Genetic variations linked with worse outcomes with use of antiplatelet drug for cardiac procedures

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An analysis of data from previously published studies indicates that use of the antiplatelet drug clopidogrel for patients who have common genetic variants of a certain gene and are undergoing a procedure such as coronary stent placement have an associated increased risk for major adverse cardiovascular events, particularly development of blood clots in stents, according to a study in the October 27 issue of *JAMA*.

Clopidogrel, one of the most commonly prescribed medications, has been shown to reduce cardiovascular events in patients undergoing percutaneous coronary intervention (PCI; procedures such as balloon angioplasty or stent placement used to open narrowed coronary arteries). "However, there is a large degree of interindividual variability in the pharmaco-dynamic response to clopidogrel," the authors write. Data suggest its pharmacologic effect varies based on variations of the gene CYP2C19, but there is uncertainty regarding the clinical risk given by certain variations.

Jessica L. Mega, M.D., M.P.H., of Brigham and Women's Hospital and Harvard Medical School, Boston, and colleagues conducted a meta-analysis to determine the risk of major adverse cardiovascular outcomes among carriers of 1 or 2 reduced-function CYP2C19 genetic variants in patients treated with clopidogrel. The analysis included data from 9 studies and 9,685 patients (of whom 91.3 percent underwent PCI and 54.5 percent had an acute coronary syndrome), 863 experienced the

composite outcome of cardiovascular death, heart attack, or stroke; and 84 patients had stent thrombosis (blood clot) among the 5,894 evaluated for such.

There were 6,923 patients (71.5 percent) with no CYP2C19 reduced-function alleles (an alternative form of a gene), 2,544 (26.3 percent) with 1 reduced-function CYP2C19 allele, and 218 (2.2 percent) with 2 reduced-function CYP2C19 alleles. "Compared with CYP2C19 noncarriers, there was a significantly increased risk of cardiovascular death, myocardial infarction, or stroke in the 26.3 percent of the overall study population who carried only 1 reduced-function CYP2C19 allele. Similarly, there was a significantly increased risk of cardiovascular death, myocardial infarction, or stroke in the 2.2 percent of the overall study population who carried 2 reduced-function CYP2C19 alleles," the researchers write.

The authors also found that both carriers of only 1 reduced-function CYP2C19 allele and carriers of 2 alleles were at significantly increased risk of stent thrombosis when compared with CYP2C19 noncarriers.

"In conclusion, the findings of this collaborative meta-analysis demonstrate that common genetic variants in the CYP2C19 gene are associated with almost 1 in 3 patients not receiving ideal protection from ischemic events when treated with standard doses of clopidogrel for PCI. Given how widely clopidogrel is used to treat patients with cardiovascular disease, determination of the optimal antiplatelet treatment doses or regimens for individual patients is needed to tailor therapy appropriately," the authors write.

More information: *JAMA*. 2010;304[16]:1821-1830.