Perspectives on Secondary Prevention of Atherothrombotic Events

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The risk of recurrent cardiovascular (CV) events in patients with a history of atherothrombosis remains high, at about 10% annually, despite the use of guideline-based, disease-modifying therapies, stated Deepak L. Bhatt, MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA.

The REACH registry demonstrated that patients with a history of ischemic events had a higher rate of CV death, myocardial infarction (MI), or stroke at 4 years and that this event rate was markedly increased in the presence of polyvascular disease or diabetes [Bhatt DL et al. *JAMA*. 2010]. Analyses from REACH also showed that polyvascular disease contributes to increased health care costs. In the United States, there was a linear increase in the number of affected vascular beds and 1-year vascular-related hospitalization costs [Mahoney EM et al. *Circ Cardiovasc Qual Outcomes*. 2008].

Strategies for secondary prevention are being investigated, including the search for novel drugs. The CHARISMA study [Bhatt DL et al. *N Engl J Med*. 2006] showed that dual antiplatelet therapy (DAPT) with aspirin and the $P2Y_{12}$ inhibitor clopidogrel alone did not reduce the primary composite outcome of CV death, MI, or stroke in primary prevention patients when compared with aspirin. However, there was evidence of a possible benefit with clopidogrel in the subgroup of patients who had coronary artery disease (CAD), cardiovascular disease (CVD), or peripheral artery disease (PAD) at baseline (RR 0.88; 95% CI, 0.77 to 0.998; $P=.046$). Similar findings were seen in the TRA 2°P study [Morrow DA et al. *N Engl J Med*. 2012], stated Dr Bhatt, which showed that the novel vorapaxar reduced the primary composite outcome of CV death, MI, or stroke (HR 0.87; 95% CI, 0.80 to 0.94; $P<.001$) in patients with either prior MI, stroke/TIA or established peripheral arterial disease.

Eric R. Bates, MD, University of Michigan Medical Center, Ann Arbor, Michigan, USA, discussed strategies to address residual risk through secondary prevention in patients following an acute coronary syndrome (ACS). Risk factor management is usually addressed through cardiac rehabilitation and includes management of weight and lipids, control of hypertension and glucose, and smoking cessation. The primary medical therapies used today are aspirin, $P2Y_{12}$ Inhibitors, β-blockers, statins, and renin-angiotensin-aldosterone system blockers [Smith SC et al. *Circulation*. 2011].

Despite the development of new antiplatelet drugs, aspirin should be a mainstay in secondary prevention of ACS, stated Dr Bates, because of its demonstrated efficacy in reducing CV events in patients with ACS. The CURE trial [Yusuf S et al. *N Engl J Med*. 2001] found that the $P2Y_{12}$ inhibitor clopidogrel, when combined with aspirin, resulted in an additional 20% relative risk reduction in patients with NSTEMI. These findings, as well as others, have led to DAPT being the standard of care for patients both with ACS and following treatment with coronary stents. The CLARITY-TIMI 28 trial [Sabatine MS et al. *N Engl J Med*. 2005] showed that, in patients with STEMI receiving aspirin and fibrinolytic therapy, adding clopidogrel produced an additional 20% reduction in CV death, MI, recurrent ischemia requiring urgent revascularization.

Prasugrel and ticagrelor are newer $P2Y_{12}$ inhibitors that are more effective than clopidogrel, a drug that has a slower onset and offset of action and a lack of response in some patients. In patients with ACS undergoing a percutaneous intervention (PCI), prasugrel was more effective than clopidogrel in reducing CV death, MI, or stroke (HR 0.81; $P<.001$) in the TRITON-TIMI 38 study [Wiviott SD et al. *N Engl J Med*. 2007]. The TRILOGY-ACS study [Roe MT et al. *N Engl J Med*. 2012] found no significant difference between prasugrel and clopidogrel (HR 0.91; $P=.21$) in patients with UA/NSTEMI not undergoing revascularization. Ticagrelor significantly reduced CV death, MI, or stroke compared with clopidogrel in ACS in the PLATO trial (HR 0.84; $P<.001$) [Wallentin L et al. *N Engl J Med*. 2009].

Additional benefit may be gained with triple therapy, as shown by the ATLAS ACS 2-TIMI 51 trial [Mega JL et al. *N Engl J Med*. 2012]. Rivaroxaban 2.5 mg twice daily added to aspirin and a thienopyridine significantly reduced the primary composite outcome of CV death, MI, and stroke as compared with placebo. CV death and all-cause death were also reduced with rivaroxaban. However, ATLAS ACS 2-TIMI 51 is the only phase III trial of triple therapy to show benefit.

