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.\(^2\) The \(\text{*2} \) and \(\text{*17} \) variants, 19,959 base pairs apart and in linkage disequilibrium, are not independent of one another. Therefore, individuals heterozygous or homozygous for the \(\text{*17} \) allele are less likely to carry the \(\text{*2} \) allele, whereas those with 0 copies of the \(\text{*17} \) allele (“wild type” at the \(\text{*17} \) locus) are more likely to carry the \(\text{*2} \) allele. It follows that greater clopidogrel response in \(\text{*17} \) allele carriers can be partly or completely attributed to decreased \(\text{*2} \) allele frequency. In our opinion, to dissect whether the \(\text{*17} \) allele is a true effector of clopidogrel response independently of the \(\text{*2} \) allele, the authors should have also genotyped for the \(\text{*2} \) variant and performed a statistical adjustment for its effect in a regression-based analysis, and/or they should have performed an analysis of \(\text{*17}-\text{*2} \) diplotypes. A similar analysis suggested that the \(\text{*2} \) variant could account for most or all of the association with clopidogrel response at the CYP2C19 locus.\(^2\) In addition, to better understand the mechanistic link implied by \(\text{*17} \) 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,\(^3\) platelet function could fully account for the association between CYP2C19*2 genotype and cardiovascular events. Finally, the higher prevalence of active smokers in \(\text{*17} \) homozygotes may have influenced platelet reactivity.\(^3\) 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.\(^3\) The work by Sibbing et al is an important contribution in this area.

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References


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"

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