Balancing the Risks and Benefits of Dual Platelet Inhibition

John F. Keaney, Jr., M.D.

Cardiovascular and cerebrovascular events commonly arise from atherosclerotic plaque rupture that produces platelet activation, thrombus formation, and reduction of blood flow to the brain or heart. The inhibition of platelets with aspirin is effective in the secondary prevention of acute coronary events.\(^1\) The addition of clopidogrel (i.e., dual antiplatelet therapy), a platelet P2Y\(_{12}\) receptor antagonist, produces even greater secondary prevention of coronary events in high-risk patients for up to 1 year.\(^2\) Second-generation P2Y\(_{12}\) inhibitors (i.e., prasugrel and ticagrelor) produce further reductions in the risk of ischemic events over the same time frame, albeit with more bleeding complications.\(^3,4\)

Dual antiplatelet therapy is recommended for 1 year after an acute coronary syndrome, but the effect of longer-term therapy is not clear. Concern exists regarding the balance between reducing the risk of cardiovascular events and the risk of bleeding complications, because bleeding complications are linked to adverse outcomes in patients with an acute coronary syndrome.\(^5\) Bonaca et al., in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial,\(^6\) provide insight into this balance in high-risk patients with a previous myocardial infarction. In their study, the results of which are now reported in the Journal, they randomly assigned 21,162 patients to placebo or ticagrelor. Because long-term P2Y\(_{12}\) inhibition increases bleeding risk, the investigators compared two doses of ticagrelor (60 mg and 90 mg) to maximize information derived from the trial concerning drug efficacy versus adverse events. As compared with placebo, either dose of ticagrelor was associated with a 15% decrease in the rate of the primary end point of death from cardiovascular causes, myocardial infarction, or stroke. However, ticagrelor treatment also increased clinically significant bleeding complications by a factor of 2.3 to 2.6 and transfusions by a factor of 3.0 to 3.7. There was similar efficacy in the reduction of the rate of the primary end point with either ticagrelor dose, suggesting that the lower dose should be preferred in this patient population because it may limit clinically significant bleeding events.

These data prompt speculation as to whether dual platelet inhibition with high-potency agents is approaching the point of diminishing returns. Bonaca et al. found that, as compared with placebo, ticagrelor was associated with an absolute benefit of 1.19 percentage points (with the 90-mg dose) and 1.27 percentage points (with the 60-mg dose) in the primary end point, as well as with absolute increases of 1.54 and 1.24 percentage points, respectively, for clinically significant bleeding events and TIMI major bleeding events — close to an even proposition. Granted, one could argue that major bleeding events do not have the same effect on patients as ischemic cardiovascular events. Nevertheless, we should note that the patient population studied by Bonaca et al. was at particularly high risk for ischemic events (e.g., diabetes, renal disease, multivessel disease, and recurrent myocardial infarction) and had had no recent bleeding episodes or indication for anticoagulation. Thus, not all patients who have a myocardial infarction will fit these same criteria.
and, as a consequence, may not be appropriate candidates for long-term treatment with ticagrelor. Patients without high-risk features for ischemia, or with higher bleeding risks, will probably not realize as much net benefit as those included in the study by Bonaca et al.

The results of the recently reported Dual Antiplatelet Therapy (DAPT) trial by Mauri et al.\(^7\) suggest that the results of Bonaca et al. apply to the thienopyridine P2Y\(_{12}\) antagonists clopidogrel and prasugrel as well. In that study, the effect of continued dual antiplatelet therapy (thienopyridine plus aspirin) was tested beyond 12 months after the implantation of a drug-eluting stent. The outcome of the study by Mauri et al. was qualitatively similar to that of the study by Bonaca et al. Long-term dual antiplatelet therapy produced a significant reduction, as compared with placebo, in the risk of ischemic cardiovascular events (hazard ratio, 0.71), at the expense of an increase of 1.56 times in the rate of moderate or severe bleeding,\(^7\) somewhat less than that observed by Bonaca et al. This distinction is probably a consequence of differences between the two patient populations. The patients studied by Mauri et al. had received 12 months of dual platelet inhibition without clinically significant bleeding or discontinuation of dual antiplatelet therapy. Thus, the patients in the study by Mauri et al. would be expected to have a lower risk of bleeding than the patients in the study by Bonaca et al., who may not have had previous P2Y\(_{12}\) inhibition. Moreover, as compared with the patients in the study by Mauri et al., the patients in the study by Bonaca et al. had a higher burden of risk factors for subsequent cardiovascular events — features that also predict increased bleeding rates with platelet inhibition.\(^8\)

An important calculus for any treatment strategy is the long-term potential for harm. The study by Mauri et al. was characterized by excess mortality with the administration of clopidogrel or prasugrel, probably related to bleeding,\(^7\) a finding that was not seen with long-term use of clopidogrel in a previous trial.\(^9\) In the study by Bonaca et al., ticagrelor did not significantly affect overall mortality, and the numerical excess of deaths from noncardiovascular causes appeared to be related to cancer, a feature not seen in the Study of Platelet Inhibition and Patient Outcomes (PLATO).\(^4\) Collectively, these data do not support a unified concern with respect to excess mortality with dual antiplatelet therapy, but they do remind us of the fragile balance between efficacy and adverse events.

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From the Division of Cardiovascular Medicine, University of Massachusetts Medical School, Worcester.

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