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EDITORIAL COMMENT

Does Platelet Reactivity Testing Predict Post-Operative Bleeding Risk?*

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Patients with acute coronary syndromes (ACS) treated with $P2Y_{12}$ platelet blockers may experience increased bleeding after coronary artery bypass graft (CABG) surgery (1). Clinical guidelines contain a Class IIb recommendation ("may be considered") to test platelet reactivity in patients exposed to $P2Y_{12}$ platelet blockers who are awaiting CABG (2), but evidence for the recommendation is mixed. Although some observational studies have reported a relation between platelet-reactivity testing (PRT) and post-operative bleeding (3,4), others have found no relation (5).

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In this issue of the *Journal*, Nakashima et al. (6) studied the value of using PRT to shorten the waiting time for CABG in 190 patients who had taken clopidogrel for an ACS. The investigators randomized patients to early CABG, scheduled the next workday after normalization of platelet reactivity measured with the Multiplate analyzer (Roche Diagnostics GmbH, Vienna, Austria) or to delayed CABG 5 to 7 days after drug discontinuation. The median waiting period for CABG was 1 day less in the early group than in the delayed group, which corresponded to a 6% decrease in hospital expenses. There was no difference in the 1° endpoint of chest-tube drainage within 24 h of CABG (350 ml vs. 350 ml, p noninferiority < 0.001).

The strengths of the study (6) include its randomized design and use of the Multiplate analyzer. Although no platelet test has been shown categorically to predict bleeding (7), a test such as the Multiplate analyzer, which uses whole blood, has theoretical advantages over a test such as VerifyNow (Accumetrics, Depew, New York) $P2Y_{12}$, which uses citrate to bind Ca^{++} and thus inactivates the central pathway in hemostasis dependent on thrombin (7). But how well do the results of PRT predict bleeding or ischemic events?

The POPular (Do Point-of-Care Platelet Function Assays Predict Clinical Outcomes in Clopidogrel Pretreated Patients Undergoing Elective Percutaneous Coronary Intervention) study assessed outcomes in 1,096 patients using 5 different tests (8). Only VerifyNow and light transmittance aggregometry could predict ischemic events. With areas under the curve (AUC) of 0.62, sensitivities of 60%, and specificities of 63%, both tests fell into the category of poor discrimination (9). None of the 5 tests could predict bleeding complications (8).

The findings of POPular were confirmed by other studies (10), which also found that no test could distinguish between patients who had or had not received clopidogrel. Identifying better cutpoints might improve the discriminatory ability of PRT. However, when the diagnostic threshold for VerifyNow was dropped to 208 (11,12) from 230 (13) or 235 (14), using PRT as a guide for escalating treatment from standard-dose clopidogrel in nonresponders to a more potent regimen failed to confer clinical benefit in every randomized trial (11-14).

To refine PRT as a predictor of bleeding, several experts have recommended using a therapeutic window, defined by a high value for platelet reactivity (HPR) that predicts ischemic events and a low value for platelet reactivity (LPR) that predicts bleeding. A consensus statement (15) proposed optimal cutoffs

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for the Multiplate analyzer (HPR 46, LPR 18) and VerifyNow (HPR 208, LPR 85), but a study (16) using a cutpoint of 46 on the Multiplate analyzer to predict post-operative bleeding after CABG reported an AUC of 0.56, sensitivity of 76%, and specificity of 46%, all of which fall into the category of discrimination that is "not much better than a coin toss" (9). In the current study (6), the investigators followed standard practice and used an HPR of 46 in place of LPR as the guide for the timing of CABG.

Clinical investigation is difficult. Otherwise, everyone would do it. Nakashima et al. (6) should be commended for an exceptional investigation of PRT in patients awaiting CABG. The trial confirms previous observational studies (4) and affirms what is commonly done in practice, but like most good research, raises more questions than it answers. Would the waiting time for CABG be shorter if decisions were based on LPR rather than HPR? Did resizing the trial and the interim analyses ensure noninferiority? How many patients undergoing daily PRT have persistently elevated values on day 5 that would delay CABG? Could "highly experienced surgeons" have achieved the same outcomes without using PRT guidance? Is the surgical and monitoring expertise in this single-center study translatable to other centers?

Nakashima et al. (6) have completed an excellent study, but it was based on the tenuous premise that PRT predicts post-operative bleeding. Bleeding after CABG is caused by many factors including time on cardiopulmonary bypass, surgical technique, patient age, diabetes, body mass index, nutritional status, vascular integrity, anemia, thrombocytopenia, ejection fraction, creatinine clearance, plasma fibrinogen, occurrence of atrial fibrillation, use of anticoagulants, and the balance between platelet activation and inhibition.

The main pathways for platelet activation include adenosine diphosphate, arachidonic acid, von Willebrand factor, protease-activated receptor-1, thrombin, and surface glycoproteins Ib and IIb/IIIa, all of which have complex interactions (7). It is unlikely that a single test of a pathway of platelet activation blocked by 1 drug could predict systemic bleeding risk or even overall platelet reactivity. PRT is based on solid science but only weakly predicts outcomes in selected populations and has failed to predict events on an individual level (7). Confidence in PRT is further compromised by using different cutoffs in different studies (11–14), which suggests that PRT remains a moving target more suitable for research than for routine clinical use. Given its limitations, writing committees will not likely give PRT a higher recommendation than Class IIb for predicting bleeding.

The current study (6) affirms that using PRT to shorten the waiting time for CABG is a plausible approach, but PRT is too inaccurate to be the linchpin for deciding when to proceed with surgery. An alternative approach in nonemergency situations is to omit PRT and wait 3 days after stopping ticagrelor (1,17), 5 days after stopping clopidogrel (17), or 7 days after stopping prasugrel (17) before proceeding with CABG. Of course, avoiding pretreatment with $P2Y_{12}$ platelet blockers until viewing the coronary anatomy eliminates the need for waiting altogether (17).

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