP2C19**2 allele versus non-carriers (35 patients, 66% vs. 66 patients, 42.3%; $p=0.007$). Authors also concluded that carriers of the *CYP2C19**2 SNP had increased basal platelet aggregability in P2Y₁₂ reactivity unit (PRU) values assessed by VerifyNow™ method [28]. Indeed, baseline PRU values were significantly higher among IM/PM as compared with either ultra-rapid (URM, $p=0.001$) or extensive metabolizers (EM, $p=0.005$). None of the other SNPs were significantly associated with differences in the basal and 30-day PRU results. Besides, doubling the clopidogrel dose (from 75 mg/day to 150 mg/day) did not result in any significant reduction of platelet reactivity among HTPR patients undergoing CAS.

Although the *CYP2C19**2 allele was found to be significantly associated with increased 30-days PRU values (G/A 212.5 ± 74.8 vs. G/G 166.7 ± 8.6 , $p=0.003$) and lower percentage (%) of platelet inhibition (basal: G/A $17.9\pm22.4\%$ vs. G/G $30.1\pm23.9\%$, $p=0.004$; 30-days: G/A $30.98\pm23.4\%$ vs. G/G $45.4\pm26.5\%$, $p=0.002$), no association with the occurrence of adverse events (TIA, any stroke, MI or death) was detected within the 30 days after the procedure ($p=0.926$).

Overall, patients who are IM/PM for *CYP2C19* exhibited significantly lower clopidogrel antiplatelet activity (i.e., higher baseline PRU and less % inhibition) and were more often non-responders to clopidogrel than those with an URM/EM status. Moreover, no significant differences were found between high- and standard-dose of clopidogrel in IM/PM patients with HTPR.

CYP2C19 Genotypes and Medical Outcomes in Cerebral Endovascular Therapy

In patients with CAD undergoing PCI, the role of *CYP2C19* polymorphisms over clinical outcomes has been well recognized [14,19]. The TRITON-TIMI 38 study, demonstrated that patients carrying *CYP2C19**2 polymorphism had a 3- fold increase of stent thrombosis when compared to noncarriers [15]. Many other studies have supported these results, though the impact of *CYP2C19* variations over clinical outcomes in patients with stable coronary artery disease, ischemic stroke and peripheral artery disease is contradictory [29–32]. To our knowledge, very few studies exploring the potential impact of *CYP2C19* polymorphisms on patients undergoing neurovascular procedures have been reported.

A prospective, longitudinal, observational study by Lin *et al.* (2016) in 108 clopidogrel-treated patients undergoing endovascular treatment was conducted to test association among *CYP2C19* genotypes and clopidogrel responsiveness and clinical outcomes [33]. Participants received DAPT with clopidogrel (75 mg daily) and aspirin (150 mg/day) since at least 3 days before interventions and were then followed up over 3 months. Based on their

findings, authors concluded that individuals who underwent elective neurointervention for intracranial aneurysms or stenosis have increased risk of ischemic events following endovascular treatment, independent of clopidogrel responsiveness, if they are carriers of the *CYP2C19**17 variant [33]. Indeed, they found a significantly higher proportion of *CYP2C19**17 carriers who experienced ischemic events (32.1%) as compared with wild-types (11.4%; $p=0.04$; $OR=3.7$), which remained significant after adjustment for age ($p=0.03$; $OR=4.0$) and *ex vivo* clopidogrel response ($p=0.04$; $OR=4.5$). No significant differences between wild-types and the other known *CYP2C19* genetic variants associated with clopidogrel resistance and adverse cardiovascular outcomes (i.e., *2 and *3) were identified [33].

The gain-of-function *CYP2C19**17 allele is generally thought to be associated with an increased incidence of bleeding events, and hence an increased risk of hemorrhage, given its hyper-functioning [14,19]. However, data on the effects of *CYP2C19**17 are still limited, and the influence of this SNP on clinical outcomes remains controversial. In this study, surprisingly, *CYP2C19**17 was associated with ischemic events instead of hemorrhage. So it seems reasonable that this unexpected finding might suggest the involvement of other pathways in the association between *CYP2C19* and clinical outcomes. Consequently, further studies are needed in order to confirm the influence of *CYP2C19**17 on clinical outcomes in a larger cohort and to understand the mechanisms for increased ischemic events.

The study by Lin *et al.* was limited for a small sample size and several cofounder or other dependent variables were not included in the correlation analysis, such as procedural and anatomical factors [33,34]. It is also important to recognize that poor response to clopidogrel can be an expression of noncompliance to therapy and drug-drug interactions. A prospective study of 125 patients with cerebral aneurysms treated with stent-assisted coiling shows that carriers of LOF *CYP2C19* alleles (*2 or *3, $p=0.001$), and especially in PM ($p=0.004$), were most likely to have clopidogrel resistance. In addition, both *CYP2C19* LOF alleles and clopidogrel resistance were predictors of cerebral ischemic events [35].

Potential complications of endovascular therapy of CAS and cerebral aneurysms

The most important complication associated with CAS is stroke [36]. Other reported complications include myocardial infarction, renal failure, access-related problems (i.e., bleeding, hematoma, pseudoaneurysm, and peripheral embolization), restenosis/thrombosis of the target lesion, hyperperfusion syndrome and carotid stent fracture. Despite CAS remains the preferred procedure among endovascular specialists to treat symptomatic or asymptomatic high-grade (>60 or 70 percent) internal carotid artery narrowing.

