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). Therefore, compliance with antiplatelet drug therapy, in particular the oral antiplatelet agents aspirin and clopidogrel, represents a pivotal secondary prevention measure in these patients. 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. 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.” 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, there is accruing evidence on the its prognostic implications suggesting that this phenomenon is more than just a laboratory curiosity.

The study from de Miguel Castro et al reported in this issue of Revista Española de Cardiología is indeed supportive of this emerging clinical entity. 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 or flow cytometry which are not universally available, time consuming, requiring experienced personnel, thus overall increasing costs. 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
TABLE 1. Platelet Reactivity Measured by the VerifyNow P2Y12 Assay and Clinical Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, No.</th>
<th>VerifyNow P2Y12 Assay Cut-off Value</th>
<th>Patient Population</th>
<th>Correlation With Outcomes</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Miguel Castro et al</td>
<td>179</td>
<td>PRU ≥175</td>
<td>NSTE-ACS</td>
<td>Yes</td>
<td>1 year MACE</td>
</tr>
<tr>
<td>Patti et al</td>
<td>380</td>
<td>PRU ≥225</td>
<td>Elective PCI</td>
<td>Yes</td>
<td>6-month MACE</td>
</tr>
<tr>
<td>Cuiisset et al</td>
<td>160</td>
<td>PRU ≥240</td>
<td>Non-urgent PCI</td>
<td>Yes</td>
<td>30-day MACE</td>
</tr>
<tr>
<td>Cuisset et al</td>
<td>106</td>
<td>Inhibition ≤15%</td>
<td>Elective PCI</td>
<td>Yes</td>
<td>Peri-procedural MI</td>
</tr>
<tr>
<td>Buch et al</td>
<td>330</td>
<td>N/A</td>
<td>Elective PCI</td>
<td>No</td>
<td>6-month MACE</td>
</tr>
</tbody>
</table>

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. 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. 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 populations and, except for only one study, always in patients undergoing PCI. 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 al 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. 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 inhibition 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. 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. Selective usage of high bolus tirofiban in patients with antiplatelet drug resistant undergoing elective PCI has shown to reduce periprocedural myocardial infarction rates. 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. However, the most promising approach to improve antiplatelet drug responsiveness will be with novel and more potent antiplatelet agents, currently under advanced clinical testing. Among these, prasugrel has shown...

REFERENCES