**EDITORIAL COMMENT**

**Bleeding and Thrombosis Risk Matters**

How Long Can We Stick to the One-Size-Fits-All Strategy of Platelet Inhibition?*

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During the last decades, a dual antiplatelet treatment with aspirin and a P2Y$_{12}$ platelet receptor inhibitor has become the cornerstone of medical therapy for patients with coronary artery disease presenting with acute coronary syndromes (ACS) or undergoing a percutaneous coronary intervention (PCI). Whereas drug response variability to antiplatelet agents and especially to P2Y$_{12}$ receptor inhibitors such as clopidogrel (1) or prasugrel (2) is a widely accepted and thoroughly investigated phenomenon, and whereas it is obvious that both bleeding and thrombotic events have an impact on overall survival of PCI-treated patients (3), a personalized and thereby tailored treatment with regard to drug choice and dosage adjustment is still not reality in clinical practice. Studies (1,4) performed a decade ago have stimulated extensive research in this field, and the idea of a therapeutic window of platelet inhibition that reflects both bleeding and thrombotic risk was postulated (5) early after the first reports on clopidogrel response variability. Initial evidence for the existence of a “sweet-spot” of P2Y$_{12}$ receptor-directed inhibition was provided by an observational study performed in clopidogrel-treated patients (n = 2,533) undergoing PCI (6). Subsequent studies (7–10) focusing on the therapeutic window concept and using different platelet function assays for drug response monitoring have confirmed these findings (for a summary of studies see Table 1).

In this issue of *JACC: Cardiovascular Interventions*, Cuisset et al. (11) provide important and interesting results on the clinical implications of very low on-treatment platelet reactivity (VLTPR) as well as on the therapeutic window of platelet inhibition in ACS patients (n = 1,542) receiving clopidogrel or prasugrel for PCI. Using the laboratory-based P2Y$_{12}$ receptor-specific vasodilator-stimulated phosphoprotein assay for platelet function monitoring, the investigators observed that VLTPR was found to be a strong and independent predictor of bleeding complications. The prognostic value of VLTPR was consistent across different types of thienopyridines used in this study. Patients within a window of normal platelet reactivity showed the lowest risk (5.7%) for adverse events (defined as the combined incidence of stent thrombosis or bleeding events grade ≥2 defined according to Bleeding Academic Research Consortium criteria) when compared with a 17.4% event rate in VLTPR patients and 8% events in patients with high on-treatment platelet reactivity ($p_{adj} = 0.02$). Interestingly, the presence of diabetes and a PCI for ST-segment elevation myocardial infarction were both associated with a lower bleeding risk in different subgroups of the study; a finding that is in line with results from the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction) trial (12), where exactly these subgroups derived the greatest benefit from prasugrel treatment and this without a higher risk for bleeding. With the present results, the investigators confirm and expand prior reports (13) on the association of an enhanced response to P2Y$_{12}$ receptor inhibitors with bleeding risk. Furthermore, this study calls for greater attention to the therapeutic window concept of platelet inhibition. Some aspects of their study require a closer look and a critical discussion.

First, the investigators assessed the response to thienopyridine treatment at 1 month after the PCI procedure. The optimal time point of testing, however, may depend on the clinical scenario and the P2Y$_{12}$ receptor inhibitor that was chosen for the initial treatment. Considering that in general, but especially in clopidogrel low responders, the majority of thrombotic events occur in the early phase after the intervention (12), any testing that aims at intensifying treatment (e.g., switch from clopidogrel to prasugrel) should be made early after the PCI procedure. Then again, it may well be that platelet function monitoring beyond the acute phase and in the subacute phase of treatment may prove useful for reducing bleeding risk by establishing a more differentiated treatment regimen that is characterized by high-level platelet inhibition in the acute phase and a more moderate level (deintensification) of inhibition in the subacute and chronic phase of treatment (e.g., switch from prasugrel back to clopidogrel). Second, the present study (11) is of observational nature, and the results reported call for randomized studies using the vasodilator-stimulated phosphoprotein technique or other near-patient testing methods in ACS patients undergoing PCI.

