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EDITORIAL COMMENT

More Evidence for Non-P2Y$_{12}$-Mediated Effects of Ticagrelor*

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The reduction in vascular mortality associated with ticagrelor therapy in the PLATO (Platelet Inhibition and Patient Outcomes) trial has been linked to non-P2Y$_{12}$-mediated mechanisms because the same mortality benefit was not associated with prasugrel, a P2Y$_{12}$ inhibitor with similar levels of receptor inhibition (1–3). The effect of ticagrelor on mortality has fueled extensive research to tease out potential responsible mechanisms beyond P2Y$_{12}$ inhibition. The most widely described mechanism is inhibition of adenosine reuptake by red blood cells, thereby increasing systemic and tissue adenosine levels. Increased myocardial adenosine levels have been associated with increased coronary blood flow, decreased expression of inflammation markers, fibrosis, infarct size and edema, and improved tissue remodeling (4,5).

Beyond effects on myocardium, the relation of adenosine-mediated effects of ticagrelor to the function of vascular and other cells has been explored. Adenosine has been shown to promote cyclooxygenase-2 activity and prostaglandin E$_2$ generation, and inhibit neutrophil trafficking, inflammatory cytokine release, and degranulation by acting through A$_{2A}$ receptors on neutrophils (6). A$_{2A}$ and A$_3$ receptors play roles in endothelial progenitor cell (EPC) migration (7). Ticagrelor but not clopidogrel was associated with increased EPC numbers during the first month after an acute coronary syndrome (ACS) (8). Higher plasma adenosine levels in ticagrelor-treated ACS patients and a correlation between higher plasma adenosine levels to a greater reactive hyperemia index (an indicator of peripheral arterial/endothelial function) have been demonstrated (9). A recent study further compared the effects of clopidogrel, prasugrel, and ticagrelor on neointimal formation and endothelial function after drug-eluting stent implantation in a porcine restenosis model. Lower mean neointimal area and less moderate to dense peristrut inflammatory cell infiltration in the ticagrelor group as compared with the clopidogrel and prasugrel groups were observed along with vasoconstriction in response to acetylcholine infusion in the prasugrel and clopidogrel groups but not in the ticagrelor group (10).

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In this issue of *JACC: Cardiovascular Interventions*, Jeong et al. (11) provide further human evidence for potential non-P2Y$_{12}$-mediated effects of ticagrelor. Sixty-two patients with type 2 diabetes mellitus and non–ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention, a high-risk population, were randomly treated with ticagrelor or prasugrel for 5 weeks followed by a direct crossover to the alternative treatment for 5 additional weeks. Greater improvement in brachial artery flow-mediated dilation, increased plasma adenosine and adiponectin levels, and a greater decrease in interleukin-6 and tumor necrosis factor-α levels were associated with ticagrelor as compared with prasugrel therapy. However, both ticagrelor and

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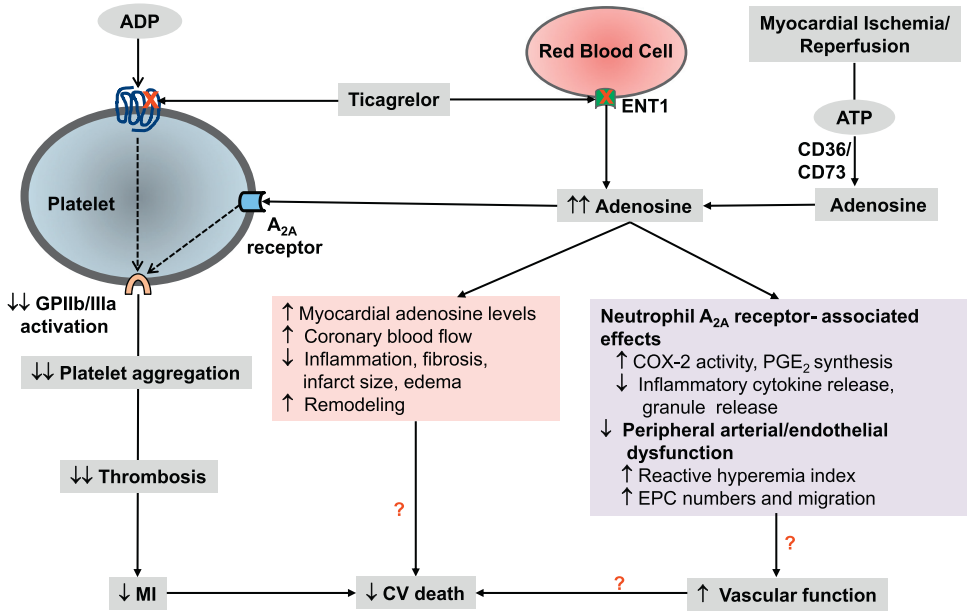
FIGURE 1 The P2Y$_{12}$- and Non-P2Y$_{12}$-Mediated Effects of Ticagrelor



