CYP2C19 Genetic Polymorphism and Pharmacodynamics of Prasugrel Maintenance Dose in Patients Undergoing Percutaneous Coronary Intervention

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Clopidogrel and prasugrel are oral thienopyridine prodrugs that require cytochrome P450 (CYP)-mediated conversion to active metabolites that antagonize irreversibly the purinergic platelet P2Y₁₂ receptor (R) leading to inhibition of adenosine diphosphate-mediated platelet activation and aggregation [1]. Since thienopyridines are metabolized by liver enzymes, there is a potential link between CYP2C19 genetic polymorphism (GP) and a high-on treatment platelet reactivity in certain carriers. CYP2C19 GPs, most importantly the *2 loss-of-function allele, have been associated with alterations in the pharmacodynamics (PD) and pharmacokinetics of clopidogrel, but not prasugrel, in patients undergoing percutaneous coronary interventions (PCI) [2–6].

The reduced susceptibility of prasugrel PD to genetic variants is possibly related to the different metabolism steps required: one esterase-mediated hydrolysis step and one CYP-mediated oxidation step for prasugrel activation process, instead of 2 CYP-mediated oxidation steps required for clopidogrel. In fact, prasugrel following its rapid absorption, is hydrolysed by esterases, such as those located in the intestine and blood, to a thiolactone intermediate metabolite R-95913. This metabolite undergoes subsequent activation by a single CYP-dependent step (predominantly CYP3A, CYP2B6 and to a lesser extent by CYP2C9 and

CYP2C19) to form the sulfhydryl-containing active metabolite R-138727. This active metabolite binds irreversibly to the platelet P2Y₁₂R by covalent linkage of a sulfhydryl group to inhibit platelet activation and aggregation. The active prasugrel metabolite contains a reactive thiol group, which forms a disulphide bridge with a free cysteine residue on the P2RY₁₂R. Once irreversibly bound to prasugrel, the receptor is unable to bind adenosine diphosphate, and platelet activation via this pathway is prevented for the rest of the platelet's lifespan of about 10 days [7, 8].

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON)-TIMI 38 study, a significantly reduced rate of the composite efficacy endpoint of cardiovascular death, myocardial infarction, or stroke was demonstrated in prasugrel-treated patients compared to clopidogrel-treated patients with acute coronary syndromes undergoing PCI [9]. However, there was an increased risk for major bleeding in very elderly (VE; ≥75 years) and low body weight (LBW; <60 kg) patients receiving the prasugrel 10-mg maintenance dose (MD). A lower prasugrel dose 5-mg was suggested in these patients to reduce the bleeding risk based on a TRITON-TIMI 38 sub-study [10].

The influence of CYP2C19 genotype on pharmacokinetics and PD response during prasugrel 5-mg MD in

LBW or VE patients undergoing PCI is not very well established. In addition, most studies utilized an early assessment of PR evaluated before or just after drug loading, while the maintenance phase data are scarce. Therefore, whether prasugrel response is consistent, or variable in outpatients, and whether the link of GP with PR differ over time needs to be explored further, among both approved prasugrel MDs.

In the last issue of *Cardiology*, Li et al. [11] prospectively studied 206 consecutive patients who underwent PCI in their centre. All patients were of Korean origin and received prasugrel loading dose of 60-mg at least 3 h before PCI. Dual antiplatelet therapy (DAPT) was later maintained with 100-mg/day of aspirin, and 10-mg/day ($n = 76$) or 5-mg/day ($n = 130$) of prasugrel in LBW and/or VE patients. Blood samples for platelet aggregation and genetic tests were obtained simultaneously from patients after 1 month following PCI with most sampling occurred between 30 and 90 days, with a mean of 64.7 days after PCI. The residual platelet aggregation (RPA) was measured by 3 different methods for platelet activity assessment (light transmittance aggregometry [LTA], multiplate electrode aggregometry, and VerifyNow [PRU]). RPA was lower after 10-mg prasugrel dose, when compared to 5-mg prasugrel daily, and there was a consistent trend toward higher aggregation in CYP2C19 carriers independently from maintenance dosing, reaching significance for 10-mg pra-

sugrel. CYP2C19 carriers had higher RPA for 5-mg ($n = 35$; LTA: $p = 0.043$, multiplate electrode aggregometry: $p = 0.023$), and reached significance for 10-mg ($n = 27$; LTA: $p = 0.001$, PRU: $p = 0.001$) prasugrel. The authors concluded that CYP2C19 GP impacts RPA during the maintenance prasugrel phase in Korean outpatients. This effect is consistent for both approved prasugrel MDs potentially affecting long-term outcomes including bleeding risks [11].

The most important message from the current study is the fact that CYP2C19 genotype carriers may still have some impact on residual post-prasugrel PR during the maintenance phase, while on DAPT in Korean outpatients. Since almost all work on prasugrel response genetics were done early post-PCI [12], or around the loading phase, the index evidence yielded from East Asian patients on long-term maintenance response is indeed new. Importantly, the link between GPs and drug-related responses are especially valid in Asians since about 50% of Asian population comprises loss-of-function allele carriers. In contrast to the negative findings at the acute in-hospital setting, and of another study which found no significant difference in PD response for prasugrel 5 or 10 mg in stable CAD patients [13] and disagrees with the index data, it seems that there could be a delayed impact of GP on PR in this population of patients. Further studies with a larger number of patients are required involving populations other than the East Asians.

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