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Balancing the Risks and Benefits of Long-Term Antiplatelet Therapies for Cardiovascular Disease: Clinical, Research, and Regulatory Implications

Joakim Alfredsson, MD, PhD; Matthew T. Roe, MD, MHS

Thrombin is a key stimulus for fibrin generation as well as a potent platelet activator through interaction with protease-activated receptors on the platelet surface.[1] Vorapaxar is a reversible and selective inhibitor of the PAR-1 receptor, the major thrombin receptor on platelets, and has been evaluated in 2 large clinical trials. A total of 12 944 patients with non–ST elevation acute coronary syndrome were randomized in the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER)[2] trial, whereas 26 449 patients with a history of myocardial infarction (MI), ischemic stroke, or peripheral artery disease (PAD) were randomized in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P)[3] trial. In both studies, vorapaxar was compared with placebo in a blinded fashion in addition to standard of care therapies, including either single antiplatelet therapy with aspirin or dual antiplatelet therapy (DAPT) with aspirin plus a P2Y12 antagonist. Although the primary efficacy end point in the TRA 2°P trial (a composite of cardiovascular death, MI, or stroke) was significantly reduced with vorapaxar compared with placebo, the primary efficacy end point in the TRACER trial (a composite of cardiovascular death, MI, stroke, or recurrent ischemia with rehospitalization or urgent revascularization) was not significantly reduced. In both trials, the addition of vorapaxar increased bleeding rates substantially, especially among patients with a history of prior stroke. When this amplified bleeding risk among patients with a prior stroke was identified by the common data safety and monitoring board in both trials (after completion of enrollment for both TRACER and TRA 2°P), follow-up in the TRACER trial was stopped prematurely, and the study drug was discontinued among patients with prior stroke in the TRA 2°P trial; patients with prior MI and prior PAD continued on the study drug until planned trial completion. Subsequently, vorapaxar was approved by the US Food and Drug Administration (FDA) in the United States in May 2014 for the subpopulation of patients from the TRA 2°P trial with prior MI or prior PAD but without a history of prior stroke.

In this issue of *JAHA: Journal of the American Heart Association*, Magnani and colleagues present data from this subpopulation of the TRA 2°P trial for which vorapaxar was ultimately approved by the FDA.[4] The study population consisted of 20 170 patients: 16 897 qualified for the trial with a history of prior MI, and 3273 qualified with a history of PAD. At the time of randomization, 97% were treated with aspirin and 71% were treated with a P2Y12 of patients antagonist (almost exclusively clopidogrel). Over 3 years of follow-up, the frequency of the combined efficacy end point of cardiovascular death, MI, or stroke was significantly reduced with vorapaxar versus placebo (7.9% versus 9.5%; hazard ratio 0.80, 95% CI 0.73 to 0.89), but the frequency of the primary safety end point—Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for moderate or severe bleeding—was significantly increased with vorapaxar (3.7% versus 2.4%; hazard ratio 1.55, 95% CI 1.30 to 1.86). Although there was no significant difference in the risks of intracranial hemorrhage or fatal bleeding with vorapaxar versus placebo, the absolute reduction in the risk of cardiovascular death, MI, or stroke of 1.6% was counterbalanced by an absolute increase of 1.3% in clinically meaningful bleeding events.

The results from the different subgroups of the TRA 2°P trials have been reported previously, but the data contained within this paper represent the first report of the unique composite patient cohort that led to the approval of vorapaxar by the FDA for the secondary prevention of cardiovascular disease. These results deserve closer consideration for a number of reasons.[5–7]

First, the optimal combinations of antiplatelet therapies and the preferred duration of antiplatelet treatment for the

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From the Duke Clinical Research Institute, Durham, NC.

Correspondence to: Matthew T. Roe, MD, MHS, 2400 Pratt Street, Room 7035, Durham, NC 27705. E-mail: matthew.roe@duke.edu