The pivotal role of P2Y$_{12}$ in amplifying platelet activation translates to powerful inhibition of thrombosis. Myocardial ischemia-reperfusion releases adenosine triphosphate that is ultimately converted to adenosine. By inhibiting ENT1, ticagrelor increases endogenous adenosine levels. Beyond effects on myocardium, adenosine also influences neutrophil and endothelial cell function including attenuation of inflammation, improvement in reactive hyperemia index, increase in human endothelial cell numbers and migration. Both P2Y$_{12}$- mediated and non-P2Y$_{12}$-mediated effects of ticagrelor appear to play a role in reducing rates of myocardial infarction and cardiovascular death. ADP = adenosine diphosphate; ATP = adenosine triphosphate; COX = cyclooxygenase; CD39 = ectonucleoside triphosphate diphosphohydrolase-1; CD73 = ecto-5′-nucleotidase; CV = cardiovascular; ENT1 = equilibrative nucleoside transporter-1; EPC = endothelial progenitor cell; G = glycoprotein; MI = myocardial infarction; PGE$_2$ = prostaglandin E$_2$. Modified with permission from Gurbel et al. (3).

prasugrel were associated with similar levels of platelet inhibition by the point-of-care VerifyNow method and reduction in C-reactive protein and soluble vascular cell adhesion molecule-1. Finally, increased levels of circulating EPCs were observed during ticagrelor therapy only.

In the current study, patients were randomized to prasugrel or ticagrelor immediately after ACS and stenting, a time of heightened inflammation. An analysis of the results suggests that ticagrelor accelerates the natural decline in inflammation biomarker release and improvement in flow-mediated dilation that occurs over 10 weeks post-ACS. Ticagrelor's potential effects on the latter markers seemed most pronounced when administered in the first 5 weeks post-stenting. A more convincing crossover effect of ticagrelor was observed with EPCs, which may be attributed to a non-P2Y$_{12}$-mediated mechanism. In summary, the results of Jeong et al. (11) and those of other recent studies discussed previously, indicate that potent inhibition of P2Y$_{12}$ along with non-P2Y$_{12}$-mediated effects of ticagrelor play mechanistic roles in lowering rates of myocardial infarction and cardiovascular death compared with thienopyridine therapy in very high-risk patients (**Figure 1**) (3).

Notwithstanding the evidence by Jeong et al. (11) suggesting mechanistic benefits of ticagrelor, is there firm clinical evidence to support the superiority of ticagrelor therapy over thienopyridine therapy in a high-risk East Asian population like those in whom the study by Jeong et al. (11) was conducted? Studies conducted in East Asians have demonstrated higher levels of drug exposure and platelet inhibition, and suggested an increased risk for serious bleeding without additional protective benefit for ischemic events with ticagrelor therapy (12–15). The latter observation of discordant linkage of the level of platelet reactivity to clinical events in the East Asian population has been described by our group as the "East-Asian paradox" (16). Taken together, these

studies suggest that the optimal dose of ticagrelor in East Asians may be lower than the standard 90-mg twice-a-day regimen that has been largely studied in a white population. The adenosine-mediated mechanistic effects of 90-mg twice-a-day ticagrelor dose observed in the current study may be applicable to only high-risk East Asian patients undergoing percutaneous coronary intervention.

