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EDITORIAL COMMENT

Prasugrel or Ticagrelor for Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Does it Matter?*

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The addition of $P2Y_{12}$ receptor inhibitors to aspirin therapy has substantially improved the care of patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI). Inhibition of the $P2Y_{12}$ receptor by clopidogrel, prasugrel, or ticagrelor reduces thrombotic atherosclerotic events in these populations because of its central role in platelet activation and aggregation. Additionally, there are emerging data regarding the pleiotropic effects of these agents, as the $P2Y_{12}$ receptor is present not just on platelets but also vascular smooth muscle cells, leukocytes, macrophages, and microglial and dendritic cells (1). Mediation of these receptors could theoretically result in modification of endothelial function, vascular tone and inflammation.

Ticagrelor in particular has been hypothesized to increase serum adenosine levels through inhibition of the sodium-independent equilibrative nucleoside transporter 1 (2) as well as through the release of adenosine triphosphate (which is subsequently degraded to adenosine) from red blood cells (3). Although this release of adenosine is believed to contribute to the dyspnea and ventricular pauses sometimes seen with initiation of ticagrelor therapy, adenosine is a known vasodilator and may have beneficial effects, including improved vascular tone and coronary blood flow.

In this issue of *JACC: Cardiovascular Interventions*, Ariotti et al. (4) report an elegant investigation to ascertain whether ticagrelor increases systemic adenosine plasma levels and improves endothelium-dependent dilation in patients who have undergone therapy for ACS. The investigators used a 3-period balanced Latin-square crossover design with 4-week periods consisting of treatment with clopidogrel, prasugrel, or ticagrelor. Patients were randomized to a treatment sequence of clopidogrel, prasugrel, and ticagrelor in 1 of 6 possible treatment sequences. Advantages of this study design include increased efficiency compared with parallel study treatments and lower associated study costs. Because of the nature of the patients being treated and potential risks of an interruption in $P2Y_{12}$ therapy, no washout time was allowed between treatments. Concerns for a carryover effect, in which treatment effects may last into the next treatment period, were mitigated by negative interaction testing for the primary endpoint with the sequence of drug administration.

The primary endpoint was an assessment of endothelial function with pulse-amplitude tonometry at steady state of the studied drug, a well-validated method to measure endothelium-dependent dilation in response to reactive hyperemia. The secondary endpoint included a measure of serum adenosine levels. After enrolling 54 patients, the investigators found no difference in the measure of pulse amplitude tonometry, suggesting no difference in endothelial function with the use of different $P2Y_{12}$ inhibitors. Systemic adenosine plasma levels were also the same in all study groups. The investigators conclude that there is no difference in these metrics among ticagrelor, prasugrel, and clopidogrel among patients who previously experienced ACS.

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The investigators should be congratulated on a rigorously performed study. Through the use of a unique translational design, they investigated potential differences in $P2Y_{12}$ inhibitors, something other investigators have examined through population-based clinical outcome trials.

The landmark trials establishing the reduction of atherosclerotic thrombotic events in patients with ACS with prasugrel or ticagrelor over clopidogrel were the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) and PLATO (Study of Platelet Inhibition and Patient Outcomes), respectively (5,6). Although the trial populations were slightly different (TRITON-TIMI 38 included patients with ACS who underwent PCI, and PLATO included a broader population of all patients with ACS), both trials demonstrated a remarkably similar 2% absolute reduction in major adverse cardiovascular events with either prasugrel or ticagrelor over clopidogrel during 12- to 15-month follow-up. As expected with more potent antiplatelet agents, both prasugrel and ticagrelor were associated with a roughly 0.5% increased risk for major bleeding compared with clopidogrel.

To address clinical differences in outcomes between prasugrel and ticagrelor directly, the PRAGUE-18 (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) study subsequently compared the safety and efficacy of these 2 agents in patients presenting with acute myocardial infarction treated with PCI (7). The study was terminated prematurely for futility with only 1,230 patients enrolled, with no observed difference in a combined endpoint of death, reinfarction, urgent target vessel revascularization, stroke, or serious bleeding requiring transfusion or prolonging hospitalization after 7 days (4.0% vs. 4.1%; odds ratio: 0.98; 95% confidence interval: 0.55 to 1.73; $p = 0.939$). These findings remained similar at 1 year as well (8).

Taken together, the evidence base would suggest that in a broad, general population of patients undergoing PCI for ACS, prasugrel and ticagrelor are quite similar in their efficacy and safety. Both reduce thrombotic events compared with clopidogrel, with both carrying a slightly increased risk for bleeding. In those patients in whom the bleeding risk of a more potent antiplatelet agent is acceptable, how does the practicing clinician choose between prasugrel and ticagrelor?

On the basis of subanalyses of the TRITON-TIMI 38 trial, prasugrel carries a U.S. Food and Drug Administration black-box warning in patients with histories of transient ischemic attack or stroke given a significantly increased risk for bleeding. It is not recommended in patients older than 75 years or those weighing <60 kg. Although there are small studies suggesting that dose-reduced prasugrel at 5 mg may be safe in these latter 2 populations, it is unclear whether the antiplatelet effect at this dose is adequate (9).

Ticagrelor does not carry these contraindications. The major limitation with the use of ticagrelor is its twice-daily dosing, compared with the once-daily dosing of prasugrel. It is well established that medication adherence improves dramatically as the prescribed dose frequency decreases, with a more than 20% absolute difference in medication compliance between thrice-daily dosing and once-daily dosing (10). Nonadherence with the twice-daily dosing of ticagrelor leaves a patient susceptible to stent thrombosis, a potentially devastating complication of PCI.

Although these limitations can help a clinician make the decision between prasugrel and ticagrelor, it is crucial to also consider the cost of these antiplatelet agents for individual patients. For many patients, the cost of these novel antiplatelet agents may be prohibitive. In the aforementioned PRAGUE-18 trial, an astonishing 34% of patients prescribed prasugrel and 44% of patients prescribed ticagrelor had to switch to clopidogrel given economic considerations (9). Among a group of insured U.S. patients younger than 65 years, rates of primary nonadherence (i.e., never filling a prescription for the drug) to $P2Y_{12}$ therapy were 20% in 2016, a rate that had tripled since 2008 with the introduction of prasugrel and ticagrelor to the market (11). Thus, although we may advocate for ticagrelor in patients who are older than 75 years or have had strokes, and prasugrel for patients who are at risk for medication nonadherence, it is imperative to ascertain whether these medications are accessible for individual patients. Although studies will attempt to identify nuanced differences among different antiplatelet agents to maximize benefits to patients, the best antiplatelet agent in the current era is likely the one the patient can afford to obtain.

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