JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 16, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.06.051

EDITORIAL COMMENT

# Platelet Reactivity

## Back to the Future?*

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Although the use of drug-eluting stents (DES) has significantly reduced the rates of ischemic events in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI), stent thrombosis (ST) remains an uncommon but life-threatening complication, warranting dual antiplatelet therapy (DAPT) for a prolonged time (1). However, several important questions regarding DAPT remain incompletely answered and continue to be debated. First, the interest of platelet function testing to stratify patients who may benefit from a more potent antiplatelet strategy after PCI has become controversial. It was highly disputed following the neutral results of large interventional trials based on platelet function monitoring (PFM) (2–4). Second, the optimal duration of DAPT to prevent ischemic complications while limiting bleeding remains uncertain. Indeed, attention has been increasingly focused on the bleeding risk, which is estimated to be at least equivalent to the ischemic risk. Moreover, the excess in ST and myocardial infarction risk observed after DAPT discontinuation with first-generation DES is not applicable to second-generation DES, which is more effective and safe. Indeed, results of recent randomized clinical trials comparing shorter with 12-month DAPT duration in stable patients suggest that a 3- or 6-month DAPT duration may be sufficient and safer with new generations of DES (5).

In this issue of *JACC: Cardiovascular Intervention*, Stuckey et al. (6) provide valuable insights contributing to these questions. ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) was a large prospective multicenter registry aiming to determine if platelet function testing to evaluate aspirin and clopidogrel biological efficacy independently predicts long-term ischemic and bleeding complications in patients after successful PCI with DES. Of note, in the current era of more potent $P2Y_{12}$ receptor antagonists, almost all ADAPT-DES patients received clopidogrel, which still remains a widely used and cheaper option.

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Results of the ADAPT-DES were previously published (7), but Stuckey et al. (6) aimed to report the ADAPT-DES 2-year outcomes in 8,583 patients treated with DAPT for at least 1 year, extending their earlier findings. In the entire study population, 42.7% of patients (n = 3,609) had an on-clopidogrel high platelet reactivity (HPR) (defined as a platelet reactivity >208 platelet reactivity unit assessed by the VerifyNow $P2Y_{12}$ test), which was significantly associated with a higher risk of definite or probable ST (adjusted hazard ratio: 1.87; 95% confidence interval: 1.18 to 2.96; p = 0.007) and myocardial infarction (adjusted hazard ratio: 1.33; 95% confidence interval: 1.06 to 1.66; p = 0.004), but with a significantly decreased risk of clinically relevant bleeding (adjusted hazard ratio: 0.79; 95% confidence interval: 0.67 to 0.93; p = 0.005). Interestingly, between years 1 and 2, during which the rates of events were notably low, these associations were not significant. Conversely, HPR to aspirin was not associated with any of the major outcomes, demonstrating the lack of predictive value of aspirin testing after DES implantation.

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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Although the small number of patients presenting HPR to aspirin (n = 478; 5.6% of patients) is a potential limit, previous trials drew similar results.

The finding that on clopidogrel HPR is an independent risk factor for ischemic complications after PCI is far from being new. Indeed, it has been clearly established for more than 10 years that about 30% to 40% of patients treated with clopidogrel had HPR. Persistence of activated platelets under clopidogrel was constantly found to be associated with early ST and ischemic complications in numerous studies, leading to an international consensus that on clopidogrel HPR was a major risk factor for post-PCI ischemic events (8). These studies mainly focus on the early outcome because most ST occurs during the first month following PCI. Data pertaining to long-term risks associated with HPR remained scarce, particularly in high-risk patients and in the setting of new-generation DES. To date, ADAPT-DES is the largest study to address this question with a strong methodology. The 2-year follow-up results strongly reaffirm the Gurbel platelet hypothesis (9), which early supported the rationale for a personalized antiplatelet therapy. Whereas first small studies using PFM to tailor antiplatelet therapy provided promising results (10,11), the GRAVITAS (Gauging Responsiveness with a VerifyNow $P2Y_{12}$ assay: Impact on Thrombosis and Safety) (2), ARCTIC (The 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) (6), and ANTARTIC (Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome) (4) trials failed to demonstrate the benefit of a PFM approach, questioning the interest of such a strategy. Interestingly, and in agreement with the current results of ADAPT-DES, which was conducted in high-risk patients with coronary artery disease, a recent meta-analysis (12) clearly demonstrated that the contribution of platelet reactivity testing for the prediction of ischemic complications was greater in high-risk patients suggesting that the usefulness of PFM depends on the patient profile and level of cardiovascular factors. Finally, 1 single test during the acute phase may not be optimal to predict events beyond 1 year because PR varies over time.

Recently, landmark DAPT registries and randomized trials have identified patients who may benefit from extended DAPT duration (13–15). In ADAPT-DES, decisions regarding DAPT continuation after 1 year were at the discretion of the physician and common, but interestingly, patients who remained on DAPT until 2 years corresponded to higher risk patients with low rates of ST (0.3%) and of clinically relevant bleeding (1.3%) between years 1 and 2, confirming the interest for a personalized rather than a "1 size fit all" approach. Of interest, the lack of association between PR and outcome is not in favor of usefulness of platelet function testing to optimize patients' selection for extended DAPT.

Over the past decade, great progress has been made to improve DAPT choice and duration following PCI; however, the optimal proven strategy is still debated. Considering the strong relationship between HPR and outcomes observed in ADAPT-DES, the negative results of the GRAVITAS (2), ARCTIC (6), and ANTARTIC (4) trials do not provide sufficient evidence to definitively refute the usefulness of PFM in patients under clopidogrel because of their design. Expected results of the ongoing prospective, randomized, parallel-group, open-label TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes) trial (NCT01959451) may help to solve this issue.

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**KEY WORDS** bleeding, $P2Y_{12}$ ADP receptor, percutaneous coronary intervention, thrombosis