Pharmacogenomic considerations for antiplatelet agents: the era of precision medicine in stroke prevention and neurointerventional practice

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Abstract Antiplatelet drugs are widely utilized in the setting of primary stroke prevention, secondary stroke prevention, and neuroendovascular device-related stroke prevention. These medications are effective in general, although significant variability in drug activity exists between patients. Although this variation may be related in part to a multitude of factors, a growing body of evidence suggests that individual genotypes are a main contributor. The PharmGKB database was mined to prioritize genetic variants with potential clinical relevance for response to aspirin, clopidogrel, prasugrel, and ticagrelor. Although variants were reported for all drugs, the highest level of evidence was found in cytochrome P450 (CYP450) genotype variation related to clopidogrel response. Individual genetic influences have an impact on the pharmacodynamics of antiplatelet agents. Current clinical practice for stroke prevention is primarily empiric or guided by functional assays; however, there now exists a third potential pathway to base treatment decisions: genotype-guided treatment.

INTRODUCTION

Antiplatelet agents are one of the cornerstones of stroke prevention and are widely utilized in the setting of primary stroke prevention, secondary stroke prevention, and neuroendovascular device-related stroke prevention. Their utility is highlighted in several seminal works, which underscore their importance in preventing brain-related ischemia from a diverse array of pathologic processes (Hass et al. 1989; Mohr et al. 2001; Diener et al. 2004; Chimowitz et al. 2005; Markus et al. 2005). Although these drugs are overwhelmingly effective from a population-based standpoint in clinical studies, their efficacy in any single patient may be varied based on a multitude of factors, primarily relating to genotype.

Aspirin (acetylsalicylic acid), the most common antiplatelet drug in use, has a long appreciated resistance phenomenon (Gum et al. 2003; Krasopoulos et al. 2008). With respect to neurovascular disease, patients who experience recurrent ischemia despite adherence to aspirin therapy have been termed aspirin “failures” (Helgason et al. 1993; Bornstein et al. 1994). The addition of a second antiplatelet agent likely increases efficacy, although the mechanism of polytherapy’s effect is not always clear. Does an additional agent act synergistically to further decrease already diminished platelet reactivity, or does it simply provide effective antiplatelet activity when an individual is a nonresponder to aspirin? In the latter scenario, continuation of aspirin therapy would provide no benefit while exposing the patient to potential adverse effects, such as gastrointestinal ulcer.
Clopidogrel, another commonly utilized drug, is well known for exhibiting a resistance phenomenon, which is associated with adverse clinical events (Matetzky et al. 2004; Wang et al. 2005). The prevalence of clopidogrel resistance ranges from 4% to 44%, depending on the population studied (Gurbel and Tantry 2007). The often essential nature of these medications mandates that an effective antiplatelet response is achieved, as failure could result in substantial morbidity or mortality.

Currently, many patients on dual antiplatelet therapy undergo platelet function testing prior to neurointerventional procedures using a variety of commercially available assays. There are several limitations to many of the currently available platelet function assays, including variability in results across assays, dependence of results on patient hematocrit and platelet counts, and high costs. No high-level evidence exists to support or refute the use of platelet function testing on neurovascular clinical practice. Additionally, the variable clinical practices inspired by the results of these tests have not been well studied.

The ability to better understand the relationship between genotype and drug activity may be able to improve stroke prevention paradigms for neurologists and neurointerventionalists alike. With the ability to perform rapid, accurate, and increasingly lower cost genomic testing, the opportunity to select a specific antiplatelet therapy based on a patient’s genotype is approaching clinical practice. The potential benefits of genotype-informed antiplatelet selection include both improved efficacy (stroke prevention) and reduced toxicity (bleeding complications). In this review, we highlight the common and rare genomic variants known to be associated with resistance to drugs most frequently used in clinical practice. From there, we explore future directions of how genomic testing can be integrated into clinical practice to improve stroke prevention.

