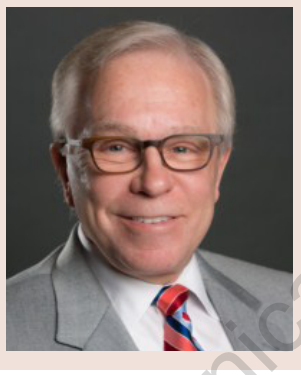
Anthony Comerota, MD, Describes Vorapaxar for Peripheral Arterial Disease

Interview by Jennifer Ford



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Anthony Comerota, MD, is a vascular surgeon from the Jobst Vascular Institute in Toledo, Ohio, and adjunct professor of surgery at the University of Michigan in Ann Arbor, Michigan. He was also a participant in the TRA 2°P study, a pivotal trial of vorapaxar for patients with peripheral arterial disease (PAD). *Vascular Disease Management* spoke with Dr. Comerota at the 2015 VEITH Symposium about data on effectiveness of vorapaxar for patients with PAD.

VDM: Share a little bit about vorapaxar and why it's different from other platelet inhibitors.

Comerota: Vorapaxar is different from other platelet inhibitors because it acts on the protease-activated receptor-1 (PAR-1) receptor of the platelet. That is the receptor activated by thrombin. When thrombin activates the PAR-1 receptor, it auto activates the platelet and stimulates a generous platelet response. Thrombin is actually one of the most potent activators of platelets, and it has a different mechanism of action than the adenosine diphosphate or thromboxane receptors on platelets.

VDM: What data have been collected about vorapaxar and specifically about its effects in the periphery?

Comerota: The pivotal trial was published by Morrow et al on behalf of the TRA 2°P investigators in *the New England Journal of Medicine* in 2012. That was a large trial evaluating 26,449 patients using vorapaxar as add-on therapy to prevent major adverse cardiovascular events (MACE) and to look at whether it prevented major adverse limb events (MALE). The patients that were entered into the trial were those with myocardial infarction, stroke, and peripheral arterial disease (PAD). After about 2 years, the investigators noticed that the patients who were entered into the trial with stroke had an unacceptably high rate of intracranial bleeds, so the data and safety monitoring board recommended that that group be eliminated and the FDA agreed. So, the target population for vorapaxar is patients who have had a myocardial infarction and patients with peripheral arterial disease.

The primary efficacy endpoints were cardiovascular death, myocardial infarction, and stroke, and the primary safety endpoints were major and moderate bleeding according to the GUSTO (Global Utilization of Streptokinase and Tpa for Occluded arteries) criteria. The results demonstrated a significant reduction in cardiovascular death, myocardial infarction, and stroke in the target population. The cost was an increased risk of bleeding, but it was a combination of both major and moderate bleeding. When you're trading off cardiovascular death, myocardial infarction, or stroke, it's a price we might be willing to pay.

VDM: How about the subset of PAD patients?

Comerota: The PAD patients were analyzed by Bonaca et al, who published their report in *Circulation* in 2013. It appears that PAD patients benefit considerably from add-on therapy with vorapaxar. In this group of 3,787 patients, there was as significant reduction in MACE, but also importantly and uniquely, there was a significant reduction in MALE. Subsequent hospitalization for acute limb ischemia and the subsequent need for lower-extremity revascularization were reduced in patients randomized to vorapaxar.

VDM: Were there any data on the diabetic patients that were remarkable?

Comerota: Yes, diabetes is a significant risk for PAD and the diabetic patients benefited more according to the subset analysis that was performed. The number needed to treat to prevent one major adverse event was 59, but in the diabetic population, the number dropped to 36. Across the board, that's considered a good return on your clinical investment.

VDM: How will this potentially change the way that vascular clinicians approach peripheral arterial disease?

Comerota: We know that patients with PAD remain at high risk for heart attack, stroke, vascular death, and limb ischemia. Even today, those patients are undertreated compared to patients with recognized heart disease. We now have a new medication, vorapaxar, which is add-on therapy that doesn't require discontinuing other drugs that patients may need. Vorapaxar reduced both MACE and MALE in the same population of patients. I believe this is a new observation. ■

Editor's note: *Dr. Comerota reports speakers' bureau payments related to the content herein.*