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EDITORIAL COMMENT

CYP2C19 in ACS Patients

Could Genotyping Have a Role in Medically Managed Patients or Beyond?*

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A dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor such as clopidogrel or prasugrel or ticagrelor is the current mainstay of pharmacological treatment in acute coronary syndrome (ACS) patients managed either medically or invasively by percutaneous coronary intervention (PCI) (1). The primary goal of dual antiplatelet therapy is to reduce the risk of ischemic events, including (re)-infarction and of stent thrombosis after PCI. The $P2Y_{12}$ receptor inhibitors clopidogrel and prasugrel require in vivo bioactivation into their active metabolites by the hepatic cytochrome P450 (CYP) system. Prior studies demonstrated that a genetically determined variability in catalytic activity of the CYP system affects the conversion of clopidogrel into its active compound and thereby attenuates the pharmacodynamic action of the drug (2). A single-nucleotide polymorphism, the *CYP2C19* 681G>A *2 allelic variant (*2 denotes the mutant 681A allele and *1 denotes the wild-type 681G allele), encoding for a cryptic splice site resulting in complete loss of CYP2C19 enzyme activity is a key genetic determinant associated with reduced clopidogrel conversion (2). Notably though, this specific single-nucleotide polymorphism and also other CYP polymorphisms apparently have no influence on prasugrel bioactivation (3).

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In this issue of the *Journal*, Doll et al. (4) present the results of a pre-specified pharmacogenetic substudy from the TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial. The primary trial (N = 9,326) aimed at comparing clopidogrel versus prasugrel in ACS patients with a planned noninvasive management and demonstrated a similar outcome in both arms of the study (5). For the 5,736 patients included in this genetic substudy, the authors observed a strong association of CYP2C19 metabolizer status (reduced metabolizer [RM] vs. extensive metabolizer [EM]) with on-clopidogrel treatment platelet reactivity (Δ VerifyNow PRU for RM vs. EM patients: 39.93; 95% confidence interval [CI]: 30.00 to 49.87), whereas no association was found in the subgroup of prasugrel-treated patients (Δ PRU for RM vs. EM patients: 3.87; 95% CI: −6.57 to 14.31). However, the observed differences on the level of platelet reactivity did not translate into a significant impact of metabolizer status (EM vs. RM) on the primary composite endpoint of cardiovascular death, myocardial infarction or stroke in the entire study cohort (hazard ratio [HR]: 0.86, 95% CI: 0.74 to 1.02) or even in the subgroup of clopidogrel-treated patients (HR: 0.91, 95% CI: 0.73 to 1.14). On the basis of the pharmacodynamic results reported here (4) and in prior studies (2,6), at least for the clopidogrel subgroup, an influence of *CYP2C19* genotype on ischemic risk would have been expected.

Doll et al. (4) are to be commended for this important study and for providing novel data on the prognostic value of the *CYP2C19* genotype in an ACS population with preferred medical management.

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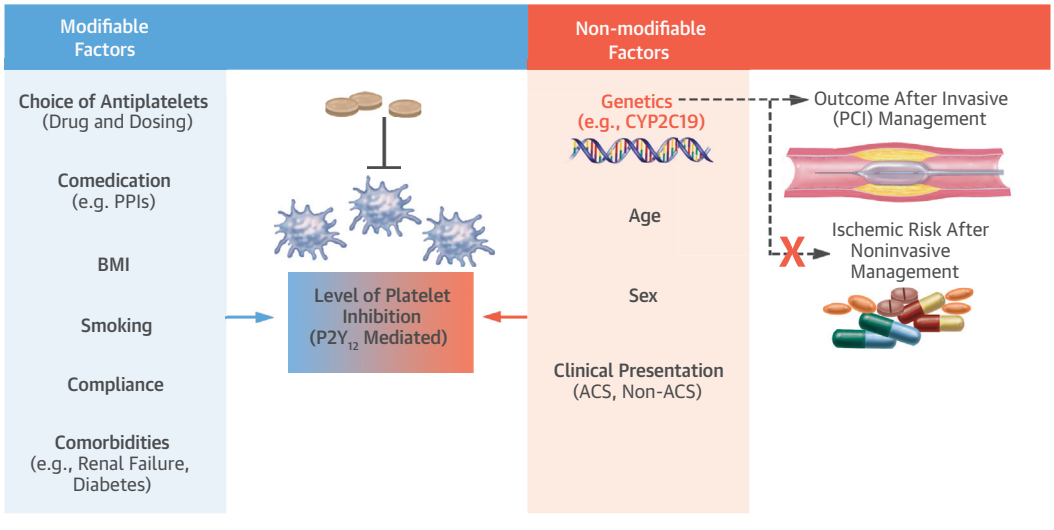
However, in interpreting the data, some issues and important aspects merit mentioning: In the context of published data (7,8) on genetics and outcomes of ACS patients, present results highlight and confirm the need for a separate assessment of the role of genotyping in invasively versus noninvasively managed patients. As outlined in **Figure 1**, a number of modifiable and nonmodifiable factors have an impact on the level of $P2Y_{12}$ receptor-mediated platelet inhibition. This is true for both invasively and noninvasively managed ACS patients. On-treatment platelet reactivity levels (phenotype) as well as genetic risk factors such as *CYP2C19*2* (genotype) have shown a strong and significant association with ischemic risk (especially stent thrombosis risk) in ACS patients undergoing PCI (6,7,9). However, an independent association for both phenotype and genotype could not be confirmed for medically managed patients in the TRILOGY-ACS platelet function (10) and genetic (4) substudies. In fact, it appears that the outcome of medically managed patients is largely driven by other factors, including age and comorbidities (11). In particular, the strong influence of age on outcome in a noninvasively managed ACS population, as it was highlighted in a post hoc analysis from the entire TRILOGY-ACS cohort (11), may mitigate or even eliminate any influence of genetics.

