Long-Term Ticagrelor Versus Prasugrel Pharmacodynamics in Patients With ST-Segment–Elevation Myocardial Infarction

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Current practice guidelines recommend a dual regimen consisting of a platelet P2Y12 receptor inhibitor in combination with aspirin for 12 months, followed by at least one antiplatelet agent lifelong in patients with ST-segment–elevation myocardial infarction (STEMI) not requiring oral anticoagulation. In particular, the direct-acting, oral cyclopentyltriazolopyrimidine ticagrelor, which reversibly blocks the adenosine diphosphate receptor P2Y12 on platelets, and the third-generation thienopyridine prasugrel, which exerts an irreversible antagonism on the same cellular target, should be preferred over the second-generation thienopyridine clopidogrel.[1]

Two large-scale randomized trials have tested either ticagrelor or prasugrel against clopidogrel in patients with acute coronary syndromes, including STEMI, and contribute to the solid scientific background supporting this recommendation. In the PLATO (Platelet Inhibition and Patient Outcomes) trial, patients with STEMI treated with ticagrelor showed less recurrent ischemic events without excess risk of bleeding compared with those receiving clopidogrel.[2] Similarly, in the TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction) 38, patients with STEMI allocated to prasugrel showed a significant clinical benefit without safety issues compared with those treated with clopidogrel.[3]

Ticagrelor and prasugrel have different biological targets and clinical profiles. Previous studies lend support to a close interaction between the pleiotropic effects of these drugs and their efficacy and safety. Among others, the off-target effects of ticagrelor have attracted considerable interest and offered a plausible mechanism for the claim of superiority over prasugrel in patients with acute coronary syndrome.[4] Hence, in the recent years, head-to-head comparisons aimed at investigating pharmacodynamics and clinical performance of these 2 medications in patients with acute coronary syndrome.[5–9]

The REDUCE MVI (Reducing Micro Vascular Dysfunction in Acute Myocardial Infarction by Ticagrelor) trial tested the hypothesis that in patients with STEMI receiving a primary percutaneous coronary intervention after 180-mg ticagrelor loading dose, a maintenance therapy with ticagrelor (90 mg twice daily) versus prasugrel (10 mg once daily) could reduce the microvascular injury at 1-month follow-up. The analysis of the primary end point, the index of microcirculatory resistance in the infarct-related artery, did not support the superiority of ticagrelor. Of note, infarct size, platelet inhibition, and plasma adenosine concentrations did not differ between groups.[9] In this issue of the *Journal of the American Heart Association* (*JAHA*), van der Hoeven and colleagues[10] report the follow-up data out to 18 months of the REDUCE MVI trial. Of 110 patients, 77 (70.0%) enrolled at 6 European centers completed the 18-month follow-up or had died, 15 (13.6%) switched to a P2Y12 receptor inhibitor different from that initially assigned, and 9 (8.1%) had stopped ticagrelor or prasugrel before 12 months. The main findings of this analysis are the absence of significant differences in terms of platelet inhibition, peripheral endothelial function, and clinical outcomes between the treatment groups in the intention-to-treat analysis. In the analysis per protocol restricted to patients who did not switch or stop the assigned treatment before 12 months, ticagrelor was associated with higher platelet inhibition and improved peripheral endothelial function compared with prasugrel.

The REDUCE MVI trial was designed to test the superiority of ticagrelor versus prasugrel for the efficacy end point of index of microcirculatory resistance at 1-month follow-up. As stated by the authors in their primary publication,[9] the study was not powered for specific differences in secondary end points. The exploratory intention-to-treat analysis out to

