CYP2C19 Variant Analysis for Clopidogrel Response

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is CYP2C19 testing for clopidogrel response

Definition

Clopidogrel (Plavix®) is a prodrug that must be converted by CYP2C19 to an active form to inhibit clot formation. Variants in the CYP2C19 gene can result in reduced or enhanced enzyme function, which in turn affects clopidogrel activity. The CYP2C19*2 genetic variant alone accounts for about 12% of the variability in clopidogrel response.

- CYP2C19 variant testing can be used to predict response to clopidogrel and modify the therapeutic strategy when necessary. CYP2C19 variant testing determines if a person is a poor, intermediate, extensive, or ultrarapid metabolizer.
  - A person with two nonfunctional alleles (any combination of *2-*8) is classified as a poor metabolizer. About 2-3% of Caucasians and blacks and up to 20% East Asians are poor metabolizers.
  - People with one loss-of-function allele (*1 and any combination of *2-*8) are intermediate metabolizers and represent 30-50% and 40-45% of these populations, respectively.
  - The CYP2C19*17 variant is associated with increased enzyme function or gain of function carriers. The CYP2C19*17 allele has multiethnic frequencies of 3-21%, on average.

- Several studies have demonstrated a reduced effectiveness of clopidogrel in people with reduced CYP2C19 metabolism. Poor metabolizers may be at increased risk of nonfatal stroke, MI, or death from any cause in patients with poor metabolism. In contrast, an analysis of the CURE trial and ACTIVE trial, involving 5059 genotyped patients with acute coronary syndromes, did not find an effect of CYP2C19 genotype on outcome in homozygous, heterozygous or in those who were not carriers of the loss of function alleles.
• CYP2C19 ultrarapid metabolizers (*17 carriers) may be at increased risk for clopidogrel-related bleeding.\textsuperscript{6,12} However, a recent study showed ultrarapid metabolizers had a greater benefit from clopidogrel therapy than non-carriers, without increased bleeding events.\textsuperscript{11}

Test information

• CYP2C19 testing identifies the most common gene variants and is performed on buccal or blood samples.
  o CYP2C19*1 is the normal functioning allele.
  o The most common loss of function alleles are *2 and *3.
  o CYP2C19*4, *5, *6, *7, and *8 alleles are much less common and are associated with absent or reduced CYP2C19 enzyme function.\textsuperscript{2}
  o CYP2C19*17 allele is associated with increased enzyme function or gain-of-function carriers.

Guidelines and evidence

• U.S. Food and Drug Administration (FDA) approved product labeling for clopidogrel (Plavix\textsuperscript{®}) was updated in July 2017 to revise a boxed warning of the diminished effectiveness in individuals with poor CYP2C19 metabolism. The revised boxed warning provides more general guidance about the impact of reduced platelet activity:\textsuperscript{1,2}
  o “The effectiveness of Plavix\textsuperscript{®} results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.”
  o “Plavix\textsuperscript{®} at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed ‘CYP2C19 poor metabolizers’).”
  o “Tests are available to identify patients who are CYP2C19 poor metabolizers. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.”

• In January 2015, the American Heart Association published a Scientific Statement on Basic Concepts and Potential Applications of Genetics and Genomics for Cardiovascular and Stroke Clinicians.\textsuperscript{13} They noted:
  o “No cardiovascular pharmacogenetic application has yet been fully validated or widely adopted.”
“In aggregate, the available data suggests that patients at highest risk for cardiovascular events (those who have undergone PCI [percutaneous coronary intervention] and are in the acute period after the procedure) may have worse outcomes on clopidogrel if they are reduced-function variant carriers.”

“...the magnitude of benefit of clopidogrel in a given patient population influences the risk associated with CYP2C19 loss-of-function variants. Specifically, if the magnitude of benefit is small, the impact of genotype on clopidogrel efficacy may also be small. Therefore, the risk of genotype appears to be greatest among patients for whom clopidogrel has the greatest efficacy (i.e., largest risk reduction), specifically those undergoing percutaneous coronary intervention with stenting. Meta-analyses suggest that this group may be at up to 3- to 4-fold increased risk for stent thrombosis among *2 variant carriers.”

In December 2013, the American Heart Association published a Scientific Statement on Genetics and Genomics for the Prevention and Treatment of Cardiovascular Disease. They surmised:

Genotype-directed therapy could identify those with ACS/PCI who benefit most from alternative antiplatelet therapy. Current data do not support the use of CYP2C19 genotype data to guide treatment in other scenarios.

Standard dosing of clopidogrel, as recommended in the product label, is warranted among ACS/PCI patients with a predicted CYP2C19 extensive metabolizer or ultrarapid metabolizer phenotype (i.e., *1/*1, *1/*17, and *17/*17).

If genotyping identifies a patient as a CYP2C19 PM (i.e., any combination of *2 through *8), literature supports the use of an alternative antiplatelet agent (e.g., prasugrel Effient® or ticagrelor Brillinta®) when not contraindicated.

