

Clopidogrel (Plavix)

Pharmacologic agent: Clopidogrel (Plavix) is a thienopyridine class inhibitor of P2Y₁₂ ADP platelet receptors. For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Clopidogrel has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

WARNING: REDUCED BENEFIT IN POOR METABOLIZERS:

The effectiveness of Clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Clopidogrel at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function¹. Tests are available to identify a patient's *CYP2C19* genotype; these tests can be used as an aid in determining therapeutic strategy. **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.** This recommendation is now reflected in a Boxed Warning from the FDA^{2,3}. **Clinical Note:** There is a previous boxed warning regarding the use of Clopidogrel in patients taking Omeprazole, as Omeprazole inhibits the CYP2C19 enzyme⁴.

Pharmacogenomic information: The following represent the different alleles of *CYP2C19* that make up a patient's genotype³:

- The *CYP2C19**1 allele has fully functional metabolism of Clopidogrel.
- The *CYP2C19**2 and *3 alleles have no functional metabolism of Clopidogrel. These two alleles account for most of the reduced function alleles in patients of Caucasian (85%) and Asian (99%) descent classified as poor metabolizers.
- The *CYP2C19**4, *5, *6, *7, and *8 and other alleles may be associated with absent or reduced metabolism of Clopidogrel, but are less frequent than the *CYP2C19**2 and *3 alleles.
- A patient with two loss-of-function alleles (as defined above) will have poor metabolizer status.

Action:

- ***CYP2C19* genotyping is now recommended prior to initiation of treatment with Clopidogrel. In patients with two loss-of-function copies (alleles) of the gene consider alternative anti-platelet medications. Preliminary studies have indicated doubling the loading and maintenance doses of Clopidogrel may increase the effectiveness of the medication, but more studies are needed to confirm this finding.**

Reference/Resources

1. Sofi F, et al. (2010) [Cytochrome P450 2C19\(*\)2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis](http://www.nature.com/tpj/journal/vaop/ncurrent/abs/tpj201021a.html). Pharmacogenomics J. Mar 30. [Epub ahead of print] (<http://www.nature.com/tpj/journal/vaop/ncurrent/abs/tpj201021a.html>)
2. Ellis KJ, et al. (2009) [Clopidogrel pharmacogenomics and risk of inadequate platelet inhibition: US FDA recommendations](http://www.ncbi.nlm.nih.gov/pubmed/19891556). Pharmacogenomics. 10:1799-817. (<http://www.ncbi.nlm.nih.gov/pubmed/19891556>)
3. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm>
4. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm>

General drug information obtained from RxList: <http://www.rxlist.com/plavix-drug.htm>