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ANTIPLATELET THERAPY

Vorapaxar beneficial in setting of prior MI, but not in patients who have experienced a stroke

Findings from a study presented at the 2012 ACC Scientific Sessions in Chicago, IL, USA, and published online in the *New England Journal of Medicine* have indicated that a new class of antiplatelet therapy could be of benefit to patients with stable atherosclerotic disease who have previously experienced a myocardial infarction (MI). The phase III randomized, double-blind, placebo-controlled trial, called TRA 2P-TIMI 50, assessed the efficacy and safety of the protease activated receptor 1 thrombin receptor antagonist vorapaxar. "This is the first study to show definitively that blocking this pathway reduces risk of suffering another cardiovascular event," first author of the study David Morrow is quoted as saying in a press release issued by the ACC.

Dr Morrow and colleagues in the TIMI study group at the Brigham & Women's Hospital in Boston, MA, USA, designed and led the phase III study of vorapaxar in 26,449 patients with a history of atherosclerosis. The data were collated from a total of 1,032 sites in 32 countries.

The primary efficacy end point of the trial was a composite of cardiovascular death, MI, or stroke. This end point originally also included recurrent ischemia leading to urgent coronary revascularization, but was amended after a review of data from the TRACER trial, in which vorapaxar was assessed for the management of acute coronary syndromes. The composite end point that included recurrent ischemia leading to urgent coronary revascularization was converted into the major secondary efficacy end point of the trial. The primary safety end point was moderate or severe bleeding, as defined using the GUSTO classification system.

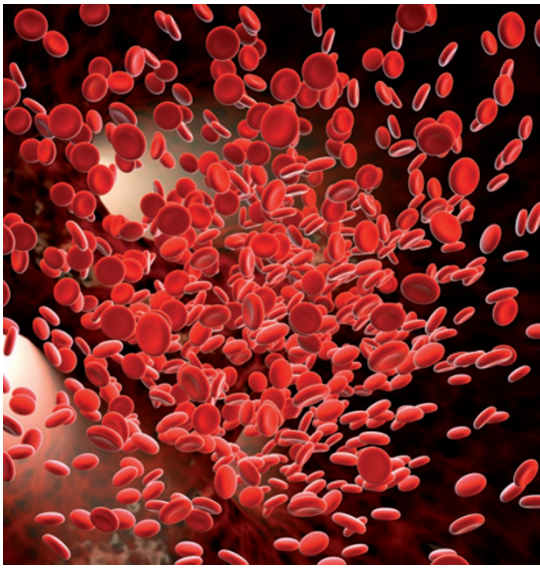
MI, stroke, and peripheral artery disease were the qualifying diagnoses for enrollment in 67.2%, 18.5%, and 14.3% of patients, respectively. In total, 13,225 patients were randomly assigned to receive vorapaxar and 13,244 patients received placebo. At baseline, 93.5% of patients were taking aspirin and 62.2% of patients were taking a thienopyridine. Median follow-up was 30 months.

Notably, in January 2011 (median follow-up of 24 months), the data and safety monitoring board recommended discontinuation of vorapaxar treatment in patients with a history of stroke, owing to an excessive rate of intracranial hemorrhage in this group of patients. All patients who had not previously experienced stroke were able to continue in the trial.

At 3 years, the composite primary efficacy end point had occurred in a smaller proportion of patients receiving vorapaxar compared with individuals receiving placebo (9.3% vs 10.5%, HR 0.87, 95% CI 0.80–0.94, $P<0.001$). Similar findings were reported for the secondary efficacy end point (11.2% vs 12.4%, HR 0.88, 95% CI 0.82–0.95, $P=0.001$).

Compared with individuals on placebo, more patients assigned to vorapaxar experienced GUSTO moderate or severe bleeding (4.2% vs 2.5% , HR 1.66, 95% CI 1.43–1.93, $P<0.001$). Occurrence of fatal bleeding did not differ significantly between the two treatment groups. In total, 1.0% of the vorapaxar group and 0.5% of the placebo group experienced intracranial hemorrhage (HR 1.94, 95% CI 1.39–2.70, $P<0.001$).

Notably, vorapaxar was found to reduce risk of cardiovascular death, MI, or stroke in patients whose qualifying diagnosis for enrollment was MI (HR 0.80, 95% CI 0.72–0.89, $P<0.001$), but not in patients whose qualifying diagnosis was stroke (HR 1.03, 95% CI 0.85–1.25) or peripheral artery disease (HR 0.94, 95% CI 0.78–1.14). In patients whose qualifying diagnosis was MI, vorapaxar was associated with a significantly increased risk of GUSTO moderate or severe bleeding (HR 1.61, 95% CI 1.31–1.97, $P<0.001$) and a trend towards increased risk of intracranial hemorrhage (HR 1.54, 95% CI 0.96–2.48, $P=0.076$).



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Among patients with a history of stroke, regardless of whether stroke was the qualifying diagnosis for enrollment, vorapaxar was not associated with a significantly reduced risk of the primary efficacy end point (HR 0.95, 95% CI 0.80–1.11). However, vorapaxar was associated with significantly higher risk of GUSTO moderate or severe bleeding (HR 1.74, 95% CI 1.26–2.39, $P<0.001$) and a substantial increase in risk of intracranial hemorrhage (HR 2.55, 95% CI 1.52–4.28, $P<0.001$), compared with placebo.

On the basis of the TRA 2P-TIMI 50 data, Dr Morrow warns that vorapaxar is probably not suitable for all patients with atherosclerosis; he points out that "the benefit was compelling to us only in patients with a prior heart attack". Nevertheless, he is excited "to find clearly that we can reduce the risk of a recurrent thrombotic event by adding another platelet inhibitor to aspirin over the long term."

Bryony M. Mearns

Original article Morrow, D. A. *et al.* Vorapaxar in the secondary prevention of atherothrombotic events. *N. Engl. J. Med.* doi:10.1056/NEJMoa1200933