VIEWPOINT

Secondary Prevention of Cardiovascular Disease With Vorapaxar

A New Era of 3-Drug Antiplatelet Therapy?

Mori J. Krantz, MD
Division of Cardiology, University of Colorado School of Medicine, Aurora; Denver Health Medical Center, Denver, Colorado; and Colorado Prevention Center, Aurora.

Sanjay Kaul, MD
Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California; and David Geffen School of Medicine at the University of California, Los Angeles.

Corresponding Author: Mori J. Krantz, MD, Denver Health Medical Center, 777 Bannock St, MC 0960, Denver, CO 80204 (mori.krantz@dhha.org).

In May 2014, the US Food and Drug Administration (FDA) approved vorapaxar (Zontivity; Merck), an oral antiplatelet agent, for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction or peripheral arterial disease.[1] The FDA acted after a 10 to 1 vote in favor of approval in January 2014 by the Cardiovascular and Renal Drugs Advisory Committee; both of us were members of this committee, and one of us (M.J.K.) cast the negative vote. Physicians should understand the benefit-risk balance of vorapaxar: the important benefit is the drug's potential role in clinical practice as part of a 3-drug antiplatelet regimen for secondary prevention of myocardial infarction and in peripheral artery disease; the serious risk is clinically significant bleeding, including intracranial hemorrhage.

Findings of Acceptable Risk?

The FDA approved vorapaxar after reviewing the results of a pivotal trial involving about 26 500 patients, the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P–TIMI 50) trial.[2] In the trial, vorapaxar reduced the rate of a combined end point of cardiovascular death, myocardial infarction, stroke, and urgent coronary revascularization.

Vorapaxar is a novel antagonist of protease-activated receptor-1 (PAR-1), the predominant thrombin receptor on human platelets. Intravascular thrombin levels are elevated after myocardial infarction; despite antiplatelet therapy with 2 drugs, typically aspirin and clopidogrel, thrombin-inducible platelet activation persists.[3] The therapeutic rationale for vorapaxar use is to diminish the interaction between thrombin and platelets. In the TRA 2P–TIMI 50 trial,[2] treatment with vorapaxar resulted in a 1.2% absolute and 12% relative risk reduction in the combined end point, which was driven primarily by a reduction in the risk of a subsequent myocardial infarction.

Although the TRA 2P–TIMI 50 trial[2] was not designed to evaluate the relative benefits and risks of vorapaxar within subgroups, patients with a history of stroke or transient ischemic attack showed an increased risk of intracranial hemorrhage. Such an increased risk was also found in another trial of vorapaxar, the Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes (TRACER) trial,[4] conducted concurrently in patients with acute coronary syndrome. In response to these findings, the combined data safety monitoring board for the trials recommended that the participants with a history of cerebrovascular disease be removed from the trial along with participants who developed a stroke while enrolled. A post hoc exploratory subgroup analysis of the TRA 2P–TIMI 50 data identified a subset of patients without a history of stroke or transient ischemic attack in whom the benefit-risk balance for secondary prevention of myocardial infarction was favorable. Although the data for secondary prevention of peripheral artery disease were lacking, the FDA concluded that they were sufficient for inclusion in the approval.

The prescribing information for vorapaxar includes a box warning that states that the medication should not be used in patients with a history of stroke, transient ischemic attack, intracranial hemorrhage, or active bleeding. Concomitant use with warfarin or other anticoagulants should be avoided. The FDA recommended that vorapaxar be used cautiously in patients being treated with potent CYP3A4 inhibitors such as ketoconazole or inducers such as rifampin.[5] Patients in the acute phase of myocardial infarction undergoing coronary intervention and receiving aggressive antithrombotic therapy should not receive vorapaxar because of the increased bleeding risk.

An Alternative Benefit-Risk Analysis

There is an inherent asymmetry in the conventional approach to the benefit-risk analysis of antithrombotic drugs. The benefit is heavily weighted toward the prevention of myocardial infarction, presumably because myocardial damage is irreversible. Bleeding is deemed reversible, and the risk is considered less serious. Nearly 80% of the myocardial infarctions in the TRA 2P–TIMI 50 trial[2] occurred spontaneously (ie, patients experienced chest pain; myocardial infarctions were not related to percutaneous coronary intervention) and required hospitalization to be counted as an event. Major bleeding events also uniformly led to hospitalization. The troponin assays currently used are ultrasensitive and measure myocardial damage to the billionth of a gram. Although evidence linking troponin elevations to subsequent ischemic events is mixed, a causal association between troponin elevations and heart failure or fatal arrhythmia has not been shown within the relatively short time frame of clinical trials. In the TRA 2P–TIMI 50 trial, the myocardial infarction events were not categorized by severity (fatal vs nonfatal, Q-wave vs non-Q wave) or by their clinical consequences (heart failure, arrhythmia, sudden death). The evidence linking adverse outcomes to bleeding associated with coronary interventions and antithrombotic therapy is also mixed. Some studies show that bleeding is independently associ-

ated with higher mortality and recurrent myocardial infarction[6]; however, other studies have failed to consistently demonstrate decreased mortality with interventions that reduce bleeding.[7]

Given all these considerations, in our view, the most reliable estimate of benefit-risk in the TRA 2P–TIMI 50[2] findings was a 1.2% absolute decrease in the primary efficacy end point (mostly myocardial infarction), counterbalanced by a 1.6% absolute increase in the primary safety end point (moderate or severe bleeding) in the overall cohort. No reduction in stroke, cardiovascular death, or all-cause mortality was observed in the TRA 2P–TIMI 50 study. Thus, the benefit-risk balance did not clearly favor vorapaxar.

