

# CASE STUDY HIGHLIGHTS: Clopidogrel

How differences in treatment response between different racial or ethnic subgroups can lead to important observations in drug discovery and development.

## BACKGROUND

Blood clotting, the process of platelets clumping, is an important response to the control of bleeding, such as after cuts, injury, or surgery. Blood clots, however, can also form without any injury and can cause serious health issues such as heart attack, stroke, difficulty breathing and other problems. People who have had a cardiovascular event are sometimes placed on medications to prevent blood clotting. Those medications include anti-platelet therapy drugs. Clopidogrel, originally marketed under the trade name Plavix®, is a drug that inhibits platelet activation and clumping.

## RESEARCH

The efficacy and safety of clopidogrel was investigated in clinical trials and found to be effective either as an alternative therapy to aspirin or in combination therapy with aspirin. Clopidogrel, alone and also when combined with aspirin, reduced the occurrence of death, heart attacks, and stroke by 20% as compared to aspirin alone.

How clopidogrel works was not discovered until after the drug was marketed, and the dose was largely determined by experience.

- Because of this, there were wide variances in drug response with a notable number of “non-responders.”

Research also focused on the differences in patient treatment responses.



# DISCOVERY

Clopidogrel is metabolized in the liver by proteins of the cytochrome P450 family, namely CYP2C19, resulting in a form of the drug that can block a receptor on platelets (P2Y12-receptor) that normally signals platelet activation and aggregation (i.e., clotting).

A genetic change (e.g., loss-of-function [LOF]) in the function of the liver protein CYP2C19 would reduce the conversion of clopidogrel to its active form and could explain “non-responders,” leading to an increased risk for a cardiovascular event. The change explains the different treatment responses to clopidogrel.

The majority of individuals with these changes for CYP2C19 were from Asian regions. Studies have found this genetic variation in more than 50% of individuals of Asian descent (mainly Chinese, Japanese, and Korean), as compared to only 28% of Whites.



# CONCLUSION

Clinically significant differences in treatment response indicate a need for further investigation.

Differences may be attributable to metabolic or genetic variation. Genetic variation results from different forms (termed “alleles”) of the same gene, and allelic frequency differs between racial and ethnic populations.

Therefore, observed differences in treatment response between different racial or ethnic subgroups can sometimes indicate genetic variants that may lead to important observations in drug discovery and development.

The importance of determining differences in treatment response between patients in clinical trials is dependent both on having good data and having diverse representation in the trials. Genotyping individuals can aid in the development of therapeutic guidelines and may help to deliver optimal treatments.

**For citations and more information on this case, please see the [MRCT Center toolkit](#).**