**DATA SYNTHESIS**

Aspirin, clopidogrel, ticagrelor, ticlopidine, and prasugrel were selected for study on the basis of being commonly used in clinical practice. The PharmGKB database (https://www.pharmgkb.org; accessed Oct 22 2018) was mined for variants associated with these drugs. Reports were cross-referenced with original source manuscripts. Annotated variants were then sorted based on levels of evidence as previously described (Whirl-Carrillo et al. 2012). Only the highest quality of annotations (levels 1 and 2) were used for reporting purposes. If high-quality annotations did not exist, then the next two levels of quality were reported. Insufficient genotype data were available to report for ticlopidine. Variants and citations are provided as representative examples and may not represent all information that is available on an allele or be comprehensive of all candidate alleles.

**ANTIPLATELET AGENTS**

**Aspirin**

Aspirin (acetylsalicylic acid) is an ubiquitous first-generation antiplatelet agent with a long clinical prescribing history. Its primary mechanism of antiplatelet action is attributed to blocking the synthesis of thromboxane A2 from arachidonic acid by irreversible inhibition of prostaglandin G/H synthase 1 (PTGS1, also known as cyclooxygenase 1) within platelets (Vane 1971). Although effective, there are certain individuals resistant to aspirin’s effects. In patients with cardiovascular disease, it has been reported that about 5% of patients are nonresponders to aspirin based on ex vivo testing (Gum et al. 2001, 2003), with up to 23% considered semiresponders (Gum et al. 2001). Clinically, the most concerning aspect of aspirin resistance is an increased risk of adverse events compared to patients who are aspirin
sensitive, a phenomenon that has been shown in prospective analyses of cardiovascular pa-
tients (Gum et al. 2003; Marcucci et al. 2006; Chen et al. 2007).

Resistance to any antiplatelet agent may be multifactorial. Impaired bioavailability, drug–
drug interactions, up-regulation of nonplatelet sources of thromboxane biosynthesis, in-
creased platelet turnover, and patient noncompliance are thought to be mechanisms of as-
pirin resistance (Hankey and Eikelboom 2006). Although these mechanisms likely play a role
in a patient’s response to aspirin, genetic variability in PTGS1 and other genes has also been
correlated with functional aspirin resistance (see Table 1).

### Clopidogrel (Plavix)

Clopidogrel is another commonly prescribed antiplatelet drug, with generic formulations
available in the United States and many other countries. The ingested form is a prodrug
and requires two sequential oxidative steps within the liver to achieve biological activity
via an active metabolite, which consists of irreversible inhibition of the platelet P2Y12 aden-
osine diphosphate receptor.

Although it is not typically considered a first-line agent for stroke prevention, clopidogrel
is often combined with aspirin for dual antiplatelet therapy. Common indications include
clinical failure of aspirin monotherapy (e.g., ischemic infarct despite aspirin compliance)
and neurovascular stent placement (e.g., cervical carotid or intracranial artery stent).
Though clopidogrel is used when there is a perceived increased risk of cerebral ischemia,
there is variation in patient responsiveness to this drug, and a fair percentage of the popu-
lation has some resistance. It has been shown that up to half of individuals may have de-
creased platelet inhibition with this drug, mostly related to common polymorphisms of
CYP2C19 alleles (see Table 2; Brandt et al. 2007). In fact, the variability of response to this
drug is so prevalent, the Clinical Pharmacogenetics Implementation Consortium (CPIC)
guideline recommends alternative antiplatelet therapy for acute coronary syndrome/percu-
taneous coronary intervention individuals predicted to be intermediate or poor metabolizers
based on genotype, underscoring its clinical relevance (Scott et al. 2013).

