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Prasugrel Therapy and *CYP* Genotype

Laura Dean, MD[1]

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Introduction

Prasugrel is a third-generation thienopyridine platelet inhibitor used in the management of patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Prasugrel is used to reduce thrombotic cardiovascular events, such as stent thrombosis, myocardial infarction, and stroke in these patients. Prasugrel, along with other antiplatelet agents such as clopidogrel and ticagrelor, inhibits platelet activation by irreversibly binding to the platelet receptor, P2RY12.

Prasugrel is metabolized to its active metabolite primarily by CYP3A5 and CYP2B6, and to a lesser extent by CYP2C9 and CYP2C19. The FDA-approved label for prasugrel states that genetic variations in *CYP2B6*, *CYP2C9*, *CYP2C19*, or *CYP3A5* genes do not have a relevant effect on prasugrel pharmacokinetics and the generation of its active metabolite or its inhibition of platelet aggregation in healthy subjects, patients with stable atherosclerosis, or ACS (1).

Another commonly prescribed antiplatelet is the second-generation thienopyridine clopidogrel, which is bioactivated primarily by CYP2C19. Consequently, clopidogrel is less effective among patients with decreased or no function variant alleles in the *CYP2C19* gene. In contrast, *CYP2C19* variants are not associated with a decrease in effectiveness of prasugrel, which is a more potent antiplatelet agent than clopidogrel, but has a higher risk of bleeding (2-5).

Drug: Prasugrel

Prasugrel is a third-generation thienopyridine antiplatelet agent that binds irreversibly to the P2RY12 receptor and inhibits ADP-mediated platelet activation and aggregation. Other P2RY12 receptor blockers include clopidogrel and ticagrelor.

As an antiplatelet agent, prasugrel inhibits the formation of blood clots in the coronary, peripheral, and cerebrovascular arteries among patients with acute coronary syndrome (ACS).

ACS reflects a decreased blood flow in the coronary arteries, and includes unstable angina, which occurs suddenly, often at rest or with minimal exertion. Unstable angina may be new in onset or it may occur with less exertion than previously. Another form of ACS is a myocardial infarction (MI), which may be classified as "STEMI" or "NSTEMI" based on EKG findings. EKG findings that include ST-segment elevation is termed "ST segment elevation MI" (STEMI). If no ST segment elevation is present but myocardial biomarkers such as troponin I or T are increased, the term "non-ST segment elevation MI" (NSTEMI) is applied.

Author Affiliation: 1 NCBI; Email: mgs@ncbi.nlm.nih.gov.

Patients with ACS are usually treated with a P2Y12 receptor blocker and aspirin (called dual antiplatelet therapy, DAPT) to reduce the risk of developing a coronary artery thrombus. Platelet adhesion and aggregation are early stages in the formation of a thrombus, which may occlude the coronary artery. Patients who undergo PCI are at risk of stent occlusion via this mechanism.

A large trial, TRITON-TMI 38, compared prasugrel with clopidogrel in 13,608 patients with ACS who were undergoing PCI. Prasugrel was found to provide more potent platelet inhibition than clopidogrel: after 15 months, the patients treated with prasugrel had a lower incidence of the combined endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke as compared with patients treated with clopidogrel (9.9% vs. 12.1%) (2, 3). However, prasugrel was associated with a higher risk of bleeding, leading to the FDA warning that prasugrel use is contraindicated in patients with active pathological bleeding, or a history of stroke or transient ischemic attack (TIA) (4, 5).

Prasugrel inhibits ADP-induced platelet aggregation by selectively binding to the platelet purinergic receptor, P2RY12. Because prasugrel is a pro-drug, it requires conversion into an active metabolite before it can act as an antiplatelet agent. Prasugrel is rapidly metabolized to thiolactone, which is then converted to an active metabolite by CYP3A5 and CYP2B6, and to a lesser extent by CYP2C9 and CYP2C19.

