Genotyping improves choice of antithrombotic regimen after coronary stenting

September 4 2019

Genotype-guided oral P2Y12 inhibition reduces bleeding without raising clotting risk in heart attack patients undergoing stent implantation, according to late breaking results from the POPular Genetics trial presented in a Hot Line Session today at ESC Congress 2019 together with the World Congress of Cardiology and published in the *New England Journal of Medicine*.

POPular Genetics is the first randomised trial to investigate the use of genotyping to guide the choice of P2Y12 inhibitor after primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI). ESC guidelines recommend dual antiplatelet therapy with aspirin and a P2Y12 inhibitor for one year.(3,4) The first choice P2Y12 inhibitors in STEMI patients are ticagrelor or prasugrel and if these are contraindicated or not available clopidogrel can be used.

First author Dr. Danny Claassens of St. Antonius Hospital, Nieuwegein, the Netherlands said: "The use of genetic testing is currently not routinely recommended, since there has never been a randomised trial showing a clinical benefit compared to the recommended strategy."

The more potent P2Y12 inhibitors ticagrelor and prasugrel are more effective in preventing thrombotic events such as myocardial infarction, but there is a higher risk of bleeding complications compared to

clopidogrel. Similar to myocardial infarction, bleeding is associated with death. In many countries, clopidogrel is used in the majority of patients because it is less expensive, and the dosing is simpler.

Clopidogrel is a prodrug which is converted into its active metabolite by the CYP2C19 enzyme in the liver. This enzyme is encoded by the CYP2C19 gene. Carriers of the CYP2C19*2 and *3 loss-of-function alleles have an impaired CYP2C19 enzyme capacity, making clopidogrel less effective.

The investigators hypothesised that if the choice of P2Y12 inhibitor was based on the CYP2C19 genotype, treating noncarriers of CYP2C19*2 and *3 (*1/*1) with clopidogrel and treating carriers of CYP2C19*2 and/or *3 with ticagrelor or prasugrel, this strategy would not increase the risk of thrombotic complications and would simultaneously decrease the risk of bleeding compared to standard treatment with ticagrelor or prasugrel.

The POPular Genetics trial was conducted in 10 centres in the Netherlands, Belgium and Italy. A total of 2,488 patients with STEMI undergoing primary PCI were randomly allocated to the standard treatment arm or the genotype-guided arm. In the standard treatment arm, patients were treated with the currently recommended P2Y12 inhibitors ticagrelor or prasugrel for one year.

In the genotype-guided arm genetic testing was performed as soon as possible after PCI. Either a blood sample was sent to a central lab with results sent back in one to two days, or a point-of-care machine was used to test a saliva sample and results were available within one hour. The method was chosen according to whether the centre had a point-of-care machine. Patients with no loss-of-function alleles (*1/*1) received clopidogrel for one year, while carriers of one or more *2 or *3 alleles were treated with ticagrelor or prasugrel.

The first objective was to determine if genotype-guided therapy was noninferior to standard care for the primary endpoint, which was a combined thrombotic and bleeding outcome including all-cause death, myocardial infarction, definite stent thrombosis, stroke, and major bleeding at one year. The endpoint was experienced by 5.1 percent of patients in the genotype-guided arm and 5.9 percent in the standard treatment arm, meeting the pre-specified criterion for noninferiority. Because noninferiority was proven, the researchers tested superiority of the genotype-guided strategy for the primary endpoint, and found no significant differences with a hazard ratio of 0.87 (95 percent confidence interval 0.62 to 1.21; p = 0.40)

The second objective was to determine whether genotype-guided therapy was superior to standard care for the co-primary endpoint of major and minor bleeding. Patients in the genotype-guided arm had significantly less bleeding events (9.8 percent) than those in the standard treatment arm (12.5 percent) with a hazard ratio of 0.78 (95 percent confidence interval 0.61 to 0.98; p = 0.04).

A secondary thrombotic outcome (without bleeding) was also tested comprising death from vascular causes, myocardial infarction, definite stent thrombosis, and stroke. Rates of this outcome were 2.7 percent in the genotype-guided arm versus 3.3 percent in the standard treatment arm, with no significant difference between groups.

Dr. Claassens said: "This study demonstrates that a CYP2C19 genotype-guided strategy benefits patients with STEMI undergoing primary PCI by reducing the risk of bleeding without increasing the risk of thrombotic events."

More information: Borja Ibanez et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, *European Heart Journal* (2017). DOI:

10.1093/eurheartj/ehx393

Marco Valgimigli et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS, *European Heart Journal* (2017). DOI: 10.1093/eurheartj/ehx419

Thomas O. Bergmeijer et al. CYP2C19 genotype–guided antiplatelet therapy in ST-segment elevation myocardial infarction patients—Rationale and design of the Patient Outcome after primary PCI (POPular) Genetics study, *American Heart Journal* (2014). DOI: 10.1016/j.ahj.2014.03.006

Provided by European Society of Cardiology