Platelet Reactivity Is Preferred Over Genotyping in Monitoring Efficacy of Antiplatelet Therapy

We read with great interest the report by Viviani Anselmi et al. (1) on the predictability of platelet reactivity as compared with gene polymorphism in patients undergoing elective percutaneous coronary intervention (PCI). The authors conclude that CYP2C19 metabolizer status independently predicts major adverse cardiac events, whereas platelet reactivity is only an independent predictor in high-risk patients.

Notwithstanding the well-performed and large study (1), we are puzzled by these results. Because the underlying hypothesis of the present study is that an inferior response to thienopyridines is associated with (recurrent) ischemic events, the question is whether genotyping or phenotyping is preferred in identifying patients at risk. Phenotyping (platelet reactivity as assessed by the VerifyNow cartridge [Accumetrics, San Diego, California]) has been explored in a large number of observational studies as well as in the pharmacodynamics analyses of several randomized clinical trials. In contrast to the findings of the present study, the bulk of these data support the supposition that among patients undergoing PCI treated with clopidogrel or prasugrel, higher values of platelet reactivity units are associated with ischemic events (2,3). In addition, platelet reactivity as assessed by the VerifyNow test is correlated with the active metabolite of clopidogrel (4). Furthermore, in the POPular (Do Platelet Function Assays Predict Clinical Outcomes in clopidogrel pretreated patients undergoing elective PCI) (the POPular Study) (2), a significant correlation between (high) on-treatment platelet reactivity and CYP2C19 metabolizer status has been established (5). This is in line with a large meta-analysis on CYP2C19 genotyping and outcome in clopidogrel-treated patients, which demonstrated an association between CYP2C19 genotype and on-treatment platelet reactivity but lacked proof of a significant association of genotype with cardiovascular events (6). An argument in favor of genotyping is that it is stable over time, whereas platelet reactivity is not, because it is influenced by multiple clinical determinants as well as laboratory parameters and comedication (7). As a result of variable baseline platelet reactivity, a response that is stable over time and equal among individuals can result in a broad range of on-treatment platelet reactivity levels (8). Therefore, we consider monitoring platelet reactivity a more appropriate approach of monitoring antiplatelet therapy.

The results of the current study point precisely in the opposite direction, and we are curious how the authors explain these differences and what their findings imply for daily clinical practice.

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Reply

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We thank Drs. Breet and ten Berg for their interest in our paper (1). When we designed our study, we aimed to confirm and expand previous observations demonstrating the clinical usefulness of clopidogrel-pathway genotyping and on-treatment platelet residual (OTR) testing in predicting major adverse cardiac events (MACE) in patients with stable coronary artery disease (CAD) receiving drug-eluting stents (DES) and under dual antiplatelet (clopidogrel plus aspirin) therapy. Our results confirmed that CYP2C19 metabolizer status is an independent predictor of MACE after DES implantation and can be used for prognostication in all stable CAD patients. In contrast, high OTR, as assessed with the
VerifyNow P2Y\textsubscript{12} test (Accumetrics, San Diego, California), has a clinically relevant role only in high-risk subsets (i.e., patients with diabetes mellitus [DM] or chronic kidney disease [CKD]). We would like to stress the following issues:

1. The majority of previous positive studies included patients with acute coronary syndromes, whereas our target population included only patients with stable CAD. When dealing with stable CAD patients, with an expected overall low MACE rate, the assessment of OTR is unlikely to have any prognostic value due to modest sensitivity and specificity. On the contrary, when dealing with a high-risk population (including stable patients with DM and/or CKD and patients with acute coronary syndrome), OTR assessment may have a relevant clinical benefit (2–6). This may explain why, for example, in the ADAPT-DES (Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents) trial, the OTR (assessed with the VerifyNow P2Y\textsubscript{12} test) was a strong independent predictor of stent thrombosis at 30 days only in patients with acute coronary syndromes, but not in patients with stable CAD (7). This result has been also confirmed by Park et al. (8).

2. The POPULAR (Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective PCI) trial demonstrated a modest accuracy of 4 platelet reactivity tests (including the VerifyNow P2Y\textsubscript{12} Test) in predicting clinical outcome (9). Possible explanations for the discrepancy between our study and the POPULAR trial are: differences in the risk at baseline of the patient populations (as suggested by the different rates of DM, CKD, and bifurcation lesions) and differences in the type of stent implanted in the 2 studies. Indeed, in our study, the extensive use of second-generation DES may have had a relevant role in reducing the MACE rate at follow-up (10).

3. Finally, our interpretation may also explain the negative findings of some recent trials aiming at demonstrating a clinically-relevant effect of antiplatelet therapy tailored to the OTR result: neither the strategy of increasing clopidogrel maintenance dose (GRAVITAS [Gauging Responsiveness With A VerifyNow Assay—Impact On Thrombosis And Safety]) nor of switching to prasugrel (Trigger PCI and 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]) improved the clinical outcome of patients with high OTR.

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