Archives of Cardiovascular Disease (2013) 106, 481—486

Available online at
SciVerse ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

SCIENTIFIC EDITORIAL

# Personalized antiplatelet therapy: The wrong approach?

## Traitement antiplaquettaire personnalisé : fait-on fausse route ?

**Jean-Philippe Collet*, Gilles Montalescot**

*Institut de Cardiologie, Inserm U 937, groupe A.C.T.I.O.N., groupe hospitalier Pitié-Salpêtrière, 47—83, boulevard de l'Hôpital, 75013 Paris, France*

Received 21 May 2013; accepted 8 August 2013
Available online 27 September 2013

**KEYWORDS**
Acute coronary syndrome;
Antiplatelet therapy;
Percutaneous coronary intervention

**MOTS CLÉS**
Syndrome coronaire aigu ;
Traitement antiplaquettaire ;
Angioplastie coronaire

The GRAVITAS (Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety) study has demonstrated the detrimental impact of high on-treatment platelet reactivity following stent implantation and the failure of a double clopidogrel maintenance dose to reduce cardiovascular events in patients deemed clopidogrel non-responders (Fig. 1) [1]. However, there was still evidence after the GRAVITAS study to support personalized medicine-based on platelet reactivity. The combination of a low-risk population together with platelet reactivity assessment after percutaneous coronary intervention (PCI) was recognized as a relevant limitation that may have accounted for the negative results of the GRAVITAS study.

The TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy with Prasugrel) study design was similar to that of the GRAVITAS study, but treatment intervention was more aggressive, using prasugrel instead of an increased clopidogrel maintenance dose (Fig. 1). The study was stopped prematurely due to a low event rate [2].

Platelet reactivity has been consistently reported as an independent predictor of 'hard' post-PCI endpoints, including stent thrombosis, myocardial infarction and cardiovascular mortality (Fig. 2) [3,4]. Notably, the hazard associated with high platelet reactivity is greater in patients with an acute coronary syndrome (ACS) than in patients undergoing PCI for stable angina; it accounts for approximately 60% of the definite/probable stent thrombosis events, demonstrating the dominant contribution that inadequate $P2Y_{12}$ receptor inhibition makes to thrombotic events [5,6]. As a consequence, the bedside platelet function test has become an opportunity to guide antiplatelet therapy, particularly when there is an unexpected complication. This is also the case when new $P2Y_{12}$ inhibitors are not available, in the absence, however, of a recommendation for this type of use [7,8].

*Abbreviations:* ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention.

* Corresponding author.
*E-mail address:* jean-philippe.collet@psl.aphp.fr (J.-P. Collet).

