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Editorial

# Value of CYP2C19 *2 and *17 Genotyping in Clinical Practice. Promising but Not Ready Yet

## Valor de la determinación del genotipo de CYP2C19 *2 y *17 en la práctica clínica. Prometedor, aunque todavía no está listo

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Numerous studies have shown the preventive effect of the use of dual antiplatelet therapy using acetylsalicylic acid and clopidogrel in reducing the risk of cardiovascular events in patients after acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI). Consequently every clinical guideline has incorporated the use of dual antiplatelet therapy for ACS and PCI patients: clopidogrel for 1 year and acetylsalicylic acid for life.

Clopidogrel is a prodrug which needs several biotransformation steps using cytochrome (CYP) P450 liver enzymes before it acquires its antiplatelet effect.[1] After the activation steps clopidogrel irreversibly blocks the $P2Y_{12}$ adenosine diphosphate receptor, which is a key mediator of platelet activation. However, despite the success of clopidogrel, making it the second most prescribed drug in the world, a substantial number of patients still suffer from recurrent atherothrombotic events after ACS with or without PCI. Stent thrombosis is an especially feared complication associated with substantial mortality (15% to 45% of cases).

## VARIABILITY OF CLOPIDOGREL RESPONSE

Great inter-individual variability exists in patient response to clopidogrel when measured by platelet function tests.[2] Thirty days after the start of antiplatelet therapy a subgroup of about 20% of patients showed very little or even no platelet inhibitory effect, this subgroup being at increased risk for atherothrombotic events.[3] The observation that patients with high platelet reactivity (HPR) despite antiplatelet drugs are at higher risk for recurrent events has been corroborated in many studies since, and there is now consensus on cut-off levels to identify these patients on 4 platelet function tests (light transmittance aggregometry, vasodilator-stimulated phosphoprotein phosphorylation levels, VerifyNow $P2Y_{12}$