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ACUTE CORONARY SYNDROMES

Thrombin-receptor antagonist increases bleeding in patients with ACS


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Vorapaxar, a first-in-class, oral antagonist of protease-activated receptor 1 (PAR-1), inhibits thrombin-induced platelet activation, but failed to reduce the primary efficacy end point, and increased bleeding compared with standard therapy in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS). "Earlier phase II studies in percutaneous coronary intervention (PCI) and ACS patients showed that vorapaxar did not increase the risk of bleeding, and had a trend towards reducing myocardial infarctions," says Dr Pierluigi Tricoci from the Duke Clinical Research Institute, NC, USA. However, Dr Udaya Tantry from the Sinai Cener for Thrombosis Research, MD, USA thinks "the vorapaxar phase II trials actually did not reveal much information regarding safety or efficacy, since they were of too short duration and underpowered." Therefore, says Dr Tricoci, "two large phase III trials with long-term follow up were designed to confirm the preliminary findings."

Investigators in the phase III TRACER trial randomly allocated 12,944 patients to receive either vorapaxar (40 mg loading dose, followed by 2.5 mg daily) or placebo. Patient treatment also followed recommended practice guidelines, so most were also on aspirin and a $P2Y_{12}$ inhibitor.

The trial was terminated after an unscheduled safety review in January 2011. After follow-up (median 502 days), the primary end point (a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) occurred at a Kaplan–Meier 2-year rate of 18.5% and 19.9% (HR 0.92, 95% CI 0.85–1.01, $P = 0.07$) in the vorapaxar and placebo groups, respectively. The secondary end point (a composite of death from cardiovascular causes, myocardial infarction, or stroke) occurred in 14.7% and 16.4% of patients (HR 0.89, 95% CI 0.81–0.98, $P = 0.02$), but "because the primary end point was negative, superiority on the key secondary end point could not be declared," says Dr Tricoci. Moreover, the rates of moderate and severe bleeding according to the GUSTO classification were 7.2% and 5.2% (HR 1.35, 95% CI 1.16–1.58, $P < 0.001$), and the rates of clinically significant bleeding by TIMI classification were 20.2% and 14.6% (HR 1.43, 95% CI 1.31–1.57, $P < 0.001$) with vorapaxar and placebo, respectively. The rate of intracranial hemorrhage was 1.1% with vorapaxar and 0.2% with placebo (HR 3.39, 95% CI 1.78–6.45, $P < 0.001$).

These data "show that the combination of triple, prolonged antiplatelet therapy in [patients with] NSTE-ACS is associated with significant bleeding risk and, in particular, intracranial hemorrhage," says Dr Tricoci. "Another PAR-1 inhibitor, atopaxar, has also been shown to be associated with a modest trend towards a reduction in the primary end point, but more adverse effects. This indicates that it might not be beneficial to inhibit PAR-1 on top of aspirin and clopidogrel, particularly for long durations," cautions Dr Tantry. "Early after a thrombotic event (ACS or PCI), when disease activity is greatest, PAR-1 inhibition might have a potential benefit, but definitely not for long-term treatment, since the rate of bleeding increases over time."

Bleeding risk was not increased in patients who were not receiving a $P2Y_{12}$ inhibitor at randomization. Dr Tricoci believes that the use of vorapaxar "as an alternative, rather than as an adjunct, to current antiplatelet medication, or even as an adjunct, but for a shorter duration of treatment with better bleeding-risk stratification" warrants further study. The efficacy and safety of vorapaxar in patients with chronic, stable atherosclerotic cardiovascular disease, in whom a dual-antiplatelet regimen is less common than in patients with ACS, is being assessed in the phase III TRA 2P–TIMI 50 trial.

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