Letter by Gurbel et al Regarding Article, “Cytochrome 2C19*17 Allelic Variant, Platelet Aggregation, Bleeding Events, and Stent Thrombosis in Clopidogrel-Treated Patients With Coronary Stent Placement”

To the Editor:

We read with interest the article by Sibbing et al on the activating CYP2C19*17 variant that unveils a more complicated picture of the CYP2C19 locus. The work by Sibbing et al complements investigations showing the opposite effect of the inactivating CYP2C19*2 variant, which accounts for 12% of clopidogrel response variability. The *2 and *17 variants, 19,959 base pairs apart and in linkage disequilibrium, are not independent of one another. Therefore, individuals heterozygous or homozygous for the *17 allele are less likely to carry the *2 allele, whereas those with 0 copies of the *17 allele (“wild type” at the *17 locus) are more likely to carry the *2 allele. It follows that greater clopidogrel response in *17 allele carriers can be partly or completely attributed to decreased *2 allele frequency. In our opinion, to dissect whether the *17 allele is a true effector of clopidogrel response independently of the *2 allele, the authors should have also genotyped for the *2 variant and performed a statistical adjustment for its effect in a regression-based analysis, and/or they should have performed an analysis of *17-*2 diplotype. A similar analysis suggested that the *2 variant could account for most or all of the association with clopidogrel response at the CYP2C19 locus. In addition, to better understand the mechanistic link implied by *17 carrier status, it would be of interest to determine whether platelet function tests were also associated with bleeding risk and whether the CYP2C19 genotype was a mediator of these effects (again through regression-based analysis). In our previous study, platelet function could fully account for the association between CYP2C19*2 genotype and cardiovascular events. Finally, the higher prevalence of active smokers in *17 homozygotes may have influenced platelet reactivity. Studies to open the previously proposed therapeutic window for thienopyridine therapy through genotype-guided antiplatelet regimens that may include tailoring clopidogrel dosing, selected use of newer reversible and irreversible P2Y12 inhibitors, and concomitant thrombin receptor blockade are on the horizon. The work by Sibbing et al is an important contribution in this area.

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Paul A. Gurbel, MD
Udaya S. Tantry, PhD
Sinai Center for Thrombosis Research
Baltimore, Md

Alan R. Shuldiner, MD
Division of Endocrinology, Diabetes, and Nutrition
Department of Medicine
University of Maryland School of Medicine
Baltimore, Md

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Paul A. Gurbel, Udaya S. Tantry and Alan R. Shuldiner

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