In 2010, the U.S. Food and Drug Administration announced a boxed warning on clopidogrel stating that the drug has a reduced effect in patients based on their *CYP2C19* genotype (12). This boxed warning highlighted the issue of clopidogrel bioactivation specifically for poor metabolizers, defined as subjects who carry 2 reduced-function alleles (*CYP2C19*2/*2*) (12). In this respect, the TRILOGY-ACS genetic substudy (4) included only a few patients with poor metabolizer status, and the authors did not report specifically on the outcome of clopidogrel-treated poor metabolizers. Thus, further investigations are needed here before definite conclusions can be drawn. We have learned from invasively managed patients in prior studies and meta-analyses that a gene-dose effect of the mutant *CYP2C19*2* allele exists (6,7). Homozygous mutant allele carriers (*CYP2C19*2/*2*) showed the strongest attenuation of platelet response to clopidogrel treatment (6), and based on the results of a large collaborative meta-analysis, exactly those patients had the highest risk of stent thrombosis (HR: 3.97; 95% CI: 1.75 to 9.02) after PCI (7).

Finally, the present results are limited by the circumstance that the authors report ischemic outcomes only. Particularly in a medically managed population that is prone to experience bleeding complications, it would be valuable information to see whether certain genetic variants in- and outside the *CYP2C19* system are associated with a higher bleeding risk in any of the study arms. Specifically, the *CYP2C19*17* allelic variant has been linked to

FIGURE 1 Factors Influencing the Level of Platelet Inhibition



Modifiable and nonmodifiable factors (including genetics) are illustrated in the figure. Genetic factors including *CYP2C19* genotype predict the outcome (ischemic and bleeding risk) after invasive management but not the ischemic risk after noninvasive management. ACS = acute coronary syndrome; BMI = body mass index; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor.

increased transcriptional activity, resulting in extensive metabolization of CYP2C19 substrates (such as clopidogrel) (13). In a study that included clopidogrel-treated patients undergoing PCI, *CYP2C19*17* carrier status was significantly associated with an enhanced response to clopidogrel and an increased risk of bleeding (14). The influence of *CYP2C19*17* and other gain-of-function genetic variants in medically managed ACS patients receiving $P2Y_{12}$ inhibitor treatment warrants further investigation.

Assessed against currently available information, data coming from the TRILOGY-ACS trial lends little support to a genotyping strategy for guidance of antiplatelet treatment in patients with preferred noninvasive management. However, the implantation of a coronary stent and the different characteristics of ACS patients with preferred invasive management may make the difference here. The prognostic value of phenotyping (platelet function testing) and genotyping (especially *CYP2C19*2*) is clearly established for PCI-treated patients (7,9). Further on, randomized controlled clinical trials in PCI-treated ACS patients are ongoing and are aiming for an individualized treatment based on phenotyping or genotyping (NCT01959451 [TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes Trial)], NCT01538446 [ANTARCTIC (Tailored Antiplatelet Therapy Versus Recommended Dose of Prasugrel)], and NCT01761786 [POPGenetics (Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment)]). It is worth pointing out that nowadays, the vast majority of ACS patients are scheduled for an invasive management, and noninvasive treatment is the exception from the rule. For the time being, we have to wait for the results of studies that pursue personalized treatment approaches including genetic (15) and platelet function parameters. The therapeutic strategies evaluated in such trials may help to optimize the antiplatelet treatment of ACS patients, and we may have to leave behind the currently practiced one-size-fits-all approach of targeting the blood platelet.

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