Evaluation of a Novel Antiplatelet Agent for Secondary Prevention in Patients With Atherosclerotic Disease: Results from the TRA 2P-TIMI 50 Trial

Written by Maria Vinall

In stable patients with a history of atherosclerosis, the investigational protease-activated receptor (PAR)-1 antagonist vorapaxar was effective at reducing further atherothrombotic events. David A. Morrow, MD, MPH, Brigham & Women's Hospital, Boston, Massachusetts, USA, presented data from the Thrombin Receptor Antagonist in Secondary Prevention-TIMI 50 Trial [TRA 2P; NCT00526474] which showed that vorapaxar significantly reduced the risk of deaths from cardiovascular disease (CVD), myocardial infarction (MI), or stroke compared with placebo.

This was a worldwide, placebo-controlled, randomized, double-blind study that enrolled 26,449 patients (median age 61 years) with a history of spontaneous MI, ischemic stroke, or peripheral arterial disease (PAD). Subjects were treated with 2.5 mg/day vorapaxar or placebo, in addition to standard care including aspirin and/or thienopyridine. Overall, patients were followed for a median of 30 months. However, after a median follow-up of 24 months, treatment was discontinued in patients with a history of stroke due to a higher risk of intracranial hemorrhage (ICH) in that population. The primary efficacy endpoint was a composite of CV death, MI, or stroke. The secondary composite endpoint also included urgent coronary revascularization. The primary safety endpoint was GUSTO moderate or severe bleeding. The primary analysis was conducted on all data from all randomized patients. Additional analyses were conducted on patients without prior stroke and those who qualified with MI (67% of subjects).

In the overall population, the primary endpoint occurred in 9.3% of subjects who were randomized to vorapaxar compared with 10.5% of those who were randomized to placebo (HR, 0.87; 95% CI, 0.80 to 0.94; p<0.001). Subjects who qualified with an MI had a significant benefit from treatment with vorapaxar (HR, 0.80; 95% CI, 0.72 to 0.89), as did all patients (MI and PAD cohorts) without a history of stroke (8.3% vs 9.6%; HR, 0.84; 95% CI, 0.76 to 0.93; both p<0.001).

Voraxapar also significantly reduced the composite secondary endpoint (HR, 0.88; 95% CI, 0.82 to 0.95; p=0.001) and the composite of CV death or MI (HR, 0.86; 95% CI, 0.78 to 0.94; p=0.002). Both GUSTO moderate or severe and clinically significant TIMI bleeding were increased with vorapaxar (HR, 1.66; 95% CI, 1.43 to 1.93; and HR, 1.46; 95% CI, 1.36 to 1.57, respectively), as was ICH (HR, 1.94; 95% CI, 1.39 to 2.70; all p<0.001). There was no difference in fatal bleeding.

The investigators concluded that PAR-1 is a valuable novel target and that adding vorapaxar to standard therapy could be an effective treatment for long-term secondary prevention of atherothrombotic events in stable patients with a history of previous MI. However, the benefits for treating patients with PAD remain uncertain, and the risk of ICH in patients with prior stroke is unacceptable with this agent. Careful patient selection is recommended when using vorapaxar [Morrow DA et al. *N Engl J Med* 2012].

The HOST-ASSURE Randomized Trial

Written by Maria Vinall

Hyo-Soo Kim, MD, Seoul National University Hospital, Seoul, South Korea, reported results from a study that compared double- with triple-dose antiplatelet therapy (DAPT vs TAPT) in acute coronary syndrome (ACS) patients who were undergoing percutaneous coronary intervention (PCI), which showed no difference in net clinical outcomes between the two treatment regimens after 1 month.

The Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis – Safety & EffectiveneSS of Drug-ElUting Stents & Antiplatelet Regimen [HOST-ASSURE; NCT01267734] trial was a 2 x 2 factorial design trial that compared the safety and long-term effectiveness of coronary stenting, the everolimus-eluting stenting system, and the zotarolimus-eluting stenting system, as well as the short term efficacy and safety of TAPT, adding cilostazol to standard aspirin + clopidogrel dosing, versus DAPT with aspirin + higher-dose clopidogrel. The presentation by Prof. Kim focused only on the results of the comparison of the two antiplatelet regimens.

The HOST-ASSURE study comprised 3750 subjects who were undergoing PCI with drug-eluting stents (DES) at 40 centers in South Korea. Subjects were randomized in a 1:1 fashion to either TAPT (aspirin 100 mg daily, clopidogrel 75 mg daily, cilostazol 200 mg loading-dose followed by 100 mg twice daily) or DAPT (aspirin 100 mg daily, clopidogrel 150 mg daily). All patients were loaded with 300 mg of aspirin and 300 to 600 mg of clopidogrel prior to PCI. Patients with a left ventricular ejection fraction <25%, cardiogenic shock, or symptomatic heart failure were excluded from the study. The hypothesis that was being tested was that the net clinical outcome at 1 month with TAPT would be noninferior to that with DAPT. The net clinical outcome was defined as a composite of cardiac