JACC VOL. 68, NO. 1, 2016
JULY 5, 2016:128–34

Factors Affecting Platelet Reactivity and Cardiovascular Outcome in CAD Patients Treated With $P2Y_{12}$ Receptor Inhibitors

We read with interest the paper by Doll et al. (1) in a previous issue of the *Journal*. The observed differences in platelet reactivity, whether resulting from genetic variation, in clopidogrel-treated patients with acute coronary syndrome (ACS) did not appear to affect ischemic outcomes.

Although these findings are interesting, other factors involved in platelet reactivity and cardiovascular outcome were not completely evaluated. The individual platelet response to antiplatelet therapy depends on a network of mechanisms including genetic factors, cellular factors (accelerated platelet turnover, reduced CYP3A metabolic activity, increased adenosine diphosphate exposure, up-regulation of $P2Y_{12}$ pathways), clinical factors (age, diabetes, smoking, body mass index, left ventricular ejection function, inflammation, vascular function, elevated plasma fibrinogen, extent of coronary artery disease [CAD], number and complexity of CAD lesions, creatinine clearance, comorbidities, noncompliance, underdosing, poor absorption, concurrent medication), and environmental factors (geographic origin) (2–4). Coexisting polymorphisms may affect platelet response variability and clinical outcome more than single polymorphisms. The individual genomic profile should include not only CYP2C19 polymorphisms, but also all the polymorphic genes involved in the pharmacokinetic and pharmacodynamic response to $P2Y_{12}$ receptor inhibitors treatment.

Moreover, the data concerning the cardiovascular outcome in patients who carry 2 reduced-function alleles (CYP2C19*2/*2) are not presented; these patients are at great cardiovascular risk. A comparison among carriers of 2 reduced-function alleles (CYP2C19*2/*2), carriers of 1 reduced-function allele (CYP2C19*1/*2, heterozygotes), and noncarriers (CYP2C19*1/*1, wild-type homozygotes) would be of great importance. The data of the current study by Doll et al. (1) showed a trend toward a lower risk of events for extensive metabolizers that reached borderline statistical significance for myocardial infarction outcome after adjustment. Similarly, in a previous study in which we compared the carriers of at least 1 CYP2C19*2 loss-of-function allele (CYP2C19*1/*2 and CYP2C19*2/*2) with noncarriers (CYP2C19*1/*1), the incidence of high on treatment platelet reactivity and cardiovascular events reached borderline statistical significance (5). However, when we compared homozygotes for the default allele (CYP2C19*2/*2) with noncarriers (CYP2C19*1/*1), we found a significant association of genotype with platelet reactivity and cardiovascular events (5).

Previous studies showed a significant impact of platelet response variability and genotype on cardiovascular outcome in patients with CAD after percutaneous coronary intervention (2). Because most patients with ACS are currently managed invasively, future randomized clinical trials will be needed to investigate the prognostic role of platelet function testing and genotyping in both medically and invasively treated patients with ACS. The precise definition of multiple genetic, cellular, and clinical determinants influencing platelet reactivity will lead to an individualized and more effective adjustment of antiplatelet treatment in CAD and in reducing cardiovascular events.

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http://dx.doi.org/10.1016/j.jacc.2016.03.585

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Matthew Price, MD, served as Guest Editor for this paper.

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