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EDITORIAL COMMENT

Prasugrel in Clopidogrel Nonresponders

A Way to Improve Secondary Prevention in Patients After Percutaneous Coronary Intervention?*

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Current European Society of Cardiology guidelines recommend prasugrel or ticagrelor over clopidogrel in patients with acute coronary syndromes (ACS) after percutaneous intervention (PCI) (1). Despite this clear recommendation, a significant percentage of patients do not benefit from more effective $P2Y_{12}$ inhibition because many patients receive clopidogrel as first-line therapy, frequently pre-hospital, without further attempt to switch to the more effective agents (2). Reasons for this situation include potential warnings against prasugrel, for example, higher age (>75 years) and/or low body weight (<69 kg). Another reason is the fear of inducing more bleeding complications when a switch from full-dose clopidogrel to full-dose prasugrel or ticagrelor is performed.

SEE PAGE 1563

In this issue of *JACC: Cardiovascular Interventions*, Valenti et al. (3) report a significant reduction of long-term cardiovascular mortality and stent thrombosis in all-comers undergoing PCI (42% ACS patients) as compared with a historical patient cohort of clopidogrel nonresponders (100% ACS patients), when clopidogrel treatment was switched to prasugrel in nonresponders to clopidogrel based on platelet function testing (PFT) by use of light transmission aggregometry (LTA) (RECLOSE-3 [REsponsiveness to CLOpidogrel and StEnt Thrombosis] trial).

CLOPIDOGREL RESPONSE VARIABILITY

A reduced action of clopidogrel, leading to high on-treatment platelet reactivity (HTPR), has been described in up to 30% of patients and is due to clinical factors including poor absorption, drug-drug interactions, ACS, diabetes mellitus, and chronic kidney disease; genetic factors (certain CYP polymorphisms); and cellular factors such as accelerated platelet turnover, reduced CYP3A4 metabolic activity, or up-regulation of $P2Y_{12}$ pathway, respectively (4).

HIGH OR LOW ON-TREATMENT PLATELET REACTIVITY MAY CAUSE ISCHEMIC OR BLEEDING EVENTS

As extensively analyzed and reported in the past, HTPR on dual antiplatelet therapy with aspirin and clopidogrel is usually related to an increase in stent thrombosis and other ischemic events, whereas a low on-treatment platelet reactivity reflects hyperresponsiveness to clopidogrel and may be related to bleeding hazards (5).

FREQUENCY, SAFETY, AND EFFICACY OF A SWITCHING STRATEGY

A recent analysis from the U.S. national data registry revealed that only up to 7% of patients on clopidogrel were switched to prasugrel, which is far below the expected rate of low- or nonresponders to clopidogrel (6).

In an observational, nonrandomized study of ST-segment elevation myocardial infarction patients, the administration of a loading dose of prasugrel in patients pre-treated with a loading dose of clopidogrel was not associated with an excess of major bleeding events (7). In a meta-analysis of 12 studies involving 3,956 patients, 35.3% received prasugrel after clopidogrel treatment. Mortality and other secondary

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efficacy endpoints were numerically, but nonstatistically, lower in those patients, and major bleedings were similar, compared with standard therapy (8).

PERSONALIZED ANTIPLATELET STRATEGIES AND CLINICAL OUTCOME?

Three large-scale randomized clinical trials in this field have failed to demonstrate any benefit of tailored antiplatelet therapy (9–11). In the GRAVITAS (Gauging Responsiveness with A VerifyNow Assay–Impact on Thrombosis And Safety) trial, standard- versus high-dose clopidogrel was investigated based on PFT after PCI without clinical benefit for increasing the dosage (9). The ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting) trial showed no significant improvements in clinical outcomes with PFT and treatment adjustment for coronary stenting (additional bolus of clopidogrel, prasugrel, or aspirin along with glycoprotein IIb/IIIa inhibitors during the procedure), as compared with standard antiplatelet therapy without monitoring (10). Finally, in the TRIGGER (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) trial, switching from clopidogrel to prasugrel in patients with HTPR led to effective platelet inhibition, but given the low rate of adverse ischemic events after PCI in stable coronary artery disease, the clinical utility of this strategy could not be demonstrated (11). It was discussed that similar clinical outcome data between clopidogrel standard dose versus clopidogrel increased dose or versus prasugrel was mainly due to the majority of low-risk stable patients in these trials.

By contrast, it could be shown in the ISAR-HPR (ISAR-High Platelet Reactivity) registry that reloading with clopidogrel or use of prasugrel exhibited a statistical benefit in 30-day all-cause mortality or stent thrombosis, whereas bleeding was nonsignificantly increased (12). Accordingly, it seems essential to switch ACS patients with HTPR undergoing PCI on clopidogrel to more effective agents. The study design of the RECLOSE-3 study, despite having almost 50% ACS patients versus 100% in the historical control, has taken advantage of this knowledge (3).

ARE THE AVAILABLE TEST SYSTEMS USEFUL FOR A PERSONALIZED ANTIPLATELET STRATEGY?

Investigating PFT after switching from clopidogrel to prasugrel has shown a significant improvement of platelet function inhibition (13). There is still discussion about the most reliable platelet function assay for clinical routine. In patients with ACS undergoing PCI, significant correlations exist between LTA, VerifyNow, and VASP tests. Also, the multiple electrode platelet aggregometry test, which is easy to perform and inexpensive, gives comparable results with other tests (4). LTA for clinical routine seems less practicable because it requires a high degree of expertise, misses a clear standardization, and does not provide a generally accepted cutoff to determine HTPR patients, which makes results between laboratories hardly comparable (4).

CONCLUSIONS

It is essential to follow international guidelines in ACS patients undergoing PCI, that is, either to use the more effective $P2Y_{12}$ inhibitors prasugrel or ticagrelor as first-line therapy, or to use clopidogrel first, perform PFT, and switch from clopidogrel to prasugrel (or ticagrelor) in case of HTPR. Such switching strategy has so far not been successful in low-risk patients, that is, in stable coronary artery disease and planned PCI. Well-standardized platelet function assays might offer an ideal tool for personalized antiplatelet therapy. These assays might also help to disclose the low percentage (up to 6%) of nonresponders to prasugrel (14) and might help to reach the optimal therapeutic range, covering efficacy and safety, because personalized antiplatelet therapy was even superior to a strategy with empiric ticagrelor (15). Whether personalized antiplatelet therapy based on PFT will influence routine mechanisms in the near future is a topic of current investigation in the prospective, randomized TROPICAL ACS trial (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes Trial; NCT01959451).

Whether all these efforts to optimize antiplatelet therapy with $P2Y_{12}$ inhibitors are sufficient is still a matter of debate because the pathology of thrombosis is a complex interplay between cellular (i.e., platelets) and plasma components (i.e., coagulation factors), as for example thrombin, which is one of the strongest stimuli for platelet activation and not inhibited by $P2Y_{12}$ antagonists.

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