

Platelet Function Testing in Clinical Practice: Are We Ready for Prime Time?

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Platelets play a key role in the development of thrombotic complications in patients with an acute coronary syndrome (ACS) and undergoing percutaneous coronary interventions (PCI).¹ Therefore, compliance with antiplatelet drug therapy, in particular the oral antiplatelet agents aspirin and clopidogrel, represents a pivotal secondary prevention measure in these patients.¹ Over the past years however, there has been accumulating data showing that despite compliance to dual antiplatelet therapy with aspirin and clopidogrel, a considerable number of patients continue to develop thrombotic complications.² This has been in part attributed to inadequate inhibition of one or both of the targets of oral antiplatelet agents, namely the COX-1 enzyme for aspirin and the ADP P2Y₁₂ receptor for clopidogrel, a phenomenon also known as antiplatelet drug “resistance.”² While controversies currently exist on the most appropriate test as well as the optimal cut-off value to define an individual as “resistant” to a specific antiplatelet agent,³ there is accruing evidence on the its prognostic implications suggesting that this phenomenon is more than just a laboratory curiosity.² The study from de Miguel Castro et al⁴ reported in this issue of *Revista Española de Cardiología* is indeed supportive of this emerging clinical entity. In the present issue of *Revista Española de Cardiología* de Miguel Castro et al⁴ assessed the impact of individual response to clopidogrel therapy on 1-year outcomes in 179 patients with non-ST

elevation ACS (NSTEMI-ACS). Complete follow-up was achieved in 90% of patients and an 11% major adverse cardiac event (MACE) rate was recorded. Platelet function was tested by means of a point-of-care device (VerifyNow P2Y₁₂ assay) showing that both the degree of platelet inhibition and post-treatment platelet reactivity were associated with an increased risk of MACE. However, only post-treatment platelet reactivity played out as an independent predictor of MACE. The authors also identified a cut-off value of 175 PRU (P2Y₁₂ reactivity units) to be the best predictor of MACE in their population with an odds ratio of 3.9.

De Miguel Castro et al⁴ should be commended for this study which not only confirms the prognostic value of platelet function testing and in particular that of post-treatment platelet reactivity, but also provides important novel insights to the field. To date most studies evaluating platelet function testing and clinical outcomes have been based on techniques such as light transmittance aggregometry or flow cytometry which are not universally available, time consuming, requiring experienced personnel, thus overall increasing costs.^{2,3} These have been factors strongly limiting the use of platelet function tests in daily clinical practice. In the present study the VerifyNow P2Y₁₂ assay, a novel point-of-care system that specifically tests for clopidogrel-induced effects, was used. Although this point-of-care assay shows good correlation with light transmittance aggregometry, only few studies have corroborated its prognostic value in the clinical setting (Table).^{4,8} The results of this study therefore represent a promising step forward in our future goals of individualized antithrombotic treatment regimens for which a more user-friendly

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TABLE 1. Platelet Reactivity Measured by the VerifyNow P2Y12 Assay and Clinical Outcomes

Study	Patients, No.	VerifyNow P2Y12 Assay Cut-off Value	Patient Population	Correlation With Outcomes	Endpoint
de Miguel Castro et al ⁴	179	PRU ≥ 175	NSTE-ACS	Yes	1 year MACE
Price et al ⁵	380	PRU ≥ 235	Elective PCI	Yes	6-month MACE
Patti et al ⁶	160	PRU ≥ 240	Non-urgent PCI	Yes	30-day MACE
Cuisset et al ⁷	106	Inhibition $\leq 15\%$	Elective PCI	Yes	Peri-procedural MI
Buch et al ⁸	330	N/A	Elective PCI	No	6-month MACE

MACE indicates major adverse cardiac event; MI, myocardial infarction; N/A, not applicable; NSTE-ACS, non ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PRU, P2Y12 reactivity index.

assay that can be used in daily clinical practice is warranted.⁹ It may be argued that the cut-off value identified in the report from de Miguel Castro et al differs (lower PRU value) from that of other studies (Table 1). However, differences in the risk profile of the study population, the definition of MACE, the length of follow-up, the antithrombotic treatment regimen used, are all factors that may influence these results.⁹ Further, the present study extends our knowledge of platelet function testing within a selected group of patients presenting with a NSTE-ACS, irrespective of their management (PCI, surgical, medical). To date many studies tested for clopidogrel responsiveness in heterogeneous patient populations¹⁰ and, except for only one study,¹¹ always in patients undergoing PCI.¹⁰ Ultimately, most studies currently available have evaluated the short-to-mid term prognostic implications of platelet function testing, while the present study is among the few which have confirmed its value at long-term.

