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LETTERS TO THE EDITOR

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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REFERENCES

1. Viviani Anselmi C, Briguori C, Roncarati R, et al. Routine assessment of on-clopidogrel platelet reactivity and gene polymorphisms in predicting clinical outcome following drug-eluting stent implantation in patients with stable coronary artery disease. J Am Coll Cardiol Intv 2013;6:1166–75.
2. Breet NJ, van Werkum JW, Bouman HJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 2010;303:754–62.
3. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261–73.
4. Bouman HJ, Parlak E, van Werkum JW, et al. Which platelet function test is suitable to monitor clopidogrel responsiveness? A pharmacokinetic analysis on the active metabolite of clopidogrel. J Thromb Haemost 2010;8:482–8.
5. Bouman HJ, Harmsze AM, van Werkum JW, et al. Variability in on-clopidogrel platelet reactivity explained by CYP2C19*2 genotype is modest in patients undergoing coronary stenting. Heart 2011;97:1239–44.
6. Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA 2011;306:2704–14.
7. Elsenberg EH, van Werkum JW, van de Wal RM, et al. The influence of clinical characteristics, laboratory and inflammatory markers on 'high on-treatment platelet reactivity' as measured with different platelet function tests. Thromb Haemost 2009;102:719–27.
8. Samara WM, Bliden KP, Tantry US, Gurbel PA. The difference between clopidogrel responsiveness and posttreatment platelet reactivity. Thromb Res 2005;115:89–94.

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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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]) or 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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REFERENCES

1. Viviani Anselmi C, Briguori C, Roncarati R. Routine assessment of on clopidogrel platelet reactivity and gene polymorphisms in predicting clinical outcome following drug-eluting stent implantation in patients with stable coronary artery disease. J Am Coll Cardiol Intv 2013;6:1166–75.
2. Machecourt J, Danchin N, Lablanche JM, et al. Risk factors for stent thrombosis after implantation of sirolimus-eluting stents in diabetic and nondiabetic patients: the EVASTENT Matched-Cohort Registry. J Am Coll Cardiol 2007;50:501–8.
3. Latif F, Kleiman NS, Cohen DJ, et al. In-hospital and 1-year outcomes among percutaneous coronary intervention patients with chronic kidney disease in the era of drug-eluting stents: a report from the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry. J Am Coll Cardiol Intv 2009;2:37–45.
4. Angiolillo DJ, Bernardo E, Ramirez C, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. J Am Coll Cardiol 2006;48:298–304.
5. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. Diabetes 2005;54:2430–5.
6. Best PJ, Steinhubl SR, Berger PB, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Am Heart J 2008;155:687–93.
7. Stone GW, Stone GW, Witzenbichler B, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet 2013;382:614–23.
8. Park DW, Ahn JM, Song HG, et al. Differential prognostic impact of high on-treatment platelet reactivity among patients with acute coronary syndromes versus stable coronary artery disease undergoing percutaneous coronary intervention. Am Heart J 2013;165:34–42.
9. Breet NJ, van Werkum JW, Bouman HJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 2010;303:754–62.
10. Sarno G, Lagerqvist B, Fröbert O, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J 2012;33:606–13.