### Table 1. Aspirin—variants

| References                     | Level | Population       | Gene  | Variant (GRCh38) | Notes                                                                 |
|--------------------------------|-------|------------------|-------|------------------|----------------------------------------------------------------------|
| Verschuren et al. 2013; Lepäntalo et al. 2006 | 2b    | Acute coronary syndrome | PTGS1 | rs10306114       | Patients with the AA genotype who are treated with aspirin may have a decreased, but not absent, risk for nonresponse to aspirin as compared to patients with the AG or GG genotype. |
| Matsubara et al. 2008; Fujiwara et al. 2007 | 2b    | Healthy volunteer | GP1BA | rs6065           | Patients with the CC genotype may have an increased risk for aspirin resistance as compared to patients with the CT or TT genotype. |
| Hwang et al. 2011; Marcucci et al. 2012; Li et al. 2013; Kupstyte et al. 2015; McDonough et al. 2015 | 2b    | PCI; acute coronary syndrome | CYP2C19 | rs4244285     | Patients with the *2/*2 diplotype may have an increased incidence of hemorrhage, stroke, and an overall worse response to clopidogrel and aspirin, such as decreased platelet reactivity, as compared to patients with the *1/*1, *1/*17, *17/*17, *1/*2 diplotype. However, this has been contradicted in some studies. |

(PCI) Percutaneous coronary intervention, (GRCh38) Genome Reference Consortium Human Build 38, (ACS) acute coronary syndrome, (CAD) coronary artery disease.
Table 2. Clopidogrel—variants

| References | Level | Population | Gene | Variant (GRCh38) | Notes |
|------------|-------|------------|------|------------------|-------|
| Wu et al. 2012; Simon et al. 2009; Mega et al. 2009; Wallentin et al. 2010; Lee et al. 2009 | 1A | Acute coronary syndrome; acute coronary syndrome undergoing PCI | CYP2C19 | rs4986893 | Patients with the GG genotype (1) may have increased metabolism of clopidogrel and formation of active drug metabolite, resulting in increased response and (2) may have a decreased, but not absent, risk for secondary cardiovascular events when treated with clopidogrel as compared to patients with the AA or AG genotype. |
| Anselmi et al. 2013; Sorich et al. 2014; Rideg et al. 2011; Simon et al. 2009; Roberts et al. 2012; Gong et al. 2012 | 1A | Healthy volunteers; acute coronary syndrome; acute coronary syndrome undergoing PCI; PCI | CYP2C19 | Multiple | Patients with two functional CYP2C19 alleles (1/1) (1) may have increased metabolism of clopidogrel and (2) may have a decreased, but not absent, risk for secondary cardiovascular events when treated with clopidogrel as compared to patients with one or two CYP2C19 loss-of-function alleles (*2 rs4244285, *3 rs4986893, *4 rs28399504, *5 rs56337013, *6 rs72552267, *8 rs41291556). |
| Sun et al. 2015; Verschuren et al. 2013; Hulot et al. 2011; Price et al. 2012 | 1A | PCI; acute coronary syndrome | CYP2C19 | rs4244285 | Patients with the GG genotype (1) may have sufficient metabolism of clopidogrel and increased formation of active drug metabolite and (2) may have a decreased risk for secondary cardiovascular events with clopidogrel as compared to patients with the AA or AG genotype. |
| Simon et al. 2009; Mega et al. 2009; Wallentin et al. 2010 | 1A | Acute coronary syndrome | CYP2C19 | rs28399504 | Patients with the AA genotype (1) may have increased metabolism of clopidogrel and (2) may have a decreased, but not absent, risk for secondary cardiovascular events when treated with clopidogrel as compared to patients with the GG and AG genotype. |
| Wu et al. 2012; 22028352; Wallentin et al. 2010; Tiroch et al. 2010 | 1A | Acute coronary syndrome, PCI | CYP2C19 | rs12248560 | Patients with the CC genotype (*1/*1) (1) may have decreased activation of clopidogrel, (2) may have a decreased, but not absent, risk for bleeding with clopidogrel as compared to patients with the CT or TT genotype, and (3) may have an increased risk for adverse cardiovascular events as compared to patients with a CT or TT genotype. Other genetic, including CYP2C19 loss-of-function alleles (e.g., *2 rs4244285, *3 rs4986893), and clinical factors may also influence a patient’s risk for bleeding and adverse cardiovascular events. (Continued on next page.) |
The CPIC recommendations are supported by several notable clinical studies. A subgroup analysis of more than 10,000 patients in the PLATO trial who underwent genotype analysis for various CYP2C19 single-nucleotide polymorphisms found that patients on clopidogrel with loss-of-function CYP2C19 alleles had higher rates of cardiovascular death, myocardial infarction, and stroke at 12 months than those without. In addition, clopidogrel patients with gain of function alleles had higher rates of major bleeding than those without (Wallentin et al. 2010). Recently, implementation of a genotype-driven prediction model for clopidogrel resistance was shown to reduce cardiovascular events in patients undergoing PCI by nearly threefold (Cavallari et al. 2018). In addition, data that correlate results of functional assays with clinical outcome, demonstrating the association between decreased platelet inhibition and clinical events, has been published (Matetzky et al. 2004). Large-scale efforts are underway to identify additional determinants of patient response to clopidogrel by cross-referencing genetic and platelet function data (Bergmeijer et al. 2018).