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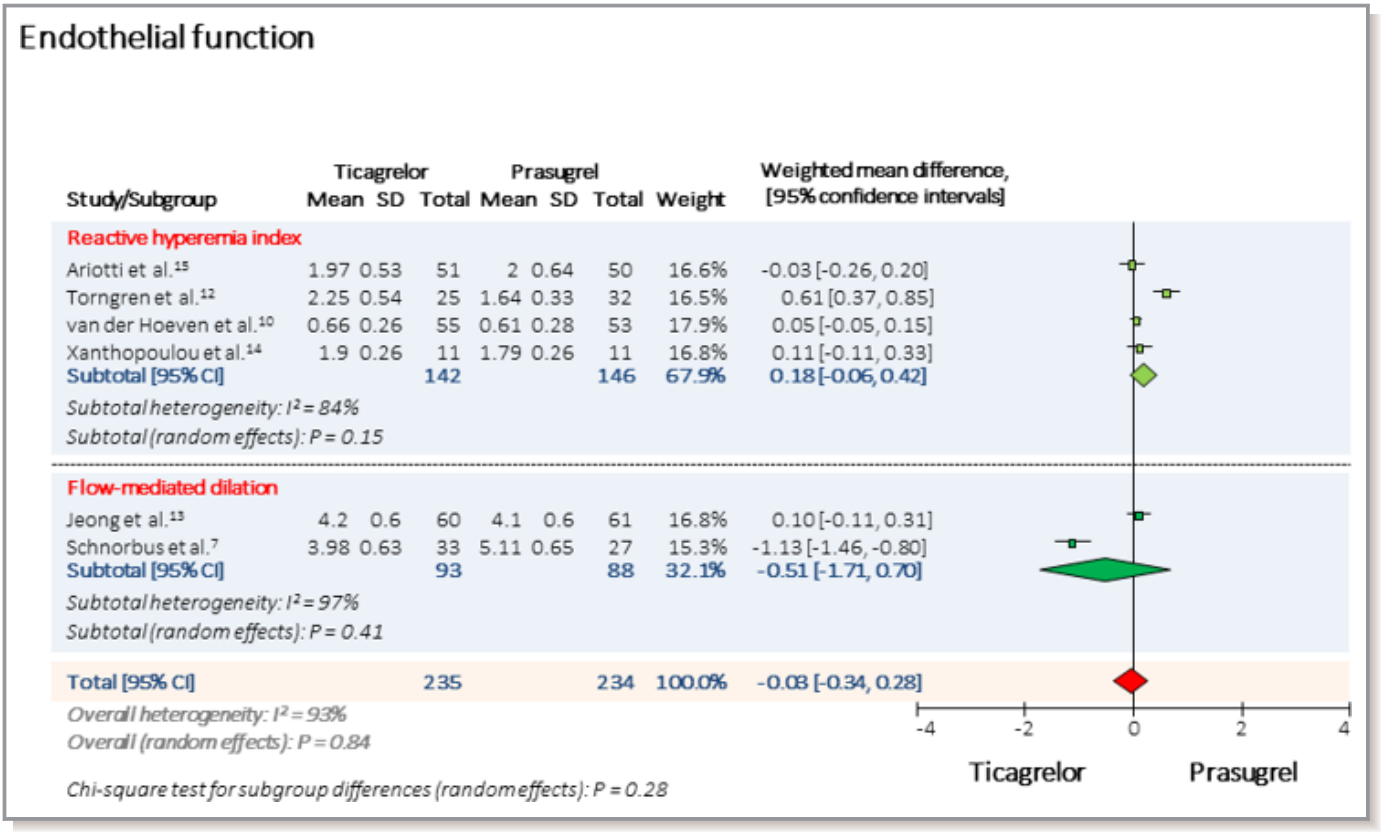

Figure. Endothelial function with ticagrelor vs prasugrel maintenance dose. The weighted mean difference, with 95% CIs, was used as summary statistic to compare the endothelial function in patients receiving either ticagrelor or prasugrel. The risk estimates were pooled using the inverse variance method for the random-effect model, and $P<0.05$ was considered statistically significant. The I^2 statistic tested heterogeneity across the trials, and the chi-square test examined whether the treatment effect was dependent on the methods quantifying the endothelial function. For the studies of Schnorbus et al[7] and Xanthopoulou et al,[14] means and standard deviations (SD) were derived from median and interquartile ranges, according to Hozo et al.[16]

18 months confirms the results of the primary analysis, with neither pharmacodynamic nor clinical differences with ticagrelor compared with prasugrel. The analysis, based on a per-protocol population, common to noninferiority trials, is not advisable for studies aimed at proving a superiority hypothesis, especially for open-label studies, as it was the case with the present work. Nonadherence to study treatment might not be a random phenomenon.

A curious characteristic of the design of the REDUCE MVI trial is that all enrolled patients received a 180-mg ticagrelor loading dose before randomization. Thereafter, patients randomized to ticagrelor received a 90-mg therapy twice daily, whereas patients randomized to prasugrel received a loading dose of 60 mg and then continued with prasugrel, 10 mg once a day. The timing of the prasugrel loading was not reported, which is a relevant point when switching from a reversible to an irreversible P2Y12 receptor inhibitor.[11]

Whether ticagrelor effectively improves endothelial function is a matter of ongoing controversy. Several randomized studies tested the endothelial function of patients treated with either ticagrelor or prasugrel for chronic coronary syndrome or acute coronary syndrome, with inconclusive results (Figure).[7,12–16]

The main limitation in interpreting previous evidence on this topic is the variation in methods and time of measurements of endothelial function. In the per-protocol analysis of the REDUCE MVI trial, ticagrelor was associated with improved peripheral endothelial function compared with prasugrel, as measured by reactive hyperemia index after 12 months. The potential link between the adenosine-independent endothelial function improvement with ticagrelor and late clinical outcomes is of relevance and, if confirmed by dedicated studies with long-term follow-up, might support the use of ticagrelor for the secondary prevention of cardiovascular events in patients at high risk for recurrences beyond 1 year. Notably, in the PEGASUS-TIMI (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, a 60-mg dose of ticagrelor on top of aspirin compared with aspirin alone reduced the incidence of ischemic events in patients enrolled

1 to 3 years after MI.[17] Similarly, the THEMES-PCI (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study–Percutaneous Coronary Intervention) has established a new option for the long-term antiplatelet therapy in patients with atherosclerotic disease, diabetes mellitus, and/or history of previous percutaneous coronary intervention. Indeed, participants assigned to long-term ticagrelor therapy compared with placebo had a reduction in the risk of cardiovascular death or stroke, with significantly fewer MIs, including STEMI.[18]

In conclusion, an objective evaluation of the data generated by the present long-term analysis of the REDUCE MVI trial shows that the lack of significant differences between ticagrelor and prasugrel observed at 1 month is maintained over 18 months. The additional per-protocol findings of long-term pharmacodynamical advantages of ticagrelor cannot serve as stand-alone evidence with clinical implications without confirmation from dedicated studies. Our practice on the role of long-term ticagrelor treatment in patients with coronary artery disease will continue to be driven by the lessons from large clinical trials conducted on this topic.[17,18]

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