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

death, nonfatal myocardial infarction (periprocedural or spontaneous), definite or probable stent thrombosis, stroke, or PLATO major bleeding. The noninferiority margin was set at 0.75% absolute. In other words, the study had 90% power to show that the rate of the net clinical outcome in patients who were assigned TAPT was not more than 0.75% higher than with DAPT, assuming that no difference in rates between the regimens truly existed.

Patients were well balanced between treatment assignments. The mean age was 63 years; one-third of subjects were women, one-third was diabetic, and one-third of subjects were current smokers. Approximately 50% of patients presented with an acute coronary syndrome (unstable angina or non-ST-segment elevation myocardial infarction [NSTEMI]), and 10% presented with STEMI. Concomitant use of beta-blockers (68%), statins (85%), and ACEI/ARB (65%) was frequent.

Thirty-five days after randomization, 1.44% of DAPT and 1.22% of TAPT-treated patients experienced the primary endpoint (ie, an absolute risk difference in favor of TAPT of 0.22%; p<0.001 for noninferiority; HR, 0.85; 95% CI, 0.49 to 1.48; p=0.57 for superiority). There were no significant differences between treatment groups when data were analyzed as individual risk components (all incidence rates were <1%), nor were there any differences in the rates of target lesion or vessel revascularization. Platelet reactivity (VerifyNow $P2Y_{12}$ Assay) was significantly (p<0.001) higher after clopidogrel loading and at the end of the study for patients who received the DAPT regimen.

Science Advisor's Note

This study has several limitations that are worthy of emphasizing. Comparing two treatment regimens for short-term noninferiority of a net clinical benefit does not easily lend itself to a clinically meaningful conclusion. In addition, the comparator treatment arm in this trial was one of the regimens that were tested in OASIS-7, which was not significantly different from standard-dose clopidogrel [*MD Conference Express*. ESC Edition 2009]. Thus, it is not clear how the investigational TAPT maintenance regimen compares with standard-dose DAPT post-DES. Prof. Kim cautioned that the event rates were also lower than expected, which biases a noninferiority comparison toward concluding that no difference exists. Since the noninferiority margin (0.75% absolute) was >50% of the observed event rate in the comparator group (1.44%), even a 50% relative increase in the event rate with TAPT (to 2.16%) would not have crossed the noninferiority margin (2.19%). In addition, it is possible that higher-than-anticipated (and differential) nonadherence rates to allocated treatment (13.5% in the DAPT regimen vs 8.4% in the TAPT regimen) biased the results toward the null. Until larger and longer duration trials are conducted with standard comparator groups and primary efficacy outcomes, it remains unclear whether either regimen is effective or safe for routine clinical practice after DES implantation.

New Monoclonal Antibody to PCSK9 Markedly Lowers LDL-C in Patients on Atorvastatin

Written by Rita Buckley

Proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) binds to low-density lipoprotein receptors (LDLRs) and plays a pivotal role in LDLR degradation [McKenney JM et al. *J Am Coll Cardiol* 2012]. James M. McKenney, PharmD, National Clinical Research, Inc., Richmond, Virginia, USA, reported outcomes on the low-density lipoprotein cholesterol (LDL-C)-lowering effects of SAR236553/REGN727 (SAR236553), a highly specific, fully human monoclonal antibody to PCSK9 [Efficacy and Safety Evaluation of SAR236553 (REGN727) In Patients With Primary Hypercholesterolemia and LDL-Cholesterol on Stable Atorvastatin Therapy; NCT01288443].

Three prior Phase 1 studies of SAR236553 have shown that the monoclonal antibody to PCSK9 significantly reduces LDL-C levels in healthy volunteers and in subjects with familial or nonfamilial hypercholesterolemia [Stein EA et al. *N Engl J Med* 2012].

The current Phase 2 dose-ranging study was a double-blind, parallel-group, placebo-controlled, multicenter trial. It included patients aged 18 to 75 years with LDL-C ≥100 mg/dL (2.59 mmol/L) who were on stable-dose atorvastatin at 10 mg, 20 mg, or 40 mg for ≥6 weeks. A total of 183 individuals were randomized to either subcutaneous placebo every 2 weeks (Q2W); SAR236553 at 50 mg, 100 mg, or 150 mg (Q2W); or SAR236553 at 200 mg and 300 mg once every 4 weeks (Q4W) with an alternating placebo injection at 2 weeks.

The primary objective of the study was to evaluate the safety and LDL-C-lowering effect of 12 weeks of treatment with SAR236553 versus placebo. The primary study endpoint was the percentage change in calculated LDL-C from baseline (mean of Week -1 and Week 0) to Week 12.

The addition of SAR236553 resulted in a significant decrease in LDL-C from baseline. A clear dose-response relationship with respect to percentage of LDL-C lowering