Data support switching to an alternative antiplatelet agent for CYP2C19 IMs (e.g., *1/*2, *1/*3, and *2/*17) when not contraindicated. However, given the wide inter-individual variability in residual platelet activity observed among clopidogrel-treated IMs, other factors that may place an IM at increased risk of a CV event (or adverse bleeding event) must be considered to most effectively individualize therapy.

It is currently premature to support an increased dosing strategy based on CYP2C19 genotype. Large clinical trials that evaluated higher-dose clopidogrel in ACS/PCI patients with high on-treatment platelet reactivity have concluded...
that adjusting clopidogrel dose on the basis of platelet function monitoring alone does not reduce the incidence of death from CV causes, nonfatal myocardial infarction, or stent thrombosis.

- In August 2012, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on Practice Guidelines, in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons \(^{15}\), commented:
  - Genetic testing for CYP2C19 loss-of-function alleles may be considered on a case-by-case basis, especially for patients who experience recurrent ACS events despite ongoing therapy with clopidogrel.

- In May 2012, the American Heart Association published a Policy Statement on Genetics and Cardiovascular Disease. \(^{16}\) They concluded:
  - “…it is now unambiguously clear that the use of standard doses of clopidogrel in patients with CYP2C19 loss-of-function variants is associated with an increased frequency of major adverse cardiovascular events and, in particular, of in-stent thrombosis among patients receiving drug-eluting stents.”

- In July 2010, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) issued a Clopidogrel Clinical Alert for approaches to the FDA black box warning which include the following points: \(^{4,5}\)
  - An emphasis on adherence to the existing ACCF/AHA guidelines for the use of antiplatelet therapy.
  - Clinicians should be aware that genetic variability in CYP enzymes alter clopidogrel metabolism and that diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.
  - The predictive value of pharmacogenomic testing is very limited at this time, but studies are ongoing.
  - Evidence is insufficient to recommend routine genetic testing or platelet function testing but may be considered for people at moderate to high risk for poor outcomes. If a person is tested and found to be a poor metabolizer, other therapies should be considered:
    - For coronary patients - consider prasugrel (Effient\(^{®}\)) (NOTE: Or ticagrelor (Brilinta\(^{®}\), now that it has been approved).
    - For TIA/stroke patients - consider aspirin or aspirin plus extended release dipyridamole. Prasugrel is contraindicated in TIA/stroke (NOTE: ticagrelor (Brilinta\(^{®}\) should not be used in patients with active pathological bleeding or a history of intracranial hemorrhage).
For people who experience adverse reactions (i.e. adverse CV event or thrombosis, not bleeding) on clopidogrel several options exist:

- Clopidogrel can be switched to prasugrel (NOTE: Or ticagrelor, now that it has been approved).
- Clopidogrel dose can be increased (though little data exists).
- Platelet function testing may be performed to determine if patients are clopidogrel non-responders.
- For stroke patients, aspirin alone or combination of aspirin plus extended-release dipyridamole can be considered.

Higher loading doses and maintenance doses of clopidogrel have been found to improve platelet inhibition and might be considered alternatives for high-risk patients who respond poorly to clopidogrel. New antiplatelet drugs such as prasugrel and if approved, ticagrelor (NOTE: ticagrelor has been approved), are additional alternatives. Other possibilities are adding cilostazol (Pletal®) to standard doses of aspirin and clopidogrel, though data with this combination is still accruing. Follow up platelet function testing might be considered to ensure adequate platelet inhibition.

• Ongoing clinical trial:
  - NCT Number NCT01742117
    - The TAILOR-PCI (Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention) trial is evaluating clinical outcomes of CYP2C19-based treatment decisions in patients with acute coronary syndrome (ACS) or stable coronary artery disease (CAD). The trial plans to enroll 5,300 patients and randomize participants to either a conventional treatment arm or a CYP2C19 genotype-based antiplatelet therapy selection approach. Participants who are heterozygous or homozygous for CYP2C19*2 or *3 will be treated with ticagrelor instead of clopidogrel. The primary endpoint will include cardiovascular mortality, non-fatal MI, non-fatal stroke, severe recurrent ischemia, and stent thrombosis. The estimated study completion date is March 2020.

Criteria
• Previous Testing:
  - No previous genetic testing of CYP2C19, AND
• Personal History:
  - Currently on clopidogrel therapy, or
Use of clopidogrel therapy is being proposed for a patient at moderate to high risk for a poor outcome, such as:

- Experiencing symptoms consistent with ACS when percutaneous coronary intervention is an option, and/or
- Considering a drug-eluting stent

Exclusions

- Current data do not support the use of CYP2C19 genotype data to guide treatment in other scenarios, including altering the dosing recommendation for clopidogrel based on the CYP2C19 genotype.

References