Although current oral antiplatelet agents inhibit pathways involving thromboxane A_2 (aspirin) and adenosine diphosphate ($P2Y_{12}$ inhibitors), Marc S. Sabatine, MD, MPH, TIMI Study Group, Brigham and Women's Hospital, Boston, Massachusetts, USA, stated they do not inhibit thrombin-mediated platelet activation via protease-activated receptor-1 (PAR-1) binding. Activation of the PAR-1 receptor by thrombin leads to platelet activation

Table 1. Major Bleeding Outcomes in TRA 2°P -TIMI 50 Trial by Stroke Status

	History of Stroke (n = 5746)				No History of Stroke (n = 20 699)			
	Vorapaxar	Placebo	HR	*P* Value	Vorapaxar	Placebo	HR	*P* Value
TIMI non-CABG major bleeding	4.1	2.1	1.87	< .001	2.5	1.8	1.35	.005
Intracranial hemorrhage	2.4	0.9	2.55	< .001	0.6	.04	1.55	.049
Fatal bleeding	0.5	0.3	1.48	.46	0.3	0.2	1.44	.30

CABG, coronary artery bypass grafting.
Source: Morrow DA et al. *N Engl J Med*. 2012.

and changes in endothelial and smooth muscle cells that play a role in the development of atherothrombosis.

The activation of PAR-1 receptors is inhibited by a new agent, vorapaxar, which has been shown to have nearly total inhibition in a pharmacodynamics study of patients undergoing coronary angiography and PCI [Becker RL et al. *Lancet*. 2009].

The TRA•CER trial [Tricoci P et al. *N Engl J Med*. 2012] in about 13,000 patients with NSTE ACS showed that vorapaxar added to standard of care did not significantly reduce the primary composite outcome of CV death, MI, stroke, hospitalization for ischemia, or urgent coronary revascularization (18.5% vs 19.9%; HR 0.92; 95% CI, 0.85 to 1.01; *P* = .07) when compared with placebo. The secondary outcome of CVD, MI, and stroke was reduced by 11% (HR 0.89; 95% CI, 0.81 to 0.98; *P* = .02). GUSTO moderate/severe bleeding was increased with vorapaxar vs placebo (HR 1.35; 95% CI, 1.16 to 1.58; *P* < .001). This increased risk of bleeding seemed to be driven by the higher rate of intracranial hemorrhage (ICH) with vorapaxar vs placebo (1.1% vs 0.2%).

The secondary prevention TRA 2°P-TIMI 50 trial [Morrow DA et al. *N Engl J Med*. 2012] showed that vorapaxar, when used in addition to standard of care, reduced the risk of the primary outcome of CV death, MI, or stroke (9.3% vs 10.5%; HR 0.87; 95% CI, 0.80 to 0.94; *P* < .001) as compared with placebo. Patients with a lower body weight (< 60 kg) and a history of stroke at baseline did not benefit with vorapaxar, while benefit was seen in all other prespecified subgroups.

Notably, vorapaxar was stopped in patients with a history of stroke (baseline or during trial) on the recommendation of the independent data safety and monitoring committee because of an increased rate of ICH. A similar pattern of more bleeding in patients with a prior stroke was seen in TRITON-TIMI 38 with prasugrel as compared with clopidogrel. The rates of major bleeding, ICH, and fatal bleeding in the patients with and without a history of stroke in TRA 2°P -TIMI 50 are detailed in Table 1.

A subgroup analysis of patients with an MI at baseline (aged < 75 years, no history of stroke/TIA, weight ≥ 60 kg) in TRA 2°P -TIMI 50 showed a greater reduction in CV death, MI, or stroke (HR 0.75; *P* < .0001) and CV death (HR 0.73; *P* = .02) [Scirica BM et al. *Lancet*. 2012]. The benefit seen with vorapaxar vs placebo at 1 year in reducing CV death and ischemic events (3.2% vs 4.0%; *P* < .003) persisted out to 3 years (5.5% vs 6.5%; *P* = .004), suggesting an accrual of benefit over time in patients who receive more potent antiplatelet therapy long term. These findings complement prior data from the TRITON-38 and PLATO studies.

Sunil V. Rao, MD, Duke University Medical Center, Durham, North Carolina, USA, stated that the CRUSADE registry showed that polyvascular disease is associated with a high risk of long-term (> 5 years) major adverse cardiac events (MACE) [Subherwal S et al. *Circulation*. 2012], predominantly due to underdiagnosis, which leads to undertreatment. The REACH registry showed that approximately 40% of patients with CVD and 25% of patients with CAD have manifestations of atherothrombosis in another vascular bed [Steg PG et al. *JAMA*. 2007]. However, this figure rises to approximately 60% in patients with PAD, mostly because these patients are often undertreated and therefore have advanced disease by the time they present. Indeed, the 1-year risk of the composite of CV death, MI, stroke, or hospitalization for atherothrombotic events was 14.5% in patients with CVD, 15.2% with CAD, and 21.1% with PAD.

To address the issue of underdiagnosis of PAD, Dr Rao stated a comprehensive vascular assessment of patients with CAD must include a visual assessment of their feet (shoes removed) and asking about symptoms of claudication. He noted that routine ankle brachial index (ABI) testing is now required for patients with CAD at his institution.

The therapeutic options are limited for treatment of polyvascular disease, stated Dr Rao. The CAPRIE trial showed a greater reduction in events with clopidogrel when compared with aspirin. PAR-1 inhibition with vorapaxar on top of standard of care therapy was effective when used for secondary prevention in the TRA 2°P-TIMI 50 trial, and reduced CV death, MI, or stroke. Although vorapaxar represents a viable option as add-on treatment to aspirin in patients with polyvascular disease to reduce the risk of thrombotic CV events, vorapaxar is contraindicated in patients with a history of stroke due to the increased risk of ICH [Morrow DA et al. *N Engl J Med*. 2012].