Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 6, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.09.051

EDITORIAL COMMENT

With Age Comes Wisdom

Is This True for Platelets?*

Laurent Bonello, MD, PhD,†‡
Corinne Frère, MD, PhD,‡
Franck Paganelli, MD, PhD,† Marc Laine, MD†
Marseille, France

Prasugrel is a new-generation thienopyridine that exhibits a more potent, less variable, and faster platelet blockade of the purinergic receptor P_2Y, G-protein coupled, 12 (P_2Y_{12}) - adenosine diphosphate (ADP) receptor compared with clopidogrel, as demonstrated by the results of early phase studies performed in healthy volunteers and stable coronary artery disease patients (1). Following these encouraging results, the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial (2) confirmed the benefit of prasugrel over clopidogrel in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI). In this study, a near-20% risk reduction was obtained regarding the ischemic endpoint, thanks to improved platelet reactivity (PR) inhibition. On the other hand, a significant increase in bleedings was observed, suggesting a link between excessive P_2Y_{12}-ADP receptor blockade and post-PCI bleedings.

See page 513

Following these clinical results, prasugrel obtained a 1b level of recommendation in guidelines for ACS. In the European Society of Cardiology guidelines, prasugrel overcame clopidogrel, which was downgraded to 1c and considered as a second-line agent in ACS patients receiving PCI (3).

In early clinical studies in ST-segment elevation myocardial infarction patients, Alexopoulos et al. (4) observed that despite its quicker onset of action, prasugrel was associated with, similar to clopidogrel, a longer delay of action compared with that observed in stable coronary artery disease patients. In addition, post-approval studies confirmed that prasugrel was associated with an inter-individual variability, although it was reduced compared with clopidogrel (5). Accordingly, some patients are considered as having high on-treatment PR under prasugrel. On the other hand, some patients exhibited low on-treatment PR. Of importance, accumulating evidence suggests that excessive PR inhibition is associated with bleeding complications. Accordingly, preliminary findings suggested that the inter-individual variability in prasugrel responsiveness may be involved in ischemic and bleeding events. Indeed, a recent prospective and observational study of prasugrel in "real-world" ACS patients undergoing PCI suggested that PR following the loading dose was predictive of both ischemic and bleedings events at 1-year follow-up (6). Gurbel's hypothesis of a therapeutic window of PR to prevent ischemic and bleeding events may, therefore, be valid for prasugrel (7). Identifying the factors associated with variability in prasugrel responsiveness is thus of potential clinical interest.

In the era of clopidogrel, several factors were shown to affect P_2Y_{12}-ADP receptor blockade, although it was not completely elucidated. Extrinsic factors mainly include drug–drug interactions affecting the biotransformation of clopidogrel into its active metabolite, noncompliance with clopidogrel therapy, and underdosing or inappropriate dosing of clopidogrel, and intrinsic factors include diabetes mellitus; polymorphisms of the P_2Y_{12} receptor gene, leading to an increased number of P_2Y_{12} receptors; and polymorphisms of the gene that encodes cytochrome P450 3A (*CYP3A*) (8).

On the contrary, there are very few data available regarding the factors associated with prasugrel variability. This is related to the facts that prasugrel is a novel antiplatelet agent and that it is associated with a reduced variability compared with clopidogrel, thus requiring a larger cohort of patients to identify its determinants.

Interestingly, a recent study by Frelinger et al. (9) suggested that among all intrinsic and extrinsic factors, baseline platelet activity may be the main factor in on-prasugrel variability.

Guthikonda et al. (10) previously demonstrated that the proportion of reticulated platelets (RPs) was a key determinant of PR in stable coronary artery disease patients during clopidogrel therapy. In line with these findings, Perl et al. (11), in this issue of the *Journal*, aimed to investigate, in a prospective study, the potential role of RPs in the inter-individual variability in PR under prasugrel (11).

RPs are newly formed platelets with high granule content and a residual amount of mRNA. They appear to be the youngest circulating platelets in animals (12). It was demonstrated that thiazole orange–positive platelets observed in dogs were <24 h old and reflected an increased platelet turnover (13). Interestingly, these newly formed platelets may have a higher thrombotic potential. Increased

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the †Département de Cardiologie, Hôpital Universitaire Nord de Marseille, Assistance-Publique Hôpitaux de Marseille, Marseille, France; and the ‡Faculté de Pharmacie, Aix-Marseille Université, Marseille, France. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

RP percentages have been found in various clinical conditions, including thrombocytopenia-associated and -disseminated intravascular coagulation and, more recently, arterial thrombosis including stent thrombosis and ACS (14,15). In addition, RPs are independent predictors of cardiovascular death at 12-month follow-up in patients with ACS treated with PCI (16). Level of RP could therefore be a marker of risk or a risk factor for ischemic events. It could act through a modulation of the response to antiplatelet therapy, as observed with clopidogrel.

