

EDITORIAL COMMENT

Impact of Ticagrelor in Patients With Prior MI and MVD for Reducing Cardiovascular Events*



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P₂Y₁₂ inhibitors, such as ticagrelor, clopidogrel, and prasugrel, given in addition to aspirin, play a pivotal role in the treatment of acute coronary syndromes (ACS) (1). Historically, aspirin in addition to clopidogrel was the combination of choice in the treatment of ACS (2). Ticagrelor, a direct-acting oral antagonist of the adenosine diphosphate receptor P₂Y₁₂, demonstrated superiority and had more consistent inhibition of platelet aggregation as compared with clopidogrel (3). Unlike clopidogrel, it does not require hepatic metabolism for its activity, allowing for more rapid onset of action (4).

Significant attention was drawn to ticagrelor after the publication of the PLATO (Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes) trial (5). In that study, patients treated with ticagrelor for ACS who underwent percutaneous coronary intervention (PCI), surgical revascularization, or were medically managed had a significantly lower rate of death from vascular causes, myocardial infarction (MI), and stroke at 12 months as compared with those treated with clopidogrel. Although there was no significant difference in the rates of major bleeding between treatment groups, fatal intracranial hemorrhage (ICH) was notably more common with ticagrelor.

The optimal duration of dual antiplatelet therapy (DAPT) with P₂Y₁₂ inhibitor and aspirin post-PCI remains a controversial topic in the medical

community (6). Currently, the optimal duration is 12 months, given the numerous beneficial outcomes cited in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial series (2). However, data reported from the REACH (Reduction of Atherothrombosis for Continued Health) (7) and GRACE (Global Registry of Acute Coronary Events) (8) registries suggest that atherosclerotic processes may endure beyond the index event, thus causing higher rates of cardiovascular (CV) events in the years following initial PCI. The DAPT trial (9) sought to address this question by randomizing patients to an additional 18 months of the thienopyridine clopidogrel or placebo. Their findings showed significant reduction in the composite endpoint of death, MI, or stroke at 30 months (4.3% vs. 5.9%; $p < 0.001$) with extended DAPT therapy, in addition to reduced rates of stent thrombosis. As expected, extended DAPT therapy was also associated with excess bleeding. However, it was also unexpectedly accompanied by a significant increase in all-cause mortality driven primarily by oncologic-related death. Given these conflicting outcomes, the question of the optimal duration of DAPT remained unanswered.

The PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial sought to expand on prior work by assessing the effect of higher intensity and extended duration antiplatelet therapy with ticagrelor compared to placebo in patients at elevated risk for recurrent atherothrombotic events (10). In this prospective, multicenter, double-blind study, 21,162 patients with a history of MI 1 to 3 years before enrollment were randomized in a 1:1:1 ratio to receive ticagrelor (90 mg or 60 mg, twice daily) or placebo on a background of aspirin. The primary endpoints were the composite of

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CV death, MI, or stroke for efficacy, and Thrombolysis In Myocardial Infarction (TIMI) major bleeding for safety at 3 years follow up. In keeping with the DAPT trial (9), the 90-mg and 60-mg dosing arms of ticagrelor-treated patients both garnered significant reduction in the primary efficacy endpoint (7.85% vs. 9.04%; $p = 0.004$, and 7.77% vs. 9.04%; $p = 0.008$, respectively); however, they experienced a 2-fold increase in major bleeding (10).

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In this issue of the *Journal*, Bansilal et al. (11) report data from a pre-specified subset analysis of 12,558 PEGASUS-TIMI 54 study patients, only including individuals with multivessel coronary disease (MVD). Again, investigators assessed the efficacy and safety of long-term ticagrelor therapy compared with placebo over the same 33-month period. The primary outcomes were a composite of CV death, MI, or stroke (major adverse cardiac events [MACE]), in addition to the composite of coronary death, MI, or stent thrombosis, and TIMI major bleeding, ICH, and fatal bleeding. Compared with individuals with single-vessel disease, patients with MVD were at higher risk for MACE and coronary events (9.37% vs. 8.57%; $p = 0.026$, and 7.67% vs. 5.34%; $p < 0.001$, respectively). Furthermore, patients treated with ticagrelor were afforded significant reductions in MACE (7.94% vs. 9.37%; $p = 0.004$), coronary events (6.02% vs. 7.67%; $p < 0.001$), and a 36% reduction in coronary death

($p = 0.002$). Predictably, ticagrelor increased the risk of major bleeding by approximately 2-fold ($p < 0.001$), but not ICH or fatal bleeds (11).

The authors' focus on higher intensity and extended duration antiplatelet therapy as opposed to revisiting revascularization strategies to manage patients with MVD is intriguing. In parallel with past work (12-14), results from the PEGASUS subset analysis further confirm that the risk for recurrent atherothrombotic coronary events and death in the years following incident MI are even higher among patients with MVD. Although the pathophysiological mechanism for this phenomenon remains poorly understood, the benefits of antiplatelet therapy in the setting of platelet aggregation after intimal plaque rupture are clear.

Taken together, the PEGASUS-TIMI 54 subset analyses give validation to existing data (15) supporting improved outcomes with higher intensity and longer duration of antiplatelet therapy with ticagrelor in certain high-risk patient cohorts. Specifically, the data support that the presence of MVD may be an indication to pursue extended DAPT with ticagrelor for up to 3 years in the absence of limiting adverse effects.

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