Clopidogrel, perhaps more so than any other drug, has several known nongenetic factors that influence response in any one individual, making interpretation of genetic variation challenging. Several prevalent conditions including diabetes mellitus and renal impairment are associated with blunted responses to clopidogrel (Geisler et al. 2007; Best et al. 2008; Park et al. 2009). Additionally, several common medications including proton pump inhibitors appear to reduce the antiplatelet effects of clopidogrel through competition for shared metabolic pathways (CYP2C19) in the liver (Gilard et al. 2006, 2008; Ho et al. 2009).

Prasugrel (Effient)
Prasugrel is a next-generation antiplatelet agent that inhibits ADP-platelet activation by irreversibly binding to the P2Y12 receptor. Like clopidogrel, the ingested form of the drug needs to be converted to an active metabolite. This occurs both by CYP450-dependent conversion and by carboxylesterase 2-mediated hydrolysis during absorption (Huber et al. 2009; Mega et al. 2009; Farid et al. 2010). In contrast to clopidogrel, prasugrel tends to have a more efficient absorption and is more rapidly converted to its active metabolite. Furthermore, although CYP450 genetic variants exist, many do not have a functional consequence on prasugrel activity (Brandt et al. 2007; Mega et al. 2009, 2010; Varenhorst et al. 2009). There are isolated reports of prasugrel resistance (Alexopoulos 2012; Fiore et al. 2014), and preliminary research suggests that polymorphisms in PEAR1 may contribute to variation in pharmacodynamics response (see Table 3; Xiang et al. 2013; Fisch et al. 2015).

Despite the potential advantage of averting resistance phenomenon seen with clopidogrel, the largest randomized trial of prasugrel versus clopidogrel (performed in patients with coronary disease) demonstrates conflicting evidence regarding increased hemorrhagic complications between different subgroups of patients (Wiviott et al. 2007; Montalescot et al. 2009).
This trial also demonstrated the feasibility of investigating the genetic underpinnings of platelet functionality and clinical outcome (Mega et al. 2010). Comparison of these drugs for the treatment of patients with neurovascular disease has not been performed, and widespread adoption of prasugrel has not occurred.

