


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

Salvatore Cassese, MD, PhD; Adnan Kastrati , MD

Current practice guidelines recommend a dual regimen consisting of a platelet P2Y<sub>12</sub> 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 P2Y<sub>12</sub> 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.<sup>1</sup>

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.<sup>2</sup> 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.<sup>3</sup>

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.<sup>4</sup> 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.<sup>5–9</sup>

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.<sup>9</sup> In this issue of the *Journal of the American Heart Association (JAHA)*, van der Hoeven and colleagues<sup>10</sup> 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 P2Y<sub>12</sub> 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,<sup>9</sup> the study was not powered for specific differences in secondary end points. The exploratory intention-to-treat analysis out to

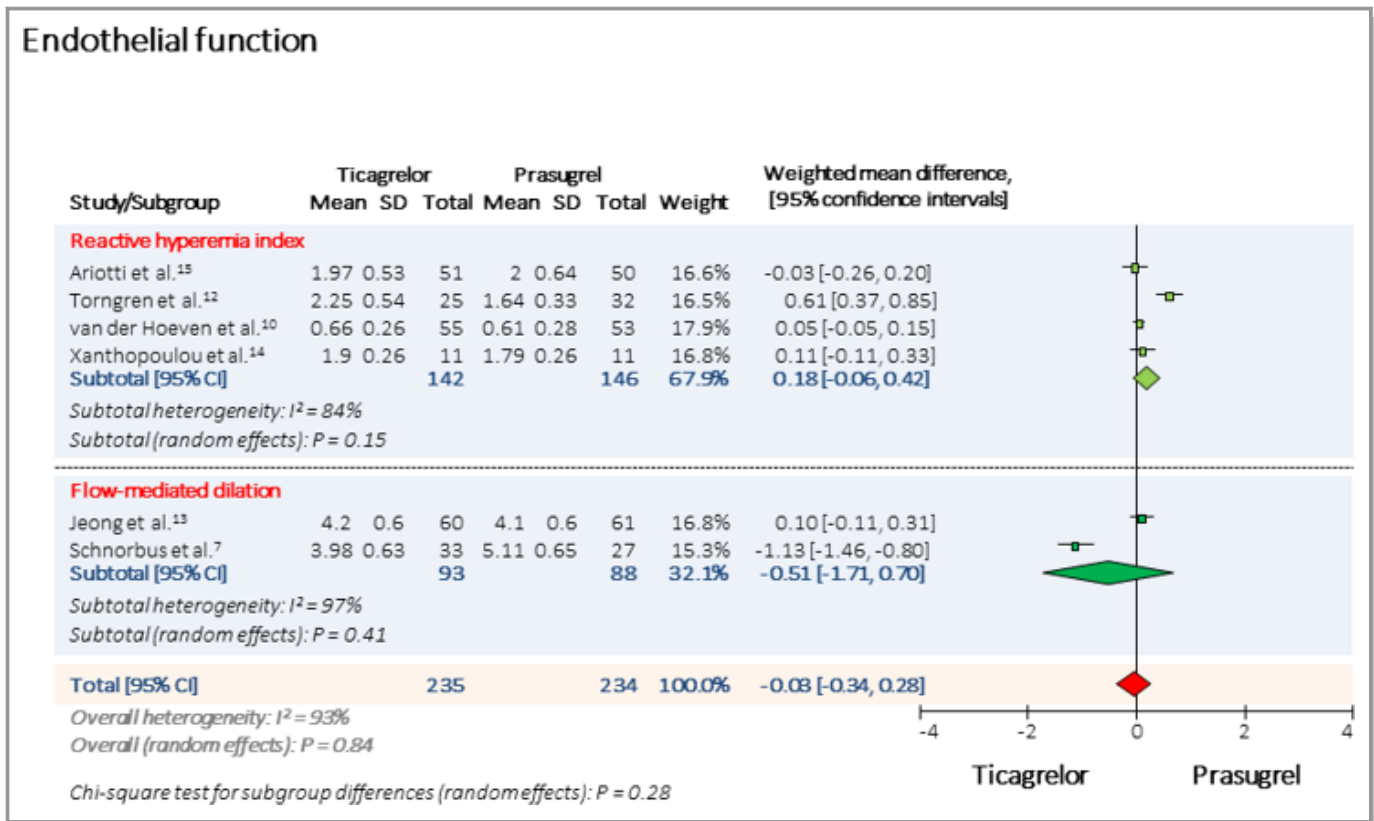
The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Deutsches Herzzentrum München, Technische Universität München, Munich, Germany (S.C., A.K.); and DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany (A.K.).

**Correspondence to:** Adnan Kastrati, MD, Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse, 36-Munich, Germany. E-mail: kastrati@dhm.mhn.de

*J Am Heart Assoc.* 2020;9:e015726 DOI: 10.1161/JAHA.120.015726.

© 2020 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.



**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.<sup>7</sup> and Xanthopoulou et al.,<sup>14</sup> means and standard deviations (SD) were derived from median and interquartile ranges, according to Hozo et al.<sup>16</sup>

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.<sup>11</sup>

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).<sup>7,12–16</sup>

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.<sup>17</sup> 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.<sup>18</sup>

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.<sup>17,18</sup>

## Source of Funding

None.

