Current Role of Platelet Function Testing in Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting

Lisa Gross, MD[a],
Dirk Sibbing, MD, MHBA, FESC[a,b,*]

KEYWORDS

• Platelet function testing • Platelet reactivity • PCI • Risk prediction
• Tailored antiplatelet therapy • Guidance of treatment • CABG • Transfusion algorithm

KEY POINTS

- There is substantial evidence for the value of $P2Y_{12}$ receptor-directed platelet function testing for the prediction of thrombotic events in patients having undergone percutaneous coronary interventions.
- There seems to be an "optimal" level of platelet reactivity during treatment with $P2Y_{12}$ inhibitors within which both thrombotic and bleeding complications are the lowest.
- The society of thoracic surgeons guidelines and the 2014 ESC/EACTS guidelines on myocardial revascularization provide a class IIa recommendation for the use of platelet function testing to time surgical procedures.

INTRODUCTION

Guidelines provide a class IA recommendation for the use of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention (PCI).[1] However, multiple studies, mostly focusing on $P2Y_{12}$-receptor directed treatment, have shown that there is great inter-individual variability in the pharmacodynamic response to standard doses of antiplatelet medications.[2–6] Several studies have demonstrated a strong association between high on-treatment platelet reactivity (HPR) on clopidogrel therapy, reflecting a failure to achieve adequate platelet inhibition, and post-PCI ischemic events, such as stent thrombosis, myocardial infarction, or cardiovascular death.[2,4,7,8] Recently, evidence has also emerged supporting the association between low on-treatment platelet reactivity (LPR) and bleeding events.[8,9]

This review presents the current evidence regarding platelet function testing in patients undergoing PCI and coronary artery bypass grafting (CABG). The possible role of platelet function testing for individualized antiplatelet treatment regimens in high-risk PCI patients and for guidance of surgical timing and transfusion management algorithms in CABG patients will also be highlighted.

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[a] Department of Cardiology, Ludwig-Maximilians-Universität München (LMU Munich), Marchioninistr. 15, Munich 81377, Germany; [b] DZHK (German Center for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany
* Corresponding author. Department of Cardiology, Ludwig-Maximilians-University, Marchioninistr. 15, Munich 81377, Germany.
E-mail address: dirk.sibbing@med.uni-muenchen.de

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METHODS FOR PLATELET FUNCTION TESTING

There are numerous assays available for the assessment of the antiplatelet effect of $P2Y_{12}$ receptor blockers. There are pharmacodynamic assays measuring in vitro platelet reactivity that use different techniques, for example, platelet aggregometry (light transmission, impedance), flow cytometry, thromboelastography, or shear-dependent aggregation. Among the available methods, near-patient assays like the VerifyNow or the Multiplate analyzer are rapid, easy to perform, standardized, and highly reproducible. Table 1 summarizes the characteristics of the most commonly used platelet function testing assays in patients undergoing PCI and CABG as well as their key advantages and disadvantages. A detailed description on assessment methodology is beyond the scope of this review and is summarized elsewhere.[8,10]

PLATELET FUNCTION TESTING FOR PREDICTION OF ADVERSE EVENTS AFTER PERCUTANEOUS CORONARY INTERVENTION

There are numerous large prospective studies that provide significant evidence for the prognostic value of $P2Y_{12}$ receptor-directed platelet function testing for risk prediction of ischemic events after PCI (Table 2).[7,11–24] HPR as a marker of inadequate platelet inhibition by clopidogrel has been shown to be an independent and strong predictor of ischemic events after PCI (see Table 2).[9,12,15,20,25,26] A large and independent metaanalysis of 17 studies including overall more than 20,000 patients confirmed that thienopyridine-treated patients with HPR have a 2.7-fold higher risk for stent thrombosis (relative risk [RR], 2.73; 95% confidence interval [CI], 2.03–3.69; $P<.00001$) and a 1.5-fold higher risk for overall mortality ($P<.05$) compared with those with optimal platelet reactivity (OPR) after PCI.[9] Importantly, consensus cutoff values[8,27] for standardized platelet function tests (VerifyNow, Multiplate, vasodilator-stimulated phosphoprotein phosphorylation) have been established to allow for risk stratification regarding ischemic events[8] (Fig. 1). Small observational studies suggest that HPR is largely, but not completely, eliminated by the new $P2Y_{12}$ inhibitors prasugrel and ticagrelor compared with clopidogrel,[28–30] suggesting a less pronounced clinical importance for platelet function testing to identify HPR in patients treated with novel potent antiplatelet agents.

Although the relationship between platelet reactivity and ischemic events has been well-established, the link between platelet reactivity and bleeding events has emerged more recently. Several observational studies provide support for the existence of an association between enhanced platelet reactivity and bleeding risk (see Table 2).[12,15,29,31–38] The metaanalysis including 20,839 patients mentioned confirmed that patients with LPR have a significantly higher risk of bleeding in contrast with those with OPR (RR, 1.74; 95% CI, 1.47–2.06; $P<.00001$).[9] This relative risk increase translates into an absolute increase in major bleeding events of 2.6% in the LPR group (Fig. 2), suggesting that platelet function testing can identify patients at high risk of significant bleeding. Uniform cutoff values for LPR for risk stratification of significant bleeding events have been defined for the standardized platelet function assays[8] (see Fig. 1).

THERAPEUTIC WINDOW FOR PLATELET REACTIVITY AFTER PERCUTANEOUS CORONARY INTERVENTION

Because bleeding events after PCI are associated with worse outcomes, in the era of new and more potent antiplatelet medications, there is heightened importance to achieve maximum ischemic benefit while avoiding excessive bleeding. In this regard, evidence is accumulating that an OPR flanked by LPR and HPR cutoffs does indeed exist, within which the rates of both thrombotic and bleeding complications are the lowest.[3,14,17,18,29,39] Such a therapeutic window was first identified in an observational study including 2533 clopidogrel-treated patients undergoing PCI.[3] The metaanalysis introduced and summarizing all relevant studies in this field of research confirmed the existence of a therapeutic window and an OPR range for $P2Y_{12}$ treatment.[9] For this analysis, consensus-defined, uniform cutoff values for standardized platelet function assays were applied. LPR–OPR–HPR categories were defined as less than 95, 95 to 208, and greater than 208 P2Y12 reaction units for VerifyNow, less than 19, 19 to 46, greater than 46 units for the Multiplate analyzer (ADPtest), and less than 16, 16 to 50, and greater than 50% for vasodilator-stimulated phosphoprotein phosphorylation assay (see Fig. 1). When platelet reactivity levels were grouped only as low or high, the results suggested that a significant reduction in stent thrombosis in the non-HPR group could only be achieved at the price of a large increase in bleeding, and vice versa. However, when an