**Ticagrelor (Brilinta)**

Ticagrelor is another next-generation antiplatelet agent. Uniquely, the drug does not require in vivo bioactivation in order to reversibly inhibit the P2Y12 receptor (Schömig 2009). Still, it undergoes metabolism via CYPP450 3A4 and 3A5 metabolism to generate an equipotent metabolite, AR-C124910XX (Teng et al. 2010; Giorgi et al. 2011). Ticagrelor has been studied extensively in the cardiovascular literature, and a randomized trial (PLATO) with subgroup analysis of genetic polymorphisms concluded that it is more efficacious at preventing cardiovascular death, myocardial infarction, or stroke than clopidogrel, irrespective of genetic makeup (Wallentin et al. 2010). Enthusiasm for the drug in stroke prevention in particular was tempered by a head-to-head randomized trial of aspirin and ticagrelor,
yielding no difference in the rate of stroke, myocardial infarction, or death in the follow-up period after stroke or transient ischemic attack (Johnston et al. 2016).

The influence of genetic polymorphisms on ticagrelor activity is not well studied. A genome-wide association study of the patients with acute coronary syndrome in the above-mentioned PLATO study revealed three loci (SLCO1B1, UGT2B7, and CYP3A4) that potentially influence its pharmacokinetics to a modest degree (Varenhorst et al. 2015). In this limited study, no difference in efficacy or safety was observed based on the variation in ticagrelor levels, leading the authors to conclude that use of ticagrelor does not require genetic testing. Other preliminary studies have identified loci potentially affecting drug levels or activity, with unclear clinical significance (see Table 4).

### DISCUSSION

Individual genetic influences have an impact on the pharmacokinetics and pharmacodynamics of antiplatelet agents. Although clopidogrel is one of the most variable in terms of individual response, it remains one of the most frequently prescribed medications for secondary stroke prevention and device-related stroke prevention. Given the limitations of clopidogrel, there is shifting precedence in the cardiology literature from using clopidogrel to using either prasugrel or ticagrelor along with aspirin for dual antiplatelet therapy. A recent joint guideline from the American College of Cardiology/American Heart Association (Level of Evidence B recommendation) states it is “reasonable to use prasugrel or ticagrelor in preference to clopidogrel” for most patients with acute coronary syndromes treated with or

| Reference      | Level | Population          | Gene  | Variant (GRCh38) | Notes                                                                                                                                 |
|----------------|-------|---------------------|-------|------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Varenhorst et al. 2015 | 3     | Acute coronary syndrome | SLCO1B1 | rs113681054      | Patients with the TT genotype and acute coronary syndrome may have decreased concentrations of ticagrelor compared to patients with the CC and CT genotypes. |
| Varenhorst et al. 2015 | 3     | Acute coronary syndrome | CYP3A4  | rs62471956       | Patients with the GG genotype and acute coronary syndrome may have decreased concentrations of ticagrelor compared to patients with the AA or AG genotypes. |
| Varenhorst et al. 2015 | 3     | Acute coronary syndrome | UGT2B7  | rs61361928       | Patients with the TT genotype and acute coronary syndrome may have decreased concentrations of ticagrelor compared to patients with the CT genotype. |
| Varenhorst et al. 2015 | 3     | Acute coronary syndrome | SLCO1B1 | rs4149056        | Patients with the TT genotype and acute coronary syndrome may have decreased concentrations of ticagrelor compared to patients with the CC and CT genotypes. |
| Varenhorst et al. 2015 | 3     | Acute coronary syndrome | CYP3A4  | rs56324128       | Patients with the CT genotype and acute coronary syndrome may have increased concentrations of ticagrelor compared to patients with the TT genotype. |
| Li et al. 2017 | 4     | Healthy volunteer   | PEAR1  | rs12041331       | Patients with the GG genotype may have deceased inhibition of platelet aggregation in response to ticagrelor compared to patients with the AA genotype. |
| Li et al. 2017 | 4     | Healthy volunteer   | PEAR1  | rs12566888       | Patients with the TT genotype may have lower maximal platelet aggregation than patients with the GT genotype when taking ticagrelor. |
| Li et al. 2017 | 4     | Healthy volunteer   | PEAR1  | rs4661012        | Patients with the TT genotype may have decreased inhibition of platelet aggregation when taking ticagrelor compared to patients with the GG genotype. |
without stenting (Levine et al. 2016). Along these lines, the rate of prescribing either prasugrel or ticagrelor is approaching the rate of prescribing clopidogrel for these patients (Dayoub et al. 2018). Similar use of next-generation antiplatelet agents has not yet occurred for stroke prevention. With the consequences of antiplatelet therapy being so profound in neurological disease—both beneficial and potentially harmful—further consideration should be given to investigating the potential of individualized regimens.