1875-2136/$ — see front matter 
http://dx.doi.org/10.1016/j.acvd.2013.08.001

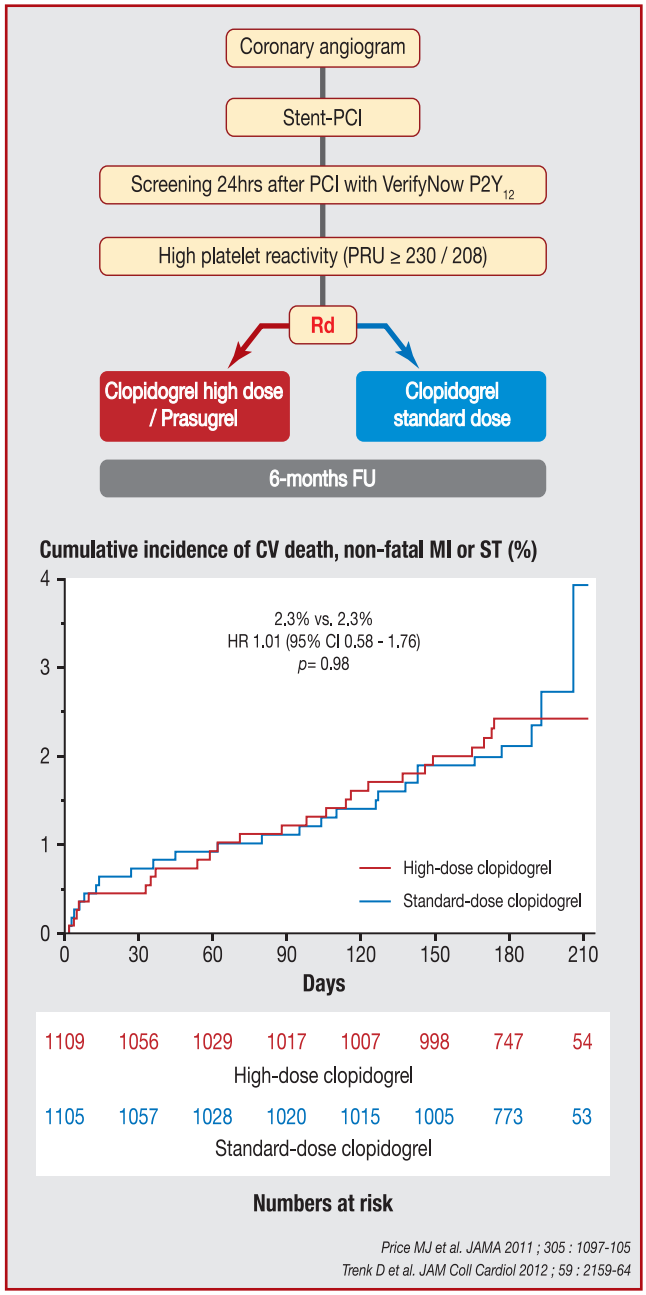


**Figure 1.** Design and results of the GRAVITAS and TRIGGER-PCI trials. CI: confidence interval; Clopi: clopidogrel; CV: cardiovascular; FU: follow-up; HR: hazard ratio; MI: myocardial infarction; PCI: percutaneous coronary intervention; PRU: $P2Y_{12}$ reaction units; ST: stent thrombosis.

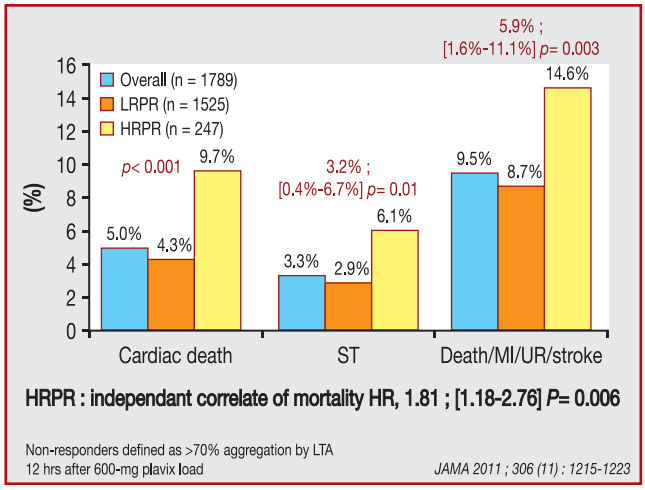


**Figure 2.** Platelet reactivity as a marker of risk in patients who underwent percutaneous coronary intervention. HR: hazard ratio; HPR: high platelet reactivity; HRPR: high residual platelet reactivity; LRPR: low residual platelet reactivity; LTA: light transmission aggregometry.

The ARCTIC (Assessment with a double Randomization of [1] a fixed dose versus a monitoring-guided dose of aspirin and Clopidogrel after drug-eluting stent implantation and [2] Treatment Interruption versus Continuation, 1 year after stenting) multicentre randomized study sought to determine whether a strategy based on systematic platelet function testing to tailor antiplatelet therapy is superior to standard care in 2440 patients with stable angina or non-ST-segment elevation ACS (NSTE-ACS) undergoing PCI [9]. In contrast to the GRAVITAS trial, this study randomized the use of platelet function testing with treatment intervention (monitoring arm) versus standard of care according to clinician's preference without platelet function test (conventional arm) (Fig. 3). In the monitoring arm, serial platelet function tests (before stent implantation and during the maintenance phase) and treatment adjustments using a predefined treatment algorithm were performed. In addition to treatment intensification due to high on-treatment platelet reactivity, patients could be switched back from prasugrel to clopidogrel after PCI if low on-treatment platelet reactivity was measured. Despite halving the rate of high platelet reactivity to adenosine diphosphate (Fig. 4), the primary endpoint of death, myocardial infarction, stent thrombosis, stroke or urgent revascularization was similar after 1 year with the two strategies (hazard ratio [HR] 1.13, 95% confidence interval [CI] 0.98—1.29; $p = 0.10$).

The take-home message is that platelet reactivity is not only a measure of drug response, but also integrates the effect of response to $P2Y_{12}$ receptor antagonists and comorbidities, such as advanced age, diabetes and renal insufficiency. Platelet reactivity should also be considered as a surrogate marker for studies on antiplatelet treatments that may be helpful to explain the results of trials. This has been confirmed by the prespecified pharmacodynamic TRILOGY-ACS (A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction Who Are Medically Managed) study, which demonstrated a real effect of treatment intensification but a lack of independent relationship between platelet reactivity and clinical outcome [10]. Such results further support the lack of benefit of intensification of antiplatelet therapy in medically managed patients [11] (Fig. 5).

What is the future of platelet function testing? The level of recommendation for routine platelet function testing in patients who undergo stent placement will remain low in accordance with the negative results of recent randomized studies (Table 1) [1,2,9]. Platelet activity rather appears as a reliable risk stratification approach but not as a modifiable