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**STATE-OF-THE-ART PAPER** CME

# Response Variability to P2Y$_{12}$ Receptor Inhibitors

## Expectations and Reality

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**CME Objective for This Article:** At the completion of this article the learner should be able to discuss: 1) identify the polymorphism playing the most important role in the inter-individual response variability to clopidogrel; 2) compare the characteristics of different methods used to assess the pharmacodynamic effect of antiplatelet drugs; and 3) explain which impact have personalized antiplatelet treatment strategies on outcome variables.

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# Response Variability to $P2Y_{12}$ Receptor Inhibitors

## Expectations and Reality

$P2Y_{12}$ inhibitors are widely used in patients with acute coronary syndromes and in the secondary prevention of thrombotic events in vascular diseases. Within the past few years, several pharmacological, genetic, and clinical limitations of the second-generation thienopyridine clopidogrel have raised major concerns. High on-treatment platelet reactivity, which is common in clopidogrel-treated patients, and its clinical implications led to the development of the more effective platelet $P2Y_{12}$ inhibitors prasugrel (a third-generation thienopyridine) and ticagrelor (a cyclopentyl-triazolo-pyrimidine). The pharmacokinetics and pharmacodynamics of prasugrel and ticagrelor indicate that they provide more consistent, more rapid, and more potent platelet inhibition than clopidogrel, which translates into improved ischemic outcomes. Nevertheless, higher efficacy, which is reflected by low on-treatment platelet reactivity, increases the risk of major bleeding events. Therefore, cardiologists might be facing a new challenge in the future: to individualize the level of platelet inhibition in order to decrease thrombotic events without increasing bleeding. The current review focuses on the use of platelet function testing and pharmacogenomic testing in order to identify patients who either do not respond to or are at risk of not responding sufficiently to $P2Y_{12}$ inhibitors. Moreover, this paper discusses randomized trials, which so far have failed to show that tailored antiplatelet therapy improves clinical outcome, and treatment options for patients with high on-treatment platelet reactivity. (J Am Coll Cardiol Intv 2013;6:1111–28) 

## Platelet Activation

Activation and aggregation of platelets play a central role in the formation and propagation of intracoronary thrombi. Platelet adhesion to the exposed matrix at the site of vascular lesions is the initial step in thrombus formation. Rupture of an atherosclerotic plaque exposes collagen and von Willebrand factor (vWF), which binds via its A3 domain to collagen and via its A1 domain to platelet glycoprotein (GP)-Ib/IX receptors (Fig. 1) (1). Collagen activates platelets directly via the GP-VI receptor and integrin $\alpha_2\beta_1$, which leads to the release of the contents from the platelet-dense granules, which in turn contain platelet agonists such as adenosine diphosphate (ADP), and alpha-granules. The latter contain fibrinogen, factor V, and P-selectin. ADP binds to platelet $P2Y_{12}$ and $P2Y_1$ receptors, and amplifies responses to other agonists such as thrombin (2). Thrombin mediates its effects through the protease-activated receptors 1 and 4, augmenting platelet activation and aggregation. Thromboxane $A_2$, a major platelet metabolite of arachidonic acid, binds to the thromboxane prostanoid receptor, thus amplifying platelet aggregation (Fig. 1). Activated platelets undergo conformational change and increase their surface area several times by re-arrangement in the cytoskeleton and protrusion of pseudopodia and secretion of storage products. Fibrinogen binds to the GP-IIb/IIIa ($\alpha_{IIb}\beta_3$) receptor, which leads to fibrinogen–platelet cross-linking and to the formation of a hemostatic plug at sites of vascular injury. The local concentration of tissue factor initiates the extrinsic clotting of more thrombin and to the propagation of a fibrin clot.

## $P2Y_{12}$ Receptor

The $P2Y_{12}$ receptor plays a crucial role in thrombus formation and stabilization: Activation of the receptor amplifies dense granule secretion and platelet aggregation induced not only by ADP but also by thromboxane $A_2$ and the protease-activated receptor 1 receptor agonists. The alpha-granule release and subsequent expression of P-selectin on activated platelets also are amplified by the $P2Y_{12}$ activation. Stimulation of the $P2Y_{12}$ receptor sustains the activation of the GP-IIb/IIIa and GP-Ia/IIa receptors, leading to stabilization of platelet aggregates (3).

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