Although most of endovascular procedures to treat cerebral aneurysms are performed through minimal invasive technique, they are not exempt of important complications. Thromboembolic complications have been reported in both, unruptured and ruptured aneurysms treatments, with rates ranging from 3.7% to 6.9% [37–39], though this might be highly variable. When a stent is placed alone or in addition to the coil, the intra-procedure risk of thrombi formation and delayed thrombosis could be slightly high [40]. Among several factors that could increase the risk of thromboembolism we could mention: the prolapse of coils into the parent artery or distal branches as well as large aneurysm size

>10mm and neck (>4mm) [41]. Additionally, clopidogrel resistance and *CYP2C19**2 polymorphism have been recently associated with these thromboembolic events [42]. Hence, many groups have recommended testing the patients for possible clopidogrel resistance and based on the result adjust the clopidogrel pre-procedure dose as a key to prevent intra-operative and delayed thrombosis. Despite this, neurointervention guidelines are unclear about what is the best pharmacotherapy approach in patients with hyporesponsiveness to clopidogrel.

Hemorrhage secondary to intra-operative aneurysm rupture represents the most feared complication of intracranial aneurysms embolization due to the resulting significant risk of neurodisability and mortality [43]. The most described risk factors of aneurysm perforation are a small aneurysm size (<3mm) and chronic obstructive pulmonary disease. To date, the role of *CYP2C19**17 polymorphism over adverse outcomes in patients undergoing cerebral aneurysm and pre-medicated with clopidogrel remains unknown. Further studies are warranted to determine whether patients at risk of aneurysm rupture might benefit from clopidogrel phenotype and *CYP2C19* polymorphisms detection in order to determine how these elements can predict negative outcomes in patients with aneurysm perforation. Representative cerebral angiography from a patient with a right superior hypophyseal artery aneurysm with complete coiling embolization is shown in Figure 2.

Implications for Clopidogrel responsiveness

Currently, there are few published studies focused on clopidogrel responsiveness in patients undergoing cerebrovascular minimal invasive procedures. However, some groups report that up to 50% of these patients might be low responders to clopidogrel [42]. Delgado-Almandoz *et al.* found that PRU values of less than 60 or more than 240 were significant associated with major hemorrhagic and thromboembolic complications, respectively, up to 6 months after Pipeline Embolization Device procedures [44]. Other study aiming to determine the relationship between antiplatelet drug resistance and periprocedural thromboembolic events in 96 patients undergoing neurovascular stent-placement procedures, clopidogrel resistance ($p=0.15$) and lack of statin use ($p=0.06$) were predictor of periprocedural thromboembolic complication [45]. Likewise, Goh *et al.* suggested that increased response to clopidogrel may be associated with higher risk of perioperative hemorrhagic complications [46]. However, cut point values of on-treatment platelet reactivity by either VerifyNow test or Light Transmission Aggregometry, have been extrapolated from CAD studies and the best values to define extreme clopidogrel phenotypes in neurovascular patients has not yet been determined. Additionally, there is paucity and contradictory data of the implication that these extreme clopidogrel phenotypes might have in intra-procedure, short-term and long-term cardiovascular outcomes. Similarly, there are no reported prospective randomized trials that demonstrate a superior benefit of targeted pharmacological therapy based on platelet function testing for this group of patients [47,48].

Concluding Remarks

Better experimental designs are required to define the real effect of *CYP2C19* genotypes on clinical outcomes and to determine whether a genotype-guided therapeutic assessment could

be valuable in decreasing clinical adverse events in this special group of patients. To date, studies of clopidogrel hyporesponsiveness in patients with neurointerventional procedures remain underpowered due to small sample. Additionally, the interaction between clopidogrel and proton-pump inhibitors (the most important drug-drug interaction ever described for clopidogrel) has not been fully considered, which represents an important limitation to be acknowledged. Research findings need to be replicated in larger cohorts to verify results. Given a growing body of evidence supporting the impact of *CYP2C19**2 and *17 on clopidogrel responsiveness and clinical outcomes, we firmly believe it is reasonable to recommend the genotype testing in patients planned for neurointerventional procedures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.

Table 1

Biomarkers selected for the review, based on the list proposed by the PharmGKB website (<https://www.pharmgkb.org/molecule/PA449053>), the US FDA and CPIC guidelines for the pharmacogenetics of clopidogrel [14, 19].

Biomarker (Pharmacogene)	Alleles	Refs.
<i>CYP2C19</i> [¶]	*2, *3, *17	[14,19,49]
<i>PON1</i>	p.Q192R; rs662	[14,19,50]
<i>ABCB1</i>	c.3435C>T; rs1045642	[14,19,49,51]
<i>P2RY12</i>	rs6785930; rs6787801; rs6809699, rs2046934/Haplotypes H1 and H2	[14,19,52–54]
<i>B4GALT2</i>	c.909C>T; c.366G>C	[55]
<i>CES1</i>	rs71647871; rs71647872; rs8192950	[56–57]
<i>CYP2B6</i>	*5, *5A, *6, *9	[15]
<i>CYP2C9</i>	*2, *3	[58–60]
<i>CYP3A4</i>	*22/rs35599367; rs2242480	[61]
<i>CYP1A2</i>	rs762551 (–163C>A)	[62]
<i>PEAR1</i>	rs12041331	[63]
<i>IRS-1</i>	rs13431554, rs10205923	[64]

[¶]Level of evidence 1A, with known clinical implications, according to PharmGKB website (<https://www.pharmgkb.org/molecule/PA449053>)