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Whereas the value of platelet function testing as a diagnostic or prognostic tool in PCI-treated patients is beyond any doubt (4), the assets and drawbacks of a personalized antiplatelet treatment based on platelet function monitoring are subject to controversial discussions. Prior randomized trials (14–16) that implemented the VerifyNow P2Y_{12} assay did not support a personalized approach of antiplatelet treatment. However, these studies had little or no utilization of potent P2Y_{12} receptor inhibitors such as prasugrel or ticagrelor (14,15) or included mainly patients with stable coronary artery disease (14–16)—a group of patients where overall event rates are low and leave little room for improvement. Similar as the case in the present study by Cuisset et al. (11) was, future trials on personalized anti-platelet treatment should focus on high-risk cohorts such as ACS patients undergoing PCI and should also focus on stent thrombosis and bleeding events with regard to the primary endpoint selection.

Concerning the optimal level of platelet inhibition in the individual patient, both mechanistic and clinical data (4,12) are not in accordance with a “1-size-fits-all” strategy of antiplatelet treatment. We have learned from the pivotal randomized trials (12,17) in this field, that the risk for bleeding and thrombotic events is also a group-specific property. Whereas, for example, diabetic or ST-segment elevation myocardial infarction patients are likely to require the adequate action of potent antiplatelet agents, the same treatment may lead to an unfavorable risk-benefit profile in other groups such as elderly patients or patients with a low body mass index.

Nowadays, it is common practice in coronary artery disease patients to adjust the dosing of lipid-lowering agents based on measured low-density lipoprotein levels and to adjust the antihypertensive medication based on measured blood pressure values. However, for antiplatelet drugs, where an adequate response is crucial for clinical outcome, an individualized treatment approach reflecting both bleeding and thrombotic risk has not yet been established. The question remains how long we can carry on regardless with this 1-size-fits-all approach of targeting the blood platelet.

**Table 1. Studies on the Therapeutic Window Concept of Platelet Inhibition in Patients Treated With PCI**

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Patients, n</th>
<th>Platelet Function Assay</th>
<th>Study Cohort</th>
<th>Drug Investigated</th>
<th>Therapeutic Window Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonello et al. (8)</td>
<td>301</td>
<td>VASP assay</td>
<td>ACS patients</td>
<td>Prasugrel</td>
<td>PRI VASP: 16%–53.5%</td>
</tr>
<tr>
<td>Campo et al. (7)</td>
<td>300</td>
<td>Verify Now P2Y_{12} assay</td>
<td>All comers (except STEMI patients)</td>
<td>Clopidogrel</td>
<td>PRU: 86–238</td>
</tr>
<tr>
<td>Cuisset et al. (11)</td>
<td>1,542</td>
<td>VASP assay</td>
<td>ACS patients</td>
<td>Clopidogrel and prasugrel</td>
<td>PRI VASP: 10%–50%</td>
</tr>
<tr>
<td>Gurbel et al. (10)</td>
<td>225</td>
<td>TEG platelet mapping assay</td>
<td>ACS patients</td>
<td>Clopidogrel</td>
<td>MA ADP: 31–47 mm</td>
</tr>
<tr>
<td>Mangiacapra et al. (9)</td>
<td>732</td>
<td>Verify Now P2Y_{12} assay</td>
<td>Stable CAD patients</td>
<td>Clopidogrel</td>
<td>PRU: 179–238</td>
</tr>
<tr>
<td>Sibbing et al. (6)</td>
<td>2,533</td>
<td>Multiplate analyzer</td>
<td>All comers</td>
<td>Clopidogrel</td>
<td>AU × min: 189–467</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndromes; ADP = adenosine diphosphate; AU = aggregation units; CAD = coronary artery disease; MA = maximal aggregation; PCI = percutaneous coronary intervention; PRI = platelet reactivity index; PRU = P2Y_{12} reactivity units; TEG = thromboelastogram; VASP = vasodilator-stimulated phosphoprotein.

**REFERENCES**


Key Words: bleeding ■ clopidogrel ■ percutaneous coronary intervention ■ prasugrel ■ stent thrombosis ■ therapeutic window.