For patients with diabetes, ticagrelor reduced heart attacks, strokes

1 September 2019

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In late-breaking clinical trial results presented in a Hot Line Session today at the European Society of Cardiology Congress 2019, investigators from Brigham and Women's Hospital and Greater Paris University Hospitals—AP-HP/Université de Paris presented the results from The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS), a clinical trial sponsored by AstraZeneca that evaluated whether adding ticagrelor to aspirin improves outcomes for patients with stable coronary artery disease and diabetes mellitus but without a history of heart attack or stroke. Taking ticagrelor in addition to aspirin reduced the risk of a composite of cardiovascular death, heart attack, or stroke. Patients on this dual-antiplatelet therapy also experienced greater risk of major bleeding. In THEMIS-PCI, a study that specifically looked at THEMIS patients with a history of previous percutaneous coronary intervention (PCI) that includes stenting, versus the overall THEMIS population, investigators found even more favorable results for patients taking ticagrelor plus aspirin. Results of THEMIS are published simultaneously in *The New England Journal of Medicine* and results from THEMIS-PCI are published simultaneously in *The Lancet*.

"With prolonged dual-antiplatelet therapy, we need to be thoughtful in considering which patients are most suited to taking the regimen—that is, those at high ischemic risk and low bleeding risk," said THEMIS co-chair Deepak L. Bhatt, MD, MPH, executive director of Interventional Cardiovascular Programs at the Brigham and professor of medicine at Harvard Medical School. "Our findings show that the greatest benefit occurred in those patients with diabetes and stable coronary artery disease with a history of prior stenting for whom ticagrelor, when added to aspirin, reduced important cardiovascular events, such as heart attacks, strokes and amputations."

THEMIS co-chair Philippe Gabriel Steg, MD, Chief of Cardiology at Hôpital Bichat, Greater Paris University Hospitals—AP-HP, and professor at Université de Paris, stated, "The THEMIS population is a critically important one in which to understand the potential benefits of taking ticagrelor in addition to aspirin. As the number of people with diabetes continues to rise globally, we need to evaluate ways of improving long-term outcomes and preventing cardiovascular and ischemic events."

In THEMIS, the largest trial of patients with diabetes to date, more than 19,000 patients with stable coronary artery disease and diabetes were randomized to receive either ticagrelor plus aspirin or a placebo plus aspirin. Patients were followed for an average of more than three years. During that time, 736 of 9,619 patients (7.7 percent) taking ticagrelor plus aspirin experienced cardiovascular death, myocardial infarction, or stroke versus 818 of 9,601 patients (8.5 percent) taking placebo plus aspirin—a 10 percent reduction.

As seen with other anti-platelet medications, ticagrelor increased the risk of major bleeding (206

patients versus 100 patients) and intracranial hemorrhage (70 patients versus 46 patients) compared with placebo. The difference in intracranial hemorrhages was driven by an increased number of traumatic bleeds, most of them subdural, and not by spontaneous or procedural bleeding.

Among participants with a history of previous PCI, the risk reductions outweighed the increased bleeding risks. Patients who had received PCI, which commonly uses devices known as stents to widen a coronary blood vessel and keep blood flowing, accounted for the majority (58 percent) of the total THEMIS population. Among these patients in THEMIS-PCI, 404 of 5,558 (7.3 percent) participants taking ticagrelor plus aspirin experienced cardiovascular death, myocardial infarction, or stroke, versus 480 of 5,596 (8.6 percent) participants taking placebo plus aspirin—a 15 percent reduction. Major bleeding occurred in 111 of 5,536 (2.0 percent) patients receiving ticagrelor and 62 of 5,564 (1.1 percent) patients receiving placebo. The risk for intracranial bleeding was similar between ticagrelor and placebo (33 patients versus 31 patients, respectively). Ticagrelor provided a very favorable balance of benefit versus risk—more than in patients without a history of PCI.

"Our results indicate that among those with diabetes and stable coronary artery disease, we should focus on ticagrelor for patients with a history of prior stenting. This is an easily identifiable, logical sub-group," said Bhatt. "Studies currently support using long-term dual antiplatelet therapy for patients with acute coronary syndrome who are at high ischemic risk but low bleeding risk. Our work suggests that a much broader population of patients with stable coronary artery disease and diabetes stand to benefit substantially."

More information: P. Gabriel Steg et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes, *New England Journal of Medicine* (2019). DOI: 10.1056/NEJMoa1908077

Deepak L Bhatt et al. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial, *The Lancet* (2019). DOI: 10.1016/S0140-6736(19)31887-2

Provided by Brigham and Women's Hospital