**EDITORIAL COMMENT**

**Platelet Function**

**Assessment to Predict Outcomes After Coronary Interventions**

**Hype or Hope?**

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The primary aim of percutaneous coronary intervention (PCI) is to obtain excellent acute results in all attempted lesions without the shadow of any procedure-related complication. Equally important is to guarantee that the benefits of revascularization are maintained in the long run (1). Currently, mainly as the result of improving technologies and adjunctive therapy, procedure-related complications remain very low. Likewise, the advent of drug-eluting stents has revolutionized the field, dissipating the fear of restenosis (1). Platelets are key players in ischemic complications in patients undergoing PCI, and antiplatelet medication represents a cornerstone treatment. Novel and more potent antiplatelet regimens have been recently incorporated into our armamentarium to minimize procedural complications and the concerns of delayed thrombotic risks associated with the profound antiproliferative effects of drug-eluting stents.

However, major issues with antiplatelet therapy remain unresolved. These include: 1) the optimal therapeutic strategy in patients undergoing PCI; 2) the optimal technique to monitor its biologic effects in the clinical setting; and 3) the optimal length of dual antiplatelet treatment, especially in patients receiving drug-eluting stents. This commentary will briefly focus on the first two problems.

**CLINICAL IMPLICATIONS OF STUDYING PLATELET FUNCTION**

In this issue of the *Journal*, Hochholzer et al. (2) present the results of the EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate) study. This study elegantly demonstrates the clinical implications of assessing the extent of platelet aggregation in patients undergoing PCI. A large cohort of relatively low-risk patients undergoing elective coronary stenting pre-treated at least 2 hours before intervention with a 600-mg loading dose of clopidogrel were evaluated. Patients showing higher degrees of 5 μmol/l adenosine diphosphate (ADP)-induced platelet aggregation assessed by light transmission aggregometry (LTA) immediately before intervention (those in the upper quartiles) suffered more 30-day major adverse cardiac events (MACE). Notably, platelet aggregation above the absolute median value of the study population (14% of aggregation) carried a 6.7-fold risk of events. Furthermore, on multivariate logistic regression models (including all potential confounders such as baseline platelet aggregation and time from clopidogrel loading to intervention), platelet aggregation emerged as an independent predictor of early clinical outcome. These in-depth analyses are of interest because the reported differences in demographic characteristics may have biased outcomes. This is the largest prospective study supporting the prognostic implications of platelet function measures performed before intervention in patients pre-treated with a high clopidogrel loading dose regimen. Importantly, the study also suggests the potential clinical utility of this tool to identify patients who may benefit from more aggressive antithrombotic approaches.

Hochholzer et al. (2) are to be commended for their landmark study. This further piece of evidence on the prognostic insights of platelet function assessment may represent a critical turning point in translational research where the interest of measuring platelet activity will definitely shift from bench to bedside. Hopefully, this will lead to increased use of platelet function studies in daily clinical practice and set the basis for specific and individualized therapeutic strategies. Nevertheless, owing to the potential major clinical implications of the study as well as the complexity of platelet function analysis, some issues should be addressed.

First, baseline platelet function accounted for a significant amount of interindividual variability in platelet function and up to 50% of residual platelet aggregation before intervention depended on the variability in individual response to clopidogrel (2). In this regard, it would be critical to readily identify the subset of patients showing higher platelet activity at baseline and reduced antiplatelet drug responsiveness in whom our therapeutic efforts may merit more attention (3). Previous studies have demonstrated that clinical status (acute coronary syndrome), risk factors (diabetes mellitus, obesity), as well as specific genetic traits may lead to different degrees of platelet reactivity and responsiveness to antiplatelet agents (4–7). However, a comprehensive picture of patients with enhanced baseline platelet activity remains elusive. In addition, the final implications of these findings and the fate of these “unprotected” patients remain to be evaluated in large scale clinical studies.

Second, the loading dose and the time-delay interval between clopidogrel administration and PCI proved to be of...
paramount importance. A 600-mg loading dose is increasingly used in daily clinical practice. This loading dose regimen is associated with more rapid platelet inhibition and improved responsiveness compared with a 300-mg loading dose (8–9). Notably, a pre-treatment approach using a 600-mg loading dose also appears to translate into better clinical outcomes without any increase in bleeding hazards (10). Despite such observations, a high clopidogrel loading dose regimen is still not approved by the U.S. Food and Drug Administration, because most clinical efficacy data have been accrued with a 300-mg dose. On the other hand, in the present study, patients in whom clopidogrel was administered relatively close to the procedure had increased platelet aggregation. These findings are in line with previous studies and emphasize the importance of considering the pharmacokinetic profile of the drug even when a 600-mg loading dose is selected (8–9). A post hoc analysis of the CREDO (Clopidogrel for Reduction of Events During Observation) trial showed that a 300-mg clopidogrel loading dose started to be clinically effective only after 12 h of pretreatment (11). In contrast, a retrospective analysis of the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment) trial, in which a pre-treatment strategy using a 600-mg loading dose regimen in low- to intermediate-risk patients was used, failed to detect an incremental 30-day clinical benefit from pre-treatment durations >2 to 3 h (12). However, from a pragmatic perspective, it should be kept in mind that despite the widely demonstrated benefits of upstream antiplatelet therapy (11), clopidogrel pre-treatment is still not systematically ensured by many interventionalists owing to logistic difficulties, performance of ad hoc procedures, and the potential fear of required by-pass surgery.

Last but not least, although the relation between the extent of platelet aggregation and the event rate was clear, and persisted despite adjusting for potential confounders, the actual rate of events (in particular, the 1% of myocardial infarction) was lower than expected (2). Moreover, the external validity of these findings could be jeopardized by the high number of patients eventually excluded from the study (one-third of those eligible) owing to thienopyridine pre-treatment (patients at higher risk?). Furthermore, a detailed classification of events (procedure-related vs. subacute stent thrombosis) would have been of interest owing to the multifaceted underlying pathophysiology. In this regard, the lack of correlation between pre-procedural platelet function and the incidence of troponin elevations after PCI (2) constitutes another area of uncertainty.

Previous clinical studies relating the extent of platelet inhibition to clinical outcome. In patients undergoing PCI, several studies have assessed the clinical implications of individual responsiveness to antiplatelet agents. The GOLD (AU-Assessing Ultegra) study demonstrated a substantial variability in the level of platelet inhibition in patients treated with intravenous glycoprotein IIb/IIIa antagonist therapy, and the degree of platelet inhibition represented an independent predictor for the risk of MACE (13). A broader number of investigations have focused on the clinical impact of individual responsiveness to oral antiplatelet agents. In particular, several studies have identified suboptimal responsiveness to aspirin as a predictor of ischemic events at follow-up in patients with different clinical manifestations of atherosclerotic disease, and there is currently growing evidence that suboptimal responsiveness to clopidogrel also may contribute to poor clinical outcomes (14). In patients undergoing PCI, the implications of the degree of platelet inhibition on myocardial infarction have been extensively investigated (15–16). Notably, Chen et al. (17) observed an increase in procedure-related myocardial infarction in aspirin-resistant patients despite clopidogrel pre-treatment.

The role of platelet inhibition on stent thrombosis has also received recent attention in retrospective analyses (18–21). Wenaweser et al. (20) showed that patients who had suffered from stent thrombosis had an impaired response to aspirin and that additional treatment with clopidogrel was unable to overcome differences in platelet aggregation compared with matched controls. The CREST (Clopidogrel Effect on Platelet REactivity in Patients With Stent Thrombosis) study (21) showed that high post-treatment platelet reactivity and incomplete P2Y12 receptor inhibition were risk factors for subacute stent thrombosis. Finally, anecdotal—but consistent—evidence from multiple clinical studies suggests a close relation between discontinuation of antiplatelet therapy and late drug-eluting stent thrombosis (22), boosting the empirical prescription of prolonged dual antiplatelet therapy in these patients.

Future challenges and expectations. Assessing platelet function currently remains a moving target. Efforts should be made to identify and standardize the criteria for optimal platelet inhibition in patients undergoing PCI. This should also involve technical and methodologic issues so that the results of different trials could be adequately compared. In the present series, late platelet aggregation was assessed on LTA at 5 min, whereas other reports (7,8) have determined “maximal” aggregation yielding higher readouts. Likewise, the present study evaluated “absolute” values of post-treatment platelet activity whereas some previous reports have focused on “percentage inhibition” of platelet activity (23). Timing of platelet function assessment is also a critical issue. Differing from the EXCELSIOR study (2), the PREPARE POST-STENTING (Platelet Reactivity in Patients and Recurrent Events Post-Stenting) study (24), in which patients undergoing nonemergency stenting were treated with a 300- or 600-mg loading dose of clopidogrel after intervention, showed that increased platelet reactivity assessed by LTA at discharge was associated with ischemic risk. Ischemic events occurred in 10% of patients at 30 days and in 20% at 6 months. Over 90% of patients with events had maximal ADP-induced platelet aggregation values above 50%. Notably, that study highlighted that, in addition to platelet reactivity, clot strength (a measure of thrombin-
induced fibrin) and rapid fibrin formation (a marker of thrombin activity) were also associated with events. These findings explain the occurrence of events despite treatment with aspirin and clopidogrel, suggesting the potential need for more aggressive thrombin inhibition during interventions in selected patients.

Other variables that may lead to different readouts and merit attention when comparing results between different studies using LTA include agonist type and concentration, use of native or platelet count-adjusted platelet-rich plasma, and anticoagulant selection (25). Further, although most clinical studies on clopidogrel rely on standard LTA, there are many other modalities to assess its effects (26). Briefly, defining the extent of platelet function in patients treated with antiplatelet agents widely varies, and the definitive answer as to which laboratory test is the best marker of clinical efficacy will require correlation with clinical outcomes in large clinical trials. Hopefully, this will also lead toward unified definitions that will be welcomed by the scientific community (14).

Measurements of individual responsiveness to antiplatelet therapy may allow customized dose titration, and identification of a threshold effect would help therapeutic targeting. The results of the EXCELSIOR study represent an important contribution to our understanding of the impact of platelet reactivity on clinical outcomes in patients undergoing relatively low-risk interventions and underscore that the “one size fits them all” concept does not apply for antiplatelet drug regimens (2). In fact, despite adequate timing of pre-treatment with a 600-mg clopidogrel loading dose, ~40% of patients were above the median value of platelet aggregation and had increased risk. The ongoing RESISTOR (Research Evaluation to Study Individuals Who Show Thromboxane or P2Y12 Receptor Resistance) trial will use in low-risk patients undergoing PCI a point-of-care assay to identify responders or nonresponders to antiplatelet therapy and then randomize them to glycoprotein IIb/IIIa inhibitors or placebo to determine the impact on myocarditis. Further studies are still required in high-risk patients to confirm that measuring platelet activity provides important and independent prognostic clues. Recent data from the ISAR-REACT II study (27) support the incremental value of upstream glycoprotein IIb/IIIa inhibitors in high-risk patients pre-treated with a 600-mg clopidogrel loading dose. What else can we do? Intensification of therapy with an even higher loading dose of clopidogrel (900 mg) failed to achieve significant reductions in platelet reactivity compared with 600 mg (28). Therefore, the answer may be in the use of more potent P2Y12 antagonists (AZD6140, prasugrel, canegrel), characterized by less response variability, currently being evaluated in phase III clinical trials or antagonists of other platelet targets, such as thrombin-inhibiting drugs (29).

The next challenge will be to identify the best marker of clinical efficacy following standardized therapeutic approaches and to select patients most likely to benefit from tedious and relatively sophisticated ex vivo functional studies. Reliable user-friendly point-of-care tests may evolve in the near future to allow their routine implementation in the clinical setting. Eventually, prospective large-scale studies should determine if direct guidance of tailored antiplatelet therapy—as the result of platelet function testing—might translate into improved clinical outcomes after coronary interventions. Only then will we be able to exchange hype for hope.

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