Another approach to assessing benefit-risk balance is the net composite outcome, which combines efficacy and safety into a single measure. The problem with such an analysis, however, is that it assumes that each component is equivalent. The common statistical approach of using equal weights to combine disparate components of a composite end point is overly simplistic. One potential solution is to assign clinically meaningful weights to the components. For example, cardiovascular death might be most heavily weighted, followed by cerebrovascular events, then major myocardial infarctions. The adjudication of myocardial infarction should not be solely reliant on a diagnosis that is primarily based on biomarkers; instead, it should also include assessment of clinical consequences. Accordingly, weighting systems should require prospective definitions based on clinical judgment and the actual effects on patients; thus, a disabling stroke should be more heavily weighted than an asymptomatic myocardial infarction that is not associated with heart failure or arrhythmia.

Conclusions

What role should vorapaxar play in treating patients with atherosclerotic vascular disease in the United States? Each year, there are about 720 000 people who have a myocardial infarction (515 000 new and 205 000 recurrent), and nearly 8.5 million people have prevalent peripheral artery disease.[8] Despite therapy with aspirin and clopidogrel, such individuals have a residual risk of recurrent atherothrombotic events.

Questions, however, remain. In the TRA 2P–TIMI 50 trial,[2] the use of new and more potent P2Y12 platelet inhibitors such as prasugrel or ticagrelor was exceedingly low: only 0.2% of patients received prasugrel, and none received ticagrelor. These agents have not been studied specifically in patients who are stable after myocardial infarction or who have peripheral artery disease. However, substitution of prasugrel or ticagrelor for clopidogrel in the acute coronary syndrome setting is associated with an absolute reduction in cardiovascular death, myocardial infarction, or stroke (approximately 2.1%) that exceeded the treatment difference related to the addition of vorapaxar to clopidogrel plus aspirin found in the TRACER trial (1.7%).[4] Nonetheless, the prescription of prasugrel and ticagrelor in clinical practice has been low because of their greater potential to cause bleeding (including fatal bleeding with prasugrel) and their cost (neither is available as a generic drug, while clopidogrel is). There are similar concerns about vorapaxar, and the bleeding risk may well be higher in routine practice than in the clinical trials. Thus, although vorapaxar has a potential role in the secondary prevention of cardiovascular disease, we remain skeptical of its widespread use as part of a 3-drug antiplatelet regimen.

ARTICLE INFORMATION

Published Online: November 3, 2014. doi:10.1001/jamainternmed.2014.5802.

Conflict of Interest Disclosures: Drs Krantz and Kaul participated as temporary voting members in the January 15, 2014, meeting of the FDA Cardiovascular and Renal Drugs Advisory Committee, where the new drug application for vorapaxar was discussed. Dr Krantz reports no relevant financial associations. The manuscript was submitted for publication on May 13, 2014. Dr Kaul reports that on July 7, 2014, he agreed to participate as a consultant in a meeting sponsored by Merck, the manufacturer of vorapaxar, about the benefit-risk profile of the drug. The meeting was held on July 19, 2014. Merck compensated Dr Kaul for his participation. Dr Kaul reports no other financial relationships with Merck since January 2011 and no planned future financial relationships. Dr Kaul also reports that he is a consultant for The Medicines Company on cangrelor, an intravenous antiplatelet agent that is not approved by the FDA.

Disclaimer: The views are those of the authors, not those of the FDA or any other branch of the US Department of Health and Human Services.

REFERENCES

1. US Food and Drug Administration. FDA approves Zontivity to reduce the risk of heart attacks and stroke in high-risk patients. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm396585.htm. Accessed June 17, 2014.

2. Morrow DA, Braunwald E, Bonaca MP, et al; TRA 2P-TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med*. 2012;366(15):1404-1413.

3. Yano Y, Ohmori T, Hoshide S, et al. Determinants of thrombin generation, fibrinolytic activity, and endothelial dysfunction in patients on dual antiplatelet therapy: involvement of factors other than platelet aggregability in Virchow's triad. *Eur Heart J*. 2008;29(14):1729-1738.

4. Tricoci P, Huang Z, Held C, et al; TRACER Investigators. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med*. 2012;366(1):20-33.

5. Merck Sharp & Dohme Corp. Prescribing information ZONTIVITY (vorapaxar). http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204886s000lbl.pdf. Accessed on 17 June 2014.

6. Chhatriwalla AK, Amin AP, Kennedy KF, et al; National Cardiovascular Data Registry. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA*. 2013;309(10):1022-1029.

7. Jolly SS, Yusuf S, Cairns J, et al; RIVAL trial group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011;377(9775):1409-1420.

8. Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129(3):e28-e292.