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EDITORIAL COMMENT

Appropriate Use of Vorapaxar in Patients With Peripheral Artery Disease*

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Antiplatelet pharmacology is an essential strategy in the management of patients with atherosclerosis. For reasons that are not entirely elucidated, there is heterogeneity in the benefits of antiplatelet therapy in patients with coronary artery disease, cerebrovascular disease, and peripheral arterial disease (PAD). In PAD patients, the benefits of antiplatelet therapy are uncertain. In 1 large study and another meta-analysis, aspirin was no better than placebo in asymptomatic PAD patients for primary prevention of major adverse cardiovascular events (MACE) (including cardiovascular death, myocardial infarction [MI], and stroke) (1,2). Although 1 study showed a significant reduction in MACE in symptomatic PAD patients treated with clopidogrel compared with aspirin (3), another showed no benefit of dual therapy with clopidogrel plus aspirin compared with aspirin alone in asymptomatic or symptomatic patients (4). Although contemporary approaches to oral antiplatelet therapy are usually achieved by inhibition of the cyclo-oxygenase-1 pathway and by inhibition of $P2Y_{12}$ adenosine diphosphate receptors, thrombin is the most potent platelet activator; oral thrombin inhibitors could have potential value in patients with atherosclerosis.

Vorapaxar (Zontivity, Merck Sharpe & Dohme Corporation, Whitehouse Station, New Jersey) is a selective inhibitor of platelet protease activated receptors-1 and -4 that mediate platelet-thrombin interactions, but has no impact on platelet activation by other agonists, and has no impact on coagulation or bleeding times. Vorapaxar acquired approval from the Food and Drug Administration in 2014 after the placebo-controlled pivotal trial (TRA 2P–TIMI 50 [Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50]) showed significant reduction in the 3-year risk of MACE among 26,449 patients with coronary artery disease, cerebrovascular disease, or PAD (5). It is notable that vorapaxar was used as an adjunct to dual antiplatelet therapy with aspirin and clopidogrel in the majority of patients. Unfortunately, compared with placebo, vorapaxar caused a significant increase in the risk of moderate or severe bleeding, including intracranial hemorrhage, resulting in early termination in patients with a history of stroke. The current Food and Drug Administration approval is for reduction in cardiovascular events among patients with history of MI or PAD, and no history of stroke or transient ischemic attacks.

In addition to the pivotal trial and studies in other patient subgroups, there are 3 substudies from TIMI-50 in patients with PAD (based on claudication plus abnormal ankle/brachial index or prior history of peripheral revascularization). In the first substudy, there were 3,787 patients who were randomized in the PAD cohort; vorapaxar did not have a significant benefit on the risk of MACE when compared with placebo, but did result in significantly more bleeding complications (6). Although not part of the primary efficacy endpoint, vorapaxar resulted in significant reduction in acute limb ischemia (ALI) and peripheral revascularization. The second substudy was performed in the 150 patients with ALI, and demonstrated a significant reduction in the risk of ALI with vorapaxar, whether caused by acute thrombosis of a bypass graft or native vessel (7). Given the small sample size, there was no difference in bleeding between ALI patients treated with vorapaxar compared with placebo.

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The third substudy from TIMI-50 is the current study by Bonaca et al. (8) that is published in this issue of *JACC: Cardiovascular Interventions*. This study includes 5,845 PAD patients among the 26,449 patients in TIMI-50. The risk of major adverse limb events (MALE) (defined as endovascular or surgical revascularization or amputation) was 16% at 3 years, and the indications for revascularization included progressive claudication in 55%, critical limb ischemia in 24%, ALI in 16%, and asymptomatic severe stenosis identified during routine surveillance in 4%. The individual components of MALE included

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endovascular intervention in 70%, surgical revascularization in 25%, and amputation in 5% (no information about the level of amputation or whether some were limited amputations were performed after revascularization). The principal findings of this study at 3 years are: 1) compared with placebo, there was significant reduction in MALE among patients treated with vorapaxar; 2) the reduction in MALE was due to a significant reduction in the need for surgical revascularization, not endovascular intervention or amputation; and 3) compared with placebo, there was a nonsignificant trend toward reduction in MALE in patients with progressive claudication, but no significant reduction in patients with ALI, critical (chronic) limb ischemia, or asymptomatic severe stenosis. The main limitation of this study is that the authors have obscured these findings by emphasizing the directional consistency of their results, in the absence of significant differences.

Nevertheless, there seem to be consistencies among the 3 published PAD substudies of TIMI 50, which may have implications for future studies and for appropriate use of vorapaxar. First, as is true of some studies of aspirin and clopidogrel, vorapaxar does not seem to be useful for secondary prevention of MACE in PAD patients, although there is benefit in patients with prior MI. Second, given issues about cost and bleeding complications, it seems unlikely that there will be much enthusiasm for vorapaxar for triple antiplatelet therapy after routine MI or stenting. However, studies of vorapaxar alone or in combination with a single antiplatelet agent might prove beneficial, possibly without the risk of major bleeding. Alternatively, there may be subgroups of high-risk patients who might benefit from triple therapy. Third, the usefulness of vorapaxar in patients with PAD and peripheral bypass conduits suggests that it may have potential value in patients with coronary artery bypass grafts, who are also at high risk for early thrombosis and accelerated atherosclerosis. Finally, further studies are needed to determine the value of vorapaxar in patients with aspirin hypersensitivity or low on-treatment platelet reactivity with other antiplatelet agents.

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