

糖尿病患者におけるチカグレロルの臨床的有用性

THEMIS試験：チカグレロルとアスピリンの併用は糖尿病を有する安定冠動脈疾患患者の虚血イベントを減少させる

THEMIS: Ticagrelor plus aspirin reduce ischemic events in stable coronary patients with diabetes

チカグレロルとアスピリンの併用は、アスピリン単剤との比較で、糖尿病を有する安定冠動脈疾患患者の虚血イベントを減少させる。このTHEMIS試験のレイトブレイキングの結果が *New England Journal of Medicine* に掲載され、ESC Congress 2019のHot Line Session で発表された。有効性主要評価項目(心血管死、心筋梗塞または脳卒中の複合)発現率は、チカグレロル群においてプラセボ群よりも低かった(7.7% vs. 8.5%, $p=0.038$)。TIMI大出血発現率は、チカグレロル群で高かった(2.2% vs. 1.0%, $p<0.001$)。チカグレロルはまた、*Lancet*に掲載された事前に規定されたサブグループ解析(THEMIS-PCI)において、PCI歴を有する糖尿病患者における虚血性イベントを減少させた。

Full Text

The combination of ticagrelor and aspirin reduces ischemic events compared with aspirin alone in patients with stable coronary artery disease and diabetes according to late breaking results of the THEMIS trial published in the *New England Journal of Medicine*. In addition, ticagrelor reduced ischemic events in patients with diabetes and previous percutaneous coronary intervention (PCI), according to results from the THEMIS-PCI study published in *The Lancet*. Both trials were presented in a Hot Line Session at ESC Congress 2019 together with the World Congress of Cardiology.

THEMIS Senior author Professor Deepak L. Bhatt of Brigham and Women's Hospital and Harvard Medical School, Boston, US said: "In the overall population studied in THEMIS, the reduction in important ischemic events was somewhat counterbalanced by the increase in bleeding. Therefore, it remains critical to identify which patients are at high ischemic risk, but low bleeding risk, who could benefit from ticagrelor and aspirin."

Patients with diabetes often develop coronary artery disease, with millions of such patients worldwide. Given the global obesity epidemic, rates of diabetes are increasing – rapidly so, in certain parts of the world. Those with both conditions are at high risk of myocardial infarction (MI), stroke, and amputations, in part due to an excess tendency for the blood to clot. Aspirin is generally used to decrease this risk, but cardiovascular events still occur at a high rate.

The THEMIS trial examined whether adding the antiplatelet drug ticagrelor to aspirin would reduce the risk of thrombotic events in these patients. The study enrolled 19,220 patients at 1,315 sites across 42 countries in North America, South America, Asia, Africa, Australia, and Europe. Patients were 50 years or older, had type 2 diabetes, and had stable coronary artery disease (defined as a history of percutaneous coronary intervention, bypass grafting, or angiographic stenosis of 50% or more in at least one coronary artery). Patients with known prior myocardial infarction or stroke were excluded.

Participants were randomly allocated to ticagrelor versus placebo, both on top of aspirin. The primary efficacy outcome was the composite of cardiovascular death, MI, or stroke. The primary safety outcome was Thrombolysis in Myocardial Infarction (TIMI) major bleeding. The median follow-up was 39.9 months.

The incidence of the primary efficacy outcome was lower in the ticagrelor group than in the placebo group (7.7% versus 8.5%; hazard ratio [HR] 0.90; 95% confidence interval [CI] 0.81–0.99; $p=0.038$). The incidence of TIMI major bleeding was higher in the ticagrelor versus placebo group (2.2% versus 1.0%; HR 2.32; 95% CI 1.82–2.94; $p<0.001$).

Prof. Bhatt said: "There was a significant reduction in the primary endpoint of cardiovascular death, MI, and stroke with ticagrelor versus placebo. In addition to heart attack and stroke, acute limb ischemia and major amputations were also reduced with ticagrelor. Major bleeding was significantly increased."

Pinpointing subgroups of patients who could benefit from ticagrelor plus aspirin is crucial, said Prof Bhatt. "These are the patients at high ischemic risk, but low bleeding risk. In particular, those who have previously tolerated dual antiplatelet therapy without any bleeding complications seem to be the best candidates for prolonged therapy with ticagrelor and aspirin."

He noted that THEMIS-PCI, a prespecified subgroup analysis also presented at ESC Congress today and published in *The Lancet*, identified patients with the best balance of benefit versus bleeding risk. Prof Bhatt said: "In patients with diabetes and stable coronary artery disease with a history of previous coronary artery stenting who have tolerated dual antiplatelet therapy previously without any bleeding, prolonged therapy with ticagrelor and aspirin provides substantial gains in reducing the full spectrum of coronary, cerebral, and peripheral ischemic events."

Senior author of the THEMIS-PCI trial, Professor Philippe Gabriel Steg of Hôpital Bichat, Paris, France said: "Treatment with ticagrelor and aspirin also increased major bleeding relative to aspirin alone, but there was a net clinical benefit with dual antiplatelet therapy."

Patients with diabetes represent 25–35% of those undergoing PCI, making it a sizeable population. Dual antiplatelet therapy is administered immediately following PCI, but in the long-term, patients are generally treated with a single antiplatelet agent (usually aspirin).

THEMIS-PCI is a prespecified subgroup analysis of the THEMIS trial, also presented at ESC Congress. THEMIS enrolled 19,220 patients at 1,315 sites across 42 countries in North America, South America, Asia, Africa, Australia, and Europe. Of those, 11,154 patients (58%) had undergone PCI and were included in the THEMIS-PCI study.

"We hypothesized that the efficacy, safety and net clinical benefit of ticagrelor may be different in the subgroup of patients with a history of PCI, who have previously been exposed to dual antiplatelet therapy with aspirin and a P2Y12 inhibitor such as ticagrelor, prasugrel or clopidogrel," noted Prof Steg.

Ticagrelor added to aspirin reduced cardiovascular death, MI, and stroke, (the relative reduction was 15% in patients with prior PCI, $p=0.013$) although with a doubling of major bleeding ($p<0.0001$). The net clinical benefit appeared more favorable in patients with previous PCI than in patients without previous PCI, when evaluated as the composite of efficacy events and bleedings (15% relative risk reduction versus 6% relative risk increase, significant interaction, $p=0.012$).

Prof Steg said: "The results suggest that long-term therapy with ticagrelor in addition to aspirin may be considered in patients with diabetes and a history of PCI who have tolerated antiplatelet therapy and have high ischemic risk and low bleeding risk. This is a novel therapeutic option for a large and easy to identify patient population."

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