## Disclosures

None.

## References

- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.
- Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A, Husted S, Katus H, Kilhamn J, Olofsson S, Storey RF, Weaver WD, Wallentin L; PLATO Study Group. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation*. 2010;122:2131–2141.
- Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009;373:723–731.
- Moulias A, Xanthopoulos I, Alexopoulos D. Does ticagrelor improve endothelial function? *J Cardiovasc Pharmacol Ther*. 2019;24:11–17.
- Franchi F, Rollini F, Angiolillo DJ. Antithrombotic therapy for patients with STEMI undergoing primary PCI. *Nat Rev Cardiol*. 2017;14:361–379.
- Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, Knot J, Jarkovsky J, Kala P, Rokyta R, Tousek F, Kramarikova P, Majtan B, Simek S, Branny M, Mrozek J, Cervinka P, Ostransky J, Widimsky P; PRAGUE-18 Study Group. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary

intervention: multicenter randomized PRAGUE-18 study. *Circulation*. 2016;134:1603–1612.

- Schnorbus B, Daiber A, Jurk K, Warnke S, Koenig J, Lackner KJ, Munzel T, Gori T. Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: a randomized, blinded, parallel study. *Eur Heart J*. 2020;pii:ehz917. DOI: 10.1093/eurheartj/ehz917. [Epub ahead of print].
- Schupke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witznbecker B, Antoniucci D, Akin I, Bott-Flugel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Mollmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schühlen H, Angiolillo DJ, Hamm CW, Hapfelmeier A, Tolg R, Trenk D, Schunkert H, Laugwitz KL, Kastrati A; ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med*. 2019;381:1524–1534.
- van Leeuwen MAH, van der Hoeven NW, Janssens GN, Everaars H, Nap A, Lemkes JS, de Waard GA, van de Ven PM, van Rossum AC, Ten Cate TJF, Piek JJ, van Birgelen C, Escaned J, Valgimigli M, Diletti R, Riksen NP, van Mieghem NM, Nijveldt R, van Royen N. Evaluation of microvascular injury in revascularized patients with ST-segment-elevation myocardial infarction treated with ticagrelor versus prasugrel. *Circulation*. 2019;139:636–646.
- van der Hoeven NW, Janssens GN, Everaars H, Nap A, Lemkes JS, de Waard GA, van de Ven PM, van Rossum AC, Escaned J, Mejia-Renteria H, Ten Cate TJF, Piek JJ, van Birgelen C, Valgimigli M, Diletti R, Riksen NP, van Mieghem NM, Nijveldt R, van Leeuwen MAH, van Royen N. Platelet inhibition, endothelial function and clinical outcome in patients presenting with ST-segment elevation myocardial infarction patients randomized to ticagrelor versus prasugrel maintenance therapy: long-term follow-up of the REDUCE-MVI trial. *J Am Heart Assoc*. 2020;9:e014411. DOI: 10.1161/JAHA.119.014411.
- Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, Sibbing D, So DYF, Trenk D, Alexopoulos D, Gurbel PA, Hochholzer W, De Luca L, Bonello L, Aradi D, Cuisset T, Tantry US, Wang TY, Valgimigli M, Waksman R, Mehran R, Montalescot G, Franchi F, Price MJ. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. *Circulation*. 2017;136:1955–1975.
- Tornegren K, Ohman J, Salmi H, Larsson J, Erlinge D. Ticagrelor improves peripheral arterial function in patients with a previous acute coronary syndrome. *Cardiology*. 2013;124:252–258.
- Jeong HS, Hong SJ, Cho SA, Kim JH, Cho JY, Lee SH, Joo HJ, Park JH, Yu CW, Lim DS. Comparison of ticagrelor versus prasugrel for inflammation, vascular function, and circulating endothelial progenitor cells in diabetic patients with non-ST-segment elevation acute coronary syndrome requiring coronary stenting: a prospective, randomized, crossover trial. *JACC Cardiovasc Interv*. 2017;10:1646–1658.
- Xanthopoulos I, Bei I, Bampouri T, Barampoutis N, Moulias A, Davlouros P, Alexopoulos D. Absence of differential effect of ticagrelor versus prasugrel maintenance dose on endothelial function in patients with stable coronary artery disease. *Hellenic J Cardiol*. 2018;59:338–343.
- Ariotti S, van Leeuwen M, Brugaletta S, Leonardi S, Akkerhuis KM, Rimoldi SF, Janssens GN, Ortega-Paz L, Gianni U, van den Berge JC, Karagiannis A, Windecker S, Valgimigli M; HI-TECH Investigators. Effects of ticagrelor, prasugrel, or clopidogrel at steady state on endothelial function. *J Am Coll Cardiol*. 2018;71:1289–1291.
- Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
- Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.
- Bhatt DL, Steg PG, Mehta SR, Leiter LA, Simon T, Fox K, Held C, Andersson M, Himmelmann A, Ridderstrale W, Chen J, Song Y, Diaz R, Goto S, James SK, Ray KK, Parkhomenko AN, Kosiborod MN, McGuire DK, Harrington RA; THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet*. 2019;394:1169–1180.

**Key Words:** Editorials • endothelial function • P2Y12 receptor • percutaneous transluminal coronary angioplasty • platelet aggregation