In the present study, Perl et al. (11) observed that in STEMI patients, on-prasugrel PR was variable both in the acute and chronic phases, with some patients with extreme PR levels. In this study PR was stable over time. The authors also confirmed that despite the use of prasugrel, there was a correlation between the proportion of RP and on-prasugrel PR. In fact, patients in the upper tertiles of RP exhibited higher PR. These findings confirmed that RP could be a good marker to predict nonresponse to prasugrel and the risk of thrombosis.

This study has several strengths. First, it is focused on a very clinically significant population: STEMI patients treated with PCI in which PR inhibition is critical. Second, 2 well-validated platelet assays were used to measure PR. Third, unlike most studies, the authors measured PR and RP proportion both in the acute and chronic phases of antiplatelet therapy. However, there are some limitations to the present findings. In particular, the small number of patients does not allow for multivariable analysis, and the clinical implications of the findings were not assessed.

Overall, the results of the present study give an interesting insight into the mechanism of platelet activity in STEMI patients in the era of potent P_2Y_{12}-ADP receptor antagonists. If confirmed, this could have a clinical impact in the selection, dose, or frequency of prasugrel use in STEMI patients. To achieve a more complete platelet-activity blockade, twice-daily thienopyridine uptake may have the ability to act more deeply on these young platelets by increasing platelets' exposition to active metabolites. With age, these young, turbulent platelets will hopefully respond more adequately to therapy.

Reprint requests and correspondence: Dr. Laurent Bonello, Département de Cardiologie, Hôpital Universitaire Nord de Marseille, Chemin des Bourrely, Marseille PACA 13015, France. E-mail: laurentbonello@yahoo.fr.

REFERENCES

1. PRINCIPLE-TIMI 44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial. Circulation 2007;116:2923–32.
2. TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
3. Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.
4. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2012;5:797–804.
5. Bonello L, Pansieri M, Mancini J, et al. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. J Am Coll Cardiol 2011;58:467–73.
6. Bonello L, Mancini J, Pansieri M, et al. Relationship between post-treatment platelet reactivity and ischemic and bleeding events at 1-year follow-up in patients receiving prasugrel. J Thromb Haemost 2012;10:1999–2005.
7. Bonello L, Tantry US, Marcucci R, et al., for the Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56:919–33.
8. Ait-Mokhtar O, Bonello L, Benamara S, Paganelli F. High on-treatment platelet reactivity. Heart Lung Circ 2012;21:12–21.
9. Frelinger AL 3rd, Michelson AD, Wiviott SD, et al. Intrinsic platelet reactivity before P2Y12 blockade contributes to residual platelet reactivity despite high-level P2Y12 blockade by prasugrel or high-dose clopidogrel. Results from PRINCIPLE-TIMI 44. Thromb Haemost 2011;106:219–26.
10. Guthikonda S, Alviar CL, Vaduganathan M, et al. Role of reticulated platelets and platelet size heterogeneity on platelet activity after dual antiplatelet therapy with aspirin and clopidogrel in patients with stable coronary artery disease. J Am Coll Cardiol 2008;52:743–9.
11. Perl L, Lerman-Shivek H, Rechavia E, et al. Response to prasugrel and levels of circulating reticulated platelets in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;63:513–7.
12. Ault KA, Knowles C. In vivo biotinylation demonstrates that reticulated platelets are the youngest platelets in circulation. Exp Hematol 1995;23:996–1001.
13. Dale GL, Friese P, Hynes LA, Burstein SA. Demonstration that thiazole-orange-positive platelets in the dog are less than 24 hours old. Blood 1995;85:1822–5.
14. Würtz M, Grove EL, Wulff LN, et al. Patients with previous definite stent thrombosis have a reduced antiplatelet effect of aspirin and a larger fraction of immature platelets. J Am Coll Cardiol Intv 2010;3:828–35.
15. Lakkis N, Dokainish H, Abuzahara M, et al. Reticulated platelets in acute coronary syndrome: a marker of platelet activity. J Am Coll Cardiol 2004;10:2087–98.
16. Cesari F, Marcucci R, Gori AM, et al. Reticulated platelets predict cardiovascular death in acute coronary syndrome patients. Insights from the AMI-Florence 2 Study. Thromb Haemost 2013;109:846–53.

Key Words: acute coronary syndrome(s) ■ antiplatelet therapy ■ ST-elevation myocardial infarction.