Ticagrelor is better than clopidogrel to prevent blood clots regardless of genetic profile

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A study published Online First and in an upcoming *Lancet* shows that anticlotting treatment using ticagrelor is better than clopidogrel, regardless of the presence of genetic variations that leads to variable efficacy of clopidogrel. Thus use of ticagrelor in patients with acute coronary syndromes eliminates the need for genetic testing that is considered necessary to avoid a poor response when treating with clopidogrel. The Article is written by Professor Lars Wallentin, Uppsala University, Sweden, and colleagues.

For patients with acute coronary syndromes, dual antiplatelet (anticlotting) treatment with aspirin and a thienopyridine (clopidogrel or prasurgrel) is recommended to prevent recurrences such as new heart attacks and clotting of implanted stents in the coronary arteries (stent thrombosis). The effects of the most commonly used drug, clopidogrel are variable and affected by genetic variations in the genes CYP2C19 (responsible for activating the drug) and ABC1B (responsible for its absorption). Patients with a genetically determined poor response to clopidogrel, therefore, had inadequate protection against new cardiovascular events. Ticagrelor operates through a completely different mechanism and has been proven to give more pronounced and consistent platelet (clotting) inhibition, with quicker action. There are no known genetic variants affecting ticagrelor metabolism, although the authors of this new work say that ABC1B, since it is responsible for absorption, could have an effect.

In this new work, the authors used data from the PLATO (PLATelet inhibition and patient Outcomes) study. In PLATO, ticagrelor reduced events of the primary composite endpoint of cardiovascular death, heart attack, or stroke by 16% and stent thrombosis with 34% without any difference in overall major bleeding, but with an 19% increase of spontaneous major bleeding during long-term treatment. In this first substudy from the PLATO genetics programme, the researchers investigated the role of CYP2C19 and ABCB1 polymorphisms on efficacy and safety outcomes both between and within the ticagrelor and clopidogrel arms of the PLATO study.

A total of 10 285 patients provided samples for genetic analysis. The primary outcome occurred less often with ticagrelor versus clopidogrel, irrespective of CYP2C19 genotype: 8.6% versus 11.2% in patients with any genetic variation (either or both copies); and 8.8% versus 10.0% in those without any variation. For the ABCB1 genotype, event rates for the primary outcome were also consistently lower in the ticagrelor than in the clopidogrel group for all genotype groups (8.8% vs 11.9% for the high-expression genotype). The study verified the effect of the genetic loss-of-function variation in the clopidgorel group since the event rate for the primary outcome at 30 days was higher in patients with any than in those without any loss-of-function variation (5.7% vs 3.8%).

In the main PLATO trial, ticagrelor treatment was associated with a 19% increase in spontaneous bleeding events. In the clopidogrel group the bleeding rates were higher in the group with any gain-of-function variation. However, the researchers recorded no significant interaction of any CYP2C19 variation when comparing bleeding risks between the treatment groups. Accordingly, spontaneous bleeding events were higher with ticagrelor treatment regardless of CYP2C19 variation.

The authors conclude: "Ticagrelor is a more efficacious treatment for acute coronary syndromes than is clopidogrel, irrespective of CYP2C19

and ABCB1 polymorphisms. Use of ticagrelor instead of clopidogrel eliminates the need for presently recommended genetic testing to identify poor responders to clopidogrel before start of dual antiplatelet treatment."

"These findings emphasise that ticagrelor will be a simple and reliable treatment to further improve survival and reduce the risk of recurrences in almost all patients with acute coronary syndrome without the need for any specific tests of its activity before or during routine treatment. The study also shows the importance of evaluating treatments not only in a diffuse large group of patients but also in relation to the individual response based on genetic or other sources of variation," adds Professor Wallentin*, the leader of the PLATO study.

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