CYP2C19 Genetic Testing for Oral P2Y12 Inhibitor Therapy

A SCIENTIFIC STATEMENT FROM THE AMERICAN HEART ASSOCIATION

CYP2C19

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Key Findings:

1. CYP2C19 GENETIC VARIANTS

- CYP2C19 is a gene that influences the metabolism of the most common oral P2Y12 inhibitor, clopidogrel.
- Loss-of-function alleles e.g. *2, *3, *4, *8 and *35 are present in up to 50% of patients and can reduce the effectiveness of clopidogrel, increasing the risk of adverse cardiovascular events.

2. CLINICAL IMPACT

- Genetic testing for CYP2C19 variants can identify individuals at higher risk for treatment failure with clopidogrel, which can be used to guide the choice of antiplatelet therapy.
- For poor metabolisers, alternative P2Y12 inhibitors like prasugrel or ticagrelor, which are not influenced by CYP2C19 metabolism, might be prescribed. Though they may increase bleeding risk.

3. RECOMMENDATIONS

- A precision medicine approach based on CYP2C19 genetic testing is recommended.
- LOF (Loss-of-Function) carriers should be prescribed ticagrelor or prasugrel.
- Noncarriers should be prescribed clopidogrel.
- This approach decreases the risk of ischaemic events compared with universal clopidogrel.
- It also decreases the risk of bleeding compared with universal ticagrelor or prasugrel.
- This method may offer a more balanced therapeutic approach.

Aim:

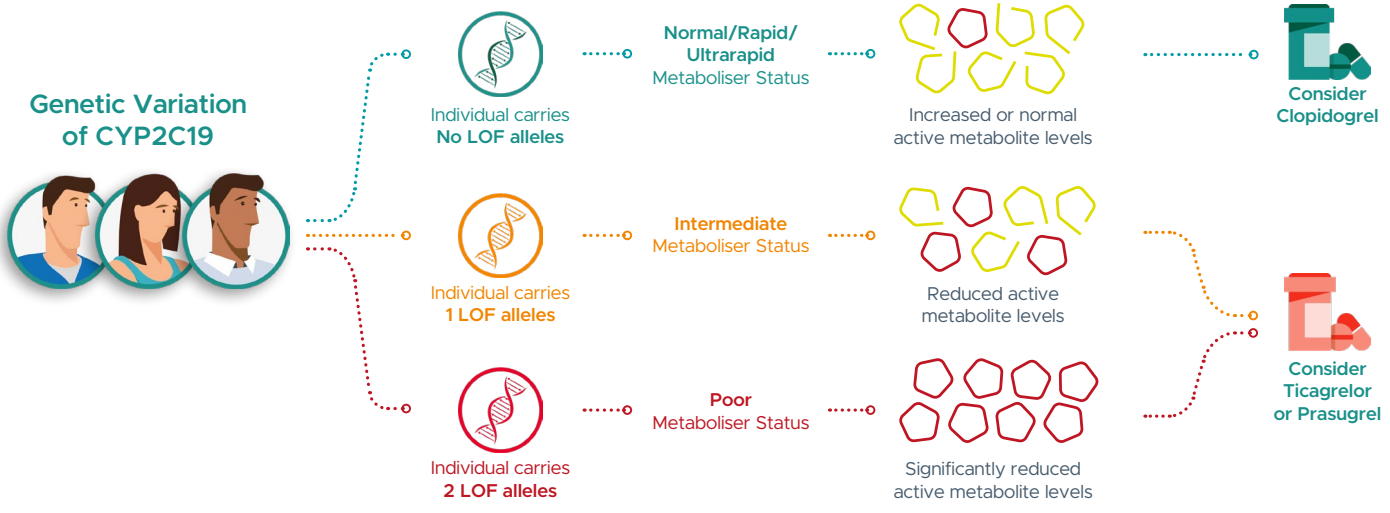
To address the role of CYP2C19 genetic testing in guiding the use of oral P2Y12 inhibitors (such as clopidogrel) in patients undergoing treatment for cardiovascular conditions, especially those at risk of ischaemic events.

Clinical indications:

Oral P2Y12 inhibitors are widely used to prevent thrombosis in:

- Stroke Treatment including (TIA)
- Coronary artery disease (CAD)
- Peripheral Arterial Disease (PAD)
- Acute Coronary Syndrome (ACS)
- Myocardial infarction (MI)
- Percutaneous coronary intervention (PCI)

Pharmacogenetic testing of CYP2C19 for prescribing of P2Y12 inhibitors



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Comparison of Genetic Testing against Platelet function testing:

Platelet function testing has an advantage in that it directly measures the platelet reactivity of the individual however in practice it proves challenging to implement because:

1. Results vary over time so multiple tests may be needed.
2. Platelet Function testing cannot guide treatment prior to administration because the patient needs to be on clopidogrel 1-2 weeks prior to testing.

- Genetic testing can deliver preemptive once in a lifetime results unaffected by medication diet or illness.
- AHA suggest that pairing this approach with ABCD-GENE (age, body mass index, chronic kidney disease, diabetes, and genotyping) score may enhance the accuracy of identifying patients with impaired clopidogrel response.

Implementation:

AHA stated that implementing CYP2C19 genetic testing is dependent on the following:

- The rapid availability of test results
- The provision of clear therapeutic guidance based on test outcomes
- The potential for preemptive genetic testing
- The seamless integration of this information into electronic health records

And that **"Rapid point-of-care assays that have been adopted in clinical trials and are easy to perform by non-laboratory personnel could potentially increase the adoption of CYP2C19 genetic testing."**

Cost Effectiveness:

CYP2C19 genotyping to guide antiplatelet therapy has been shown to be highly cost effective with one study reporting that **"CYP2C19 testing (compared with no testing) was dominant in 97% of simulations, making it cost-effective and high value."**

- PCI, acute stroke patients and TIA patients have all been shown to be highly cost-effective cohorts across several studies.
- De-escalation of patients from more potent, more expensive alternatives such as Ticagrelor and Prasugrel to clopidogrel is key.
- In these models CYP2C19 genotype is known prior - indicating that methods which aren't preemptive or at the point of care may not be as cost effective.

Conclusions:

- An extensive number of studies have demonstrated that patients with Loss of Function CYP2C19 variants respond poorly, and are at an increased risk of ischaemic events, when treated with clopidogrel.
- The use of alternative therapies should be carefully considered, especially in high-risk patients or those with significant contraindications.
- **CYP2C19 genetic testing before prescription of clopidogrel or ticagrelor/prasugrel can be beneficial in guiding a precision medicine** approach but hinges on the ability to overcome implementation challenges such as rapid availability of results and integration of results into the electronic patient record.

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