Genetic variation in key cell pumping mechanism reduces effects of clopidogrel treatment

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A study published Online First and in an upcoming *Lancet* shows that patients with a genetic variation affecting a key protein pump in drug transport do not respond as well to the anticlotting drug clopidogrel—as such, patients with this variation at are at increased risk of cardiovascular events with standard clopidogrel treatment. However, no association exists between this genetic variation and another anticlotting drug, prasugrel.

This, and other work on a separate genetic variation, shows that more than half the population have a genetic profile making them less amenable to clopidogrel treatment, and the authors of this new work say such profiling should be considered when looking at anticlotting regimens in patients requiring anticlotting treatment. The Article is by Dr Jessica Mega, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, and colleagues.

Both clopidogrel and prasugel are prodrugs, meaning that they are metabolically activated once inside the body. Both are used to prevent blood clots forming in patients with coronary artery diseases, peripheral vascular disease, and cerebrovascular disease.

Previous work has already identified CYP2C19 as another genetic variation affecting clopidogrel (but not prasugrel) metabolism. In this case, patients with the variation in CYP2C19 have inadequate

clopidogrel activation (but not prasugrel). In this study, Mega and co-workers look at another part in the chain vital for drug absorption: ABCB1 is a gene that encodes P-glycoprotein, a protein pump which transports molecules across cell membranes. The pump is found, among other places, on the epithelial cells lining the gut wall. The researchers aimed to discover whether variation in the ABCB1 gene caused further problems in clopidogrel metabolism, in addition to those caused by CYP2C19. They looked at the population studied in the TRITON-TIMI 38 trial published in 2007 (which compared clopidogrel and prasugrel treatment in patients with acute coronary syndromes) as the basis for their analysis. The primary endpoint in this study was cardiovascular death, heart attack, or stroke.

Participants in TRITON-TIMI 38 had three possible variants for ABCB1 3435C--T: TT, CT, and CC (C=cystosine and T=thymine, both building blocks of DNA). The researchers showed that patients on clopidogrel with the TT variation had a 72% increased risk of hitting the primary endpoint compared with CT/CC collectively. No association was recorded with prasugrel and ABCB1 variation. The authors speculate that prasugrel is metabolised more rapidly, mitigating the effects of the variation.

The authors also showed that the ABCB1 and CYP2C19 variations have separate but complementary effects on the response to clopidgrel. Collectively, patients with either variation or both were twice as likely to hit the primary end point as those with neither. The authors say: "When both ABCB1 and CYP2C19 were taken into account, in this population following an acute coronary syndrome and percutaneous coronary intervention, nearly half the population carried a genotype associated with increased risk of major adverse events during treatment with standard doses of clopidogrel."

They conclude: "As clinicians, professional societies, and patients

integrate information about genetic factors affecting the response to these drugs, the roles of both ABCB1 and CYP2C19 should be considered."

In a linked Comment covering both the Wallentin and Mega genetics papers, Dr Betti Giusti and Dr Rosanna Abbate, University of Florence-Careggi Hospital, Florence, Italy, say: "The issue is not to choose the lesser of the evils, but the better of the goods—by identifying the therapeutic strategy that, in consideration of individual characteristics, warrants the higher benefit/risk ratio."

They conclude: "Prospective studies evaluating different antiplatelet treatments tailored to individual characteristics of patients—genetic profile, residual platelet reactivity, drug-drug interactions, and traditional and procedural risk factors—are urgently needed to identify therapeutic strategies that will provide the best benefit for the single patient in this high-risk clinical setting."

More information: www.thelancet.com/journals/lan … (10)61274-3/abstract

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