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secondary prevention of cardiovascular disease are being reconsidered in light of other studies. The most recent version of the American College of Cardiology/American Heart Association (ACC/AHA) non-ST elevation acute coronary syndrome practice guidelines published in September 2014 recommends DAPT with aspirin plus a P2Y12 antagonist (clopidogrel, prasugrel, or ticagrelor for specific indications) for up to 12 months after non-ST-segment elevation MI (with shorter durations to be considered for patients with a high bleeding risk) and indefinite aspirin therapy.[8] Conversely, the most recent version of the PAD guidelines, published in April 2013, recommends either aspirin or clopidogrel monotherapy for the long-term treatment of PAD.[9] Both sets of practice guidelines were published before or just after the FDA recommendation for vorapaxar was announced, so currently there are no clear recommendations from professional societies on the use of vorapaxar for the secondary prevention after MI or following the identification of PAD. Newly published data for prolonged DAPT from 12 to 30 months following coronary stent placement from the Dual Antiplatelet Therapy (DAPT) trial[10] and for extended DAPT beyond 12 months for patients with a prior MI from the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin (PEGASUS) trial[11,12] suggest that prolonged DAPT with aspirin plus a P2Y12 antagonist may receive a strong endorsement in future guideline recommendations for the secondary prevention of patients with cardiovascular disease. Within this context, the positioning of vorapaxar in combination with other antiplatelet therapies is expected to be nuanced, especially because vorapaxar has not been studied with the more potent P2Y12 antagonists (prasugrel and ticagrelor).

Second, balancing the risks and benefits with combinations of antiplatelet therapies for the secondary prevention of cardiovascular disease is an evolving and challenging conundrum. Although treatment regimens with DAPT and those with vorapaxar plus aspirin or vorapaxar plus DAPT have been shown to reduce ischemic events, there has been a consistent increase in major bleeding events with additional and/or intensified antiplatelet agents beyond aspirin as a cornerstone therapy.[2,3,10,13–15] Major bleeding events are clearly associated with a higher risk of mortality and other ischemic events, but the mechanisms behind this association are complex and likely are related to multiple concurrent factors including patient comorbidities that track with bleeding risk (eg, advanced age, renal insufficiency), adverse consequences of premature discontinuation of antiplatelet agents following a major bleeding event, and residual confounding.[16,17] Patients with prior stroke are an especially vulnerable group because they are at a disproportionate increased risk of bleeding, specifically intracranial hemorrhage, if treated with intensified antiplatelet therapy or combinations of antiplatelet agents.[2,3,14,15,18] The ACC/AHA non-ST elevation acute coronary syndrome practice guidelines provide a glimpse into the challenging nature of decision making for individual patients by designating a class IIaC recommendation for shorter durations of DAPT following stent implantation (<12 months) if the perceived risks of morbidity associated with bleeding outweigh the potential benefits of the recommended 12 months of DAPT in this setting.[19] Notwithstanding the complex interplay between ischemic benefits and bleeding risks for multiple different antiplatelet regimens for the secondary prevention of cardiovascular disease, improved risk prediction tools are needed to more precisely estimate patient-specific long-term ischemic and bleeding risks and to guide clinical decision making in the future.

Finally, the decision of the FDA to accept a subgroup analysis of a clinical trial for the approval of a new antithrombotic therapy is unprecedented. Publicly available documents from the regulatory review process provide some insight into the process that led to the approved indication for vorapaxar.[20] The reported reason for the FDA to consider the approval of vorapaxar for a subpopulation of the TRA 2°P trial was that the overall trial results demonstrated a significant reduction in the primary composite end point of cardiovascular death, MI, or stroke as well as in key secondary end points. Nevertheless, 2 key issues arose. First, it was clearly shown that there was no ischemic benefit for patients with a prior stroke as qualifying event, but those patients had an increased risk of bleeding and intracranial hemorrhage with vorapaxar.[7] Based on these data, it was concluded that all prior stroke patients should be removed from the indicated population for safety reasons. Patients with a prior transient ischemic attack were also excluded because of the difficulties of distinguishing the diagnosis of transient ischemic attack from stroke. Second, it was determined that for patients with PAD as qualifying event, there was no significant ischemic benefit with vorapaxar in the primary composite end point; however, when patients with a prior stroke were excluded from the PAD population,[6] the hazard ratio for vorapaxar versus placebo for the primary end point was similar to that of the overall population (hazard ratio 0.87, 95% CI 0.71 to 1.06). In contrast, similar safety concerns among patients with prior stroke or transient ischemic attack seen with prasugrel plus aspirin compared with clopidogrel plus aspirin for acute coronary syndrome patients undergoing percutaneous coronary intervention prompted a black box warning for prior stroke or transient ischemic attack on the prasugrel label.[14] The decision to carve out a subpopulation of patients from the TRA 2°P trial for the approval of vorapaxar versus requiring a black box warning similar to that on the prasugrel label may be related to the diverse nature of the different qualifying subgroups of patients (prior MI, prior stroke, or

PAD) but also may reflect an evolution of the regulatory review and decision-making process for antithrombotic therapies. Nonetheless, the entire regulatory process for vorapaxar deserves closer scrutiny to provide insight into how future development programs for novel antiplatelet and antithrombotic therapies should be structured to bring safe and effective treatments into practice.

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