EDITORIAL

Prasugrel: The Triton Shell to Soothe Platelet Reactivity

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Over the past decade, the benefits of dual therapy with aspirin and clopidogrel, a second-generation thienopyridine, has been widely demonstrated by several clinical trials in high risk patients with acute coronary syndrome (ACS), particularly in those undergoing percutaneous coronary intervention (PCI). (1, 2) However, a considerable number of patients continue to have atherothrombotic events, including stent thrombosis, despite adequate treatment compliance. (3, 4) The variability of clopidogrel-induced antiplatelet effect has been recently demonstrated, with a positive correlation with the recurrence of thrombotic events. In fact, inadequate inhibition of the P2Y12 adenosine diphosphate receptor has been proposed as one of the causes of variability of clopidogrel therapy. (3, 4) These findings have encouraged looking for a greater inhibition of the P2Y12 receptor, either by increasing clopidogrel dose or by developing new more potent antiplatelet drugs to reduce the incidence of recurrent thrombotic events. (5)

Prasugrel, a third-generation thienopyridine which has been recently approved for human use, has a more favorable pharmacokinetic and metabolic profile compared to clopidogrel. (6) Like clopidogrel, prasugrel is an inactive pro-drug that requires oxidation by the hepatic cytochrome P450 (CYP) system to generate an active metabolite with an antiplatelet effect equivalent to that of clopidogrel. (7, 8) However, compared with clopidogrel which is activated in a two-step process, prasugrel is more efficiently transformed into its active metabolite (reactive thiol group) in a single-step process. (7, 8) Thus, prasugrel produces a better and more potent blockade of the P2Y12 receptors, (6) demonstrated by a faster, more potent and more predictable platelet inhibition observed in pharmacodynamic studies comparing prasugrel versus high dose clopidogrel. In general, platelet inhibition occurs 30 minutes after an oral loading dose of 60 mg prasugrel, with the maximum inhibition seen at 2-4 hours. (9, 10) In this issue of the Revista, Candiello et al. (11) confirm greater platelet inhibition in patients receiving a loading dose of 60 mg prasugrel compared with clopidogrel in a population of 83 consecutive and stable patients after successful PCI (clopidogrel = 42; prasugrel = 41). Twelve to 24 hours after receiving the loading dose, patients treated with prasugrel presented greater platelet inhibition compared to those treated with clopidogrel evaluated with the VerifyNow-P2Y12 system [median 49 (9-78) vs. 160 (82-224), respectively, $p < 0.001$]. Prasugrel has greater clinical efficacy compared to clopidogrel due to its better pharmacodynamic profile. This was demonstrated by the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) - TIMI (Thrombolysis in Myocardial Infarction) trial, which reported a significant reduction in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. (12) Yet, this reduction in the incidence of ischemic events was at the expense of a higher rate of bleeding in patients treated with prasugrel, although these patients had greater net clinical benefit. (12)

THE STRONGER THE BETTER, OR A DEFINED LEVEL OF CALM?

Several investigations have demonstrated the relationship between inadequate blockade of the P2Y12 receptor and the presence of recurrent adverse events evaluated by platelet function tests. Of particular interest, point-of-care or near-bedside platelet function tests as the VerifyNow-P2Y12 system are easy to use and provide rapid results in about 5 minutes. (13) Previous observational studies and a recent meta-analysis have demonstrated the association between the levels of platelet inhibition measured by the VerifyNow-P2Y12 system with the presence of long-term adverse events after PCI, including death from cardiovascular causes, myocardial infarction and stent thrombosis. In addition, a cutoff point of ≥230 P2Y12 reaction units (PRUs) to define high residual platelet reactivity (HRPR) despite antiplatelet therapy may predict greater incidence of adverse events. (13, 14) The level of platelet inhibition and HRPR achieved with prasugrel is more predictable. (6)

In their study, Candiello et al. show that using a cutoff point of > 230 PRUs,24% (n = 10) of patients treated with clopidogrel presented HRPR versus no

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patients in the prasugrel group.

