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Prasugrel Therapy and *CYP* Genotype

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Introduction

Prasugrel (also known as Efient) is a third-generation thienopyridine platelet inhibitor used in individuals with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Prasugrel is prescribed to reduce thrombotic cardiovascular events, such as stent thrombosis, myocardial infarction, and stroke in these individuals. Along with other antiplatelet agents such as clopidogrel and ticagrelor, prasugrel inhibits platelet activation by irreversibly binding to the platelet receptor, P2RY12. (1)

Prasugrel is metabolized into 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 significantly affect prasugrel's pharmacokinetics, the generation of its active metabolite, or its inhibition of platelet aggregation in healthy subjects, individuals with stable atherosclerosis, or those with ACS (1).

Another commonly prescribed antiplatelet agent is the second-generation thienopyridine clopidogrel, which is bioactivated primarily by CYP2C19. As a result,, clopidogrel is less effective in individuals with decreased or non-function variant alleles of the *CYP2C19* gene. In contrast, *CYP2C19* variants do not decrease the effectiveness of prasugrel, which is a more potent antiplatelet agent compared to clopidogrel, though it carries a higher risk of bleeding (2, 3, 4, 5).

Drug: Prasugrel

Prasugrel is a third-generation thienopyridine antiplatelet agent that binds irreversibly to the P2RY12 receptor and inhibits adenosine diphosphate (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 individuals with ACS.

A decrease in blood flow in the coronary arteries, known as ACS, includes unstable angina, which occurs suddenly, often at rest or with minimal exertion. Unstable angina may be new in onset or may occur with less exertion than previously. Another form of ACS is a myocardial infarction (MI), which may be classified as ST-segment elevation myocardial infarction (STEMI), or non-ST-segment elevation myocardial infarction

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(NSTEMI) based on electrocardiogram (EKG) findings. A STEMI is identified when EKG findings show ST-segment elevation. If no ST-segment elevation is present but myocardial biomarkers such as troponin I or T are increased, the term NSTEMI is applied.

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

The TRITON-TMI 38 trial compared prasugrel with clopidogrel in 13,608 individuals with ACS undergoing PCI. Prasugrel provided more potent platelet inhibition than clopidogrel: after 15 months, individuals treated with prasugrel had a lower incidence of cardiovascular death, nonfatal MI, or nonfatal stroke as compared with those treated with clopidogrel (9.9% versus 12.1%) (2, 3). However, prasugrel was associated with a higher risk of bleeding, leading to the FDA warning that its use is contraindicated in individuals 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 P2RY12. As a pro-drug, prasugrel requires conversion into its active metabolite to function as an antiplatelet agent. It is rapidly metabolized to thioacetone, which is further 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 that 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 platelet's lifespan, approximately 10 days (6).

Despite the general efficacy of clopidogrel, interindividual variability in metabolite levels, platelet inhibition, and clinical response has been observed. It has been estimated that between 16–50% of individuals treated with clopidogrel exhibit high on-treatment platelet reactivity (HTPR), meaning that some P2RY12 receptors remain unblocked (7). This is partially due to genetic variants in the *CYP2C19* gene, which encodes the enzyme responsible for converting clopidogrel to its active metabolite. Individuals with no-function *CYP2C19* alleles (for example, *CYP2C19*2*) have reduced plasma levels of the active clopidogrel metabolites and an increased risk for HTPR.

In contrast, genetic variation in *CYP3A5*, *CYP2B6*, *CYP2C9*, or *CYP2C19* does not have a relevant effect on the prasugrel pharmacokinetics, active metabolite formation, or platelet aggregation inhibition(8, 9, 10, 11, 12). Therefore, although both clopidogrel and prasugrel form active metabolites with similar potency, prasugrel is a more potent antiplatelet agent due to its more efficient active metabolite formation (13).

While prasugrel is more effective than standard-dose clopidogrel, DAPT with clopidogrel and aspirin remains the standard of care at some institutions for certain ACS individuals undergoing PCI (14). This preference is mainly because clopidogrel has a lower bleeding risk and is less expensive (15). However, the availability of *CYP2C19* genetic testing allows for personalized antiplatelet therapy, where individuals with impaired CYP2C19 activity can be identified and offered an alternative antiplatelet agent, such as prasugrel (16, 17, 18, 19). Recent studies have shown that *CYP2C19*-genotype guided antiplatelet therapy results in the therapeutic goal of reduced on-treatment platelet reactivity more frequently than standard therapy (20, 21, 22), which may also be cost-effective in ACS individuals 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, which can result in no, decreased, normal, or increased enzyme activity.

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

Conversely, administration of prasugrel is not expected to impact the efficacy of other medications that depend on CYP2C19, CYP2C9, CYP3A5, or CYP2B6 metabolism, despite in vitro assays showing an induction of CYP3A enzymes (1, 24, 25).

Genetic Testing

The NIH Genetic Testing Registry (GTR) lists genetic tests available for *CYP2C19*, *CYP2C9*, *CYP3A5*, and *CYP2B6* genes. Since the formation of the active metabolite of prasugrel is not known to be affected by CYP variants, genetic testing before prasugrel use is not recommended.

For clopidogrel, its effectiveness depends on its activation to an active metabolite, primarily by CYP2C19. Therefore, the FDA states that tests identifying an individual's CYP2C19 genotype can be used as an aid in 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.

2024 Statement from the US Food and Drug Administration (FDA): There is 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.

[...]

Prasugrel can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes.

Please review the complete therapeutic recommendations that are located here: (1)

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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.

Version History

Version 1.0 of this chapter was published on April 10, 2017.

Version 1.1 of this chapter was published on October 15, 2024. This minor revision features an update to a more recent FDA-approved drug label reference, inclusion of references for international drug package labelling (Canada, Japan). There are no changes to the recommendations or guidelines for genotype-guided dosing of this medication relative to the prior version.

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