Several recent transformational advances in medicine have occurred to facilitate the potential for individualized pharmacologic stroke prevention. In terms of discovery potential, the ability to perform high-throughput, large-scale sequencing in a large population is now a reality. In a study of more than 50,000 patients, whole-exome sequencing was performed and correlated with phenotypes extracted from the clinical medical record to discover novel disease-associated variants (Dewey et al. 2016). For neurovascular patients, this powerful technique has the potential to survey the entire genomic landscape in an unbiased fashion. Exome sequencing has been applied in limited fashion to identify novel variants associated with platelet reactivity to clopidogrel, an approach that may be fruitful in larger studies (Scott et al. 2016; Lewis and Shuldiner 2017). This is an attractive approach, linking genetic data with platelet function assays and clinical outcomes to study a population comprehensively, forgoing the need to make a priori inferences about clinical significance.

Beyond discovery, genomic characterization is also poised to transform therapeutic decision-making for neurovascular patients. In a proof-of-principle study, investigators randomized patients to genotype-based or clinically based (typical) dosing of warfarin to prevent venous thromboembolism after orthopedic surgery (Gage et al. 2017). Because warfarin has variation in bioactivity secondary to different genotypes, similar to antiplatelet agents like clopidogrel, it was hypothesized that genotype-based dosing would optimize treatment within the therapeutic index. Indeed, the genotype-based dosing group experienced a lower combined risk of bleeding, international normalized ratio of 4 or greater, venous thromboembolism, or death. This idea was recently replicated for clopidogrel in cardiovascular disease, in which patients were treated with prasugrel or ticagrelor in the event of pharmacogenetic evidence of clopidogrel resistance (Cavallari et al. 2018). Patients with predicted clopidogrel resistance, assessed by CYP2C19 genotyping for loss-of-function alleles, who were treated with an alternative antiplatelet agent experienced adverse thrombotic events at a lesser rate than those treated with clopidogrel and at a similar rate to those without clopidogrel resistance who were treated with clopidogrel. In similar fashion, could genotype-based antiplatelet selection improve the safety and efficacy of treatment in neurovascular patients? Further study is needed (Table 5).

Certain challenges arise when translating genetic discovery to clinical practice for stroke prevention. For one, robust genotype–phenotype associations do not yet exist with regard to genotype and response to antiplatelet therapy in this specific population. Given the widespread use of platelet function assays (albeit inconsistent in frequency and with different techniques) and the availability to perform follow-up surveillance neuroimaging, clinical data can be collected to bridge the understanding between genetic variation and clinical outcomes. Additionally, the umbrella of neurovascular disease encompasses a heterogeneous group of pathophysiology, from cervical carotid artery stenosis to flow-diverting stents for giant aneurysms, and identifying patients at similar risk/mechanism for thrombosis is essential.

Although current clinical practice for stroke prevention is primarily empiric antiplatelet therapy with aspirin and/or clopidogrel, a large proportion of the population with genetic variation resulting in varied drug bioactivity exists. Whether this variation stems from genetic ancestry or otherwise (Johnson et al. 2017), genotyping is essential for a better understanding. For patients undergoing interventional procedures, ex vivo platelet function assays used to tailor dosing regimens to meet arbitrary therapeutic windows is fraught with individual experimentation. In addition to purely empiric treatment and functional assay-guided

Competing Interest Statement
The authors have declared no competing interest.

Referees
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treatment, a third potential pathway to base treatment decisions is now available: genotype-guided treatment.

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