

# Increasing dosage of clopidogrel for patients with genetic variation improves response to medication

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Among patients with stable cardiovascular disease who have a genetic variation that diminishes the response to the antiplatelet drug clopidogrel, tripling the standard daily dosage of this medication resulted in improved platelet reactivity, according to a study appearing in *JAMA*. The study is being released early online to coincide with its presentation at the American Heart Association Scientific Sessions.

"Variants in the CYP2C19 gene influence the pharmacologic and [clinical response](#) to the standard 75-mg daily maintenance dose of the antiplatelet drug [clopidogrel](#)," according to background information in the article. Variability in the pharmacodynamic response to clopidogrel is well recognized, and patients with higher platelet reactivity while receiving clopidogrel are at increased risk of adverse [cardiovascular events](#). "... data are needed to offer guidance as to what might constitute optimal treatment strategies in patients with loss-of-function CYP2C19 alleles [an alternative form of a gene]."

Jessica L. Mega, M.D., M.P.H., and Marc S. Sabatine, M.D., M.P.H., of Brigham and Women's Hospital and Harvard [Medical School](#), Boston, and colleagues conducted a multicenter, randomized trial to test whether maintenance doses of up to 300 mg daily of clopidogrel can improve platelet reactivity in the setting of loss-of-function CYP2C19 genotypes, particularly among heterozygotes (a person possessing one copy of a variant gene), who constitute approximately 25 percent to 45 percent of

the population, depending on racial background. The trial (ELEVATE-TIMI 56) enrolled and genotyped 333 patients with cardiovascular disease across 32 sites from October 2010 until September 2011.

Patients received maintenance doses of clopidogrel for 4 treatment periods, each lasting approximately 14 days, based on genotype. In total, 247 noncarriers of a CYP2C19\*2 loss-of-function allele were randomized to receive 75 and 150 mg daily of clopidogrel (2 periods each), whereas 86 carriers (80 heterozygotes, 6 homozygotes [having two copies of the variant gene]) were randomized to receive 75, 150, 225, and 300 mg daily. Two methods were used to measure platelet function. The average age of the patients was 60 years, 75 percent were male, 57 percent had a history of heart attack, and 97 percent had a history of percutaneous coronary intervention (procedures such as balloon angioplasty or stent placement used to open narrowed coronary arteries).

Among the main findings of the researchers was that higher maintenance doses of clopidogrel in patients carrying a CYP2C19\*2 allele significantly reduced platelet reactivity. Also, daily maintenance doses of 225 mg of clopidogrel or greater in CYP2C19\*2 heterozygotes improved platelet reactivity levels that were at least equivalent to what is achieved with 75 mg daily of clopidogrel in noncarrier patients with [cardiovascular disease](#). When evaluating the CYP2C19\*2 homozygotes, the researchers saw a trend toward less platelet [reactivity](#) with higher maintenance doses of clopidogrel; however, even with 300 mg daily of clopidogrel, these individuals were unlikely to achieve optimal degrees of platelet inhibition.

"These data help define how patients with different CYP2C19 genotypes respond to clopidogrel maintenance dosing strategies and provides useful information to guide further clinical studies," the authors conclude.

**More information:** [doi:10.1001/jama.2011.1703](https://doi.org/10.1001/jama.2011.1703)

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