Non-P2Y$_{12}$-mediated effects of ticagrelor are being further investigated in ongoing studies. The left ventricular remodeling process is an important determinant for long-term mortality and morbidity following acute myocardial infarction. We have recently demonstrated that enhanced platelet activation and inflammation are associated with adverse left ventricular expansion after ST-segment elevation myocardial infarction. Intensive platelet inhibition and non-P2Y$_{12}$-mediated effects on myocardium and vascular endothelium by ticagrelor may play important roles in left ventricular remodeling (17). This hypothesis is being explored in the HEALING-AMI trial (High PlatElet Inhibition With TicAgrelor to Improve Left Ventricular RemodeLING in Patients With ST-segment ElevAtion Myocardial Infarction [NCT02224534]). In another trial, the effect of ticagrelor on adenosine-induced coronary flow reserve in patients with microvascular angina is also being studied (NCT02284048).

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REFERENCES

1. Wallentin L, Becker RC, Budaj A, et al., PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.

2. Wiviott SD, Braunwald E, McCabe CH, et al., for the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

3. Gurbel PA, Jeong YH, Tantry US. The dogged search for cryptic effects of ticagrelor: wishful thinking or real benefits beyond P2Y$_{12}$ inhibition? Circulation 2016;134:1720–3.

4. Nanhwan MK, Ling S, Kodakandla M, et al. Chronic treatment with ticagrelor limits myocardial infarct size: an adenosine and cyclooxygenase-2-dependent effect. Arterioscler Thromb Vasc Biol 2014;34:2078–85.

5. Vilahur G, Gutiérrez M, Casani L, et al. Protective effects of ticagrelor on myocardial injury after infarction. Circulation 2016;134:1708–19.

6. Barletta KE, Ley K, Mehrad B. Regulation of neutrophil function by adenosine. Arterioscler Thromb Vasc Biol 2012;32:856–64.

7. Fernandez P, Jara C, Aguilera V, et al. Adenosine A$_2$A and A$_3$ receptors are involved in the human endothelial progenitor cells migration. J Cardiovasc Pharmacol 2012;59:397–404.

8. Bonello L, Frere C, Cointe S, et al. Ticagrelor increases endothelial progenitor cell level compared to clopidogrel in acute coronary syndromes: a prospective randomized study. Int J Cardiol 2015;187:502–7.

9. Fromonot J, Dignat-Georges F, Rossi P, et al. Ticagrelor improves peripheral arterial function in acute coronary syndrome patients: relationship with adenosine plasma level. J Am Coll Cardiol 2016;67:1967–8.

10. Kim HK, Jeong MH, Lim KS, et al. Effects of ticagrelor on neointimal hyperplasia and endothelial function, compared with clopidogrel and prasugrel, in a porcine coronary stent restenosis model. Int J Cardiol 2017;240:326–31.

11. Jeong HS, Hong SJ, Cho S-A, et al. 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. J Am Coll Cardiol Intv 2017;10:1646–58.

12. Teng R, Butler K. Pharmacokinetics, pharmacodynamics, and tolerability of single and multiple doses of ticagrelor in Japanese and Caucasian volunteers. Int J Clin Pharmacol Ther 2014;52:478–91.

13. Lee YS, Jin CD, Kim MH, et al. Comparison of prasugrel and ticagrelor antiplatelet effects in Korean patients presenting with ST-segment elevation myocardial infarction. Circ J 2015;79:1248–54.

14. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome randomized, double-blind, phase III PHILO study. Circ J 2015;79:2452–60.

15. He MJ, Liu B, Sun DH, et al. One-quarter standard-dose ticagrelor better than standard-dose clopidogrel in Chinese patients with stable coronary artery disease: a randomized, single-blind, crossover clinical study. Int J Cardiol 2016;215:209–13.

16. Jeong YH, Tantry US, Gurbel P. What is the "East Asian paradox"? Cardiosource Interventional News 2012;1:38–9.

17. Park Y, Tantry US, Koh JS, et al. Novel role of platelet reactivity in adverse left ventricular remodelling after ST-segment elevation myocardial infarction: the REMODELING Trial. Thromb Haemost 2017;117:911–22.

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