The active prasugrel metabolite (R-138727) contains a reactive thiol group, which forms a disulfide bridge with a free cysteine residue on the P2RY12 receptor. Once irreversibly bound to prasugrel, the receptor is unable to bind ADP, and platelet activation via this pathway is prevented for the rest of the platelet's lifespan of about 10 days (6).

Despite the general efficacy of clopidogrel as an antiplatelet agent, interindividual variability in metabolite levels, platelet inhibition, and clinical response has been reported. It has been estimated that between 16–50% of patients treated with clopidogrel have high on-treatment platelet reactivity (HTPR), indicating that despite clopidogrel treatment, a portion of P2RY12 receptors are not blocked (7). This is due, in part, to genetic variants in the *CYP2C19* gene, which encodes the principal hepatic enzyme involved in converting clopidogrel to its active metabolite. Patients that carry no function *CYP2C19* alleles (e.g., *CYP2C19*2*) have reduced plasma active clopidogrel metabolites and an increased risk for HTPR.

In contrast, there is no relevant effect of genetic variation in *CYP3A5*, *CYP2B6*, *CYP2C9*, or *CYP2C19* on the prasugrel pharmacokinetics and generation of active metabolites, or its inhibition of platelet aggregation (8-12). Therefore, although both clopidogrel and prasugrel form active metabolites with similar potency, prasugrel is a more potent antiplatelet agent than clopidogrel due to the more efficient formation of the active metabolite from the prodrug (13).

Although prasugrel is more effective than standard-dose clopidogrel, DAPT with clopidogrel and aspirin remains the standard of care at some institutions for some patients with ACS undergoing PCI (14). This is mainly because clopidogrel has a lower bleeding risk and is less expensive (15). However, the availability of *CYP2C19* genetic testing can facilitate personalized antiplatelet therapy, as individuals with impaired CYP2C19 activity could be identified and offered an alternative antiplatelet agent, such as prasugrel (16-19). Recent studies have found that *CYP2C19*-genotype guided antiplatelet therapy results in a higher likelihood of achieving a therapeutic level of on-treatment platelet reactivity (20-22), which may also be cost effective among ACS patients undergoing PCI (23).

The Cytochrome P450 Superfamily

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The CYP450 genes are highly polymorphic and can result in no, decreased, normal, or increased enzyme activity.

CYP2C19, CYP2C9, CYP3A5, and CYP2B6 are involved in the metabolism of prasugrel, but genetic variations in these genes do not appear to influence the pharmokinetics of prasugrel. In contrast, genetic variation in the *CYP2C19* gene may lead to decreased effectiveness of the related drug, clopidogrel. To read more about CYP variants and the clopidogrel drug response, please see "Clopidogrel Therapy and *CYP2C19* Genotype".

Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are currently available for the genes *CYP2C19*, *CYP2C9*, *CYP3A5*, and *CYP2B6*. Given that the formation of the active metabolite of prasugrel is not known to be affected by CYP variants, genetic testing prior to the use of prasugrel is not currently recommended.

For clopidogrel, its effectiveness is dependant on its activation to an active metabolite, principally by CYP2C19. Therefore, the FDA states that tests that identify a patient's CYP2C19 genotype can be used as an aid to determining therapeutic strategy.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA): In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.

[...]

In TRITON-TIMI 38, prasugrel reduced ischemic events (mainly nonfatal MIs) and increased bleeding events relative to clopidogrel. The findings are consistent with the intended greater inhibition of platelet aggregation by prasugrel at the doses used in the study. There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel's active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel's active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. Moreover, certain proton pump inhibitors, widely used in the ACS patient population and used in TRITON-TIMI 38, inhibit CYP2C19, thereby decreasing formation of clopidogrel's active metabolite. Thus, reduced-metabolizer status and use of proton pump inhibitors may diminish clopidogrel's activity in a fraction of the population, and may have contributed to prasugrel's greater treatment effect and greater bleeding rate in TRITON-TIMI 38. The extent to which these factors were operational, however, is unknown.

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[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

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