There are several limitations to the study from de Miguel Castro et al⁴ which are worthy of being addressed. The event rate was overall low (11%) which increases the play of chance probability of the obtained results. There were a considerable number of patients (34%) medically managed. It cannot be excluded that a more aggressive management of these patients in the acute setting would have resulted in different outcomes. This is of relevance as the authors considered the need for revascularization, which occurred in 28% of patients, among the endpoints. Also, the fact that a 300 mg rather a 600 mg loading dose of clopidogrel was used, which leads to higher post treatment platelet reactivity, may be an index of undertreatment. In fact lower platelet reactivity associated with a 300 mg loading dose regimen has been associated with an increased risk of myocardial infarction.¹⁰ The latter event

occurred in 33% of patients in this study. Clinical follow-up was achieved in only 90% of patients. It is therefore intuitive that understanding the outcomes of the 10% of the missing population is of relevance and this may have influenced the outcome of the study results.

At this point it may be questioned if the use of platelet function tests in clinical practice ready for prime time. The challenge in addressing this question is determining what to do from a clinical standpoint with the results obtained. Several strategies can be proposed to overcome inadequate antiplatelet drug responsiveness such as: *a)* increasing the loading and maintenance dose of clopidogrel; *b)* adding an additional antiplatelet agent such as a glycoprotein IIb/IIIa inhibitor or cilostazol; or *c)* using a novel and more potent antiplatelet agent. High clopidogrel loading doses (≥ 600 mg) enhance platelet inhibition¹² and repeated loading doses of 600 mg (up to 2400 mg) with the goal to make “resistant” patients more responsive has been associated with improved outcomes in a small pilot study.¹³ Increasing the maintenance dose of clopidogrel in suboptimal responders enhances platelet inhibition, the prognostic value of which is being evaluating in several large scale clinical studies.¹⁴ Selective usage of high bolus tirofiban in patients with antiplatelet drug resistant undergoing elective PCI has shown to reduce periprocedural myocardial infarction rates.¹⁵ Adjunctive therapy with cilostazol in addition to aspirin and clopidogrel enhances P2Y12 inhibition in diabetic patients which may contribute their improved clinical outcomes while on such triple antiplatelet drug regimen.^{16,17} However, the most promising approach to improve antiplatelet drug responsiveness will be with novel and more potent antiplatelet agents, currently under advanced clinical testing.¹⁸ Among these, prasugrel has shown

to be associated with better clinical outcomes compared with clopidogrel in high risk ACS patients undergoing PCI.¹⁹ Pharmacodynamic studies have shown better platelet inhibition achieved with prasugrel compared with clopidogrel even when high loading and maintenance doses are used.²⁰ The better clinical outcomes obtained with prasugrel occur at the expense of an increased bleeding rate, particularly in certain subgroups.¹⁹ These data overall underscore the need for individualized antithrombotic treatment regimens not only to reduce the risk of ischemic events, but also to minimize bleeding hazards.

In summary, accumulating data suggest platelet function testing as a valid tool to define the short and long-term prognosis in ACS/PCI patients. The development of point-of-care assays able to assess platelet function at the bedside will allow its more broad scale use and thus better define its prognostic value in various clinical scenarios. Most importantly, these devices will facilitate the performance of large scale clinical trials in which individualized antithrombotic treatment regimens are applied. However, only with the results of the latter will it be possible to define if high platelet reactivity while on recommended antiplatelet drug regimens defined by functional testing represents simply a “marker” of risk or represents a key element in the etiopathogenesis of ischemic complications in ACS/PCI patients. Until then, platelet function testing should be reserved as a research tool.

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