After the administration of a loading dose of 60 mg prasugrel in patients pre-treated with clopidogrel, the level of platelet reactivity was below the cutoff point established (from PRU 279 [262-322] to PRU 49 [7-104]). The study by Candiello et al. has multiple limitations: the small sample size, the inclusion of low-risk patients and the use of a single blood sample in a pharmacodynamic study, among others. However, the question is if we should use these new and more potent antiplatelet agents in all our patients in daily practice or, on the contrary, we should only think of prescribing them to patients with high residual platelet reactivity despite the correct treatment with the "old" regime. Interestingly, patients with very high levels of platelet inhibition or hyperresponders are associated with greater risk of bleeding, (15) which might explain the results of the TRITON-TIMI 38 (12) clinical trial. Therefore, the ideal situation would be to keep our patients below the threshold HRPR level to prevent thrombotic events but also above the lower limit to avoid bleeding events. This concept, which has been defined as "therapeutic window" of the levels of platelet inhibition associating less thrombotic and bleeding events, is currently under investigation. (16, 17)

MONITORING ANTIAGGREGATION THERAPY: A MYTH OR (CLOSE TO) REALITY?

The levels of platelet reactivity, particularly those measured by the VerifyNow-P2Y12 system have been associated with recurrent events in observational studies. Yet, the attempts to confirm this association have failed in randomized clinical trials using different dose regimes. (15) In the Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy with Prasugrel(TRIGGER-PCI) trial, (18) stable coronary artery disease patients with HRPR (>208 P2Y12 reaction units [PRU] by the VerifyNow test) after elective PCI with at least 1 drug-eluting stent were randomly assigned to either prasugrel 10 mg daily or clopidogrel 75 mg daily. Despite the reduction in the levels of platelet reactivity achieved in patients of the prasugrel arm (94.%) vs. those in the clopidogrel arm, reaching values of HRPR below the levels defined, the study was stopped prematurely for futility of this therapeutic strategy because of a lower than expected incidence of the primary endpoint.

The use of platelet function tests for personalized antiplatelet treatment should not be recommended in all cases until the results of new ongoing clinical trials, as the Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy (ARCTIC) trial (19) are published. (20) Anyway, the better definition of the cutoff point or of the group of more appropriate patients for such measures are some of the numerous limitations which may explain the negative results previously obtained. (15) The proper identification of patients seems to be important, as most clinical trials recruited almost all low-risk patients, while observational studies included patients with a wide range of risk. Interestingly, a meta-analysis recently published included randomized trials that reported the clinical impact of using an intensified antiplatelet protocol (repeated loading or elevated maintenance doses, or adding other more potent antiplatelet agents, as prasugrel or glycoprotein IIb/IIIa inhibitor) on the basis of platelet reactivity testing (including the VerifyNow-P2Y12 system), compared to standard-dose clopidogrel. The study suggested that intensifying antiplatelet therapy reduces cardiovascular mortality and stent thrombosis, depending on the baseline risk during standard-dose clopidogrel. (21) Although the results of using personalized antiplatelet treatment with more potent agents are still not promising, the ongoing clinical trials might help to define better cutoff values to define thrombotic and bleeding risks. This might contribute to a better design of the "therapeutic windows" based on patients' risks and clinical scenarios, offering a better balance between efficacy and safety for the variety of antiplatelet agents currently available.

In conclusion, prasugrel is a third-generation thienopyridine that presents a more potent and predictable phamacodynamic profile compared to clopidogrel, which is produced by a more favorable pharmacokinetic profile, as it is a pro-drug that is activated in a more efficient fashion. All these properties produce better clinical efficacy; therefore, prasugrel may be recommended as first-line therapy for the treatment of ACS. However, personalized antiplatelet treatment with prasugrel or other antiaggregant agent based on platelet function tests is not recommended in all patients. Further studies are required to define the adequate scenarios in which these measures could be applied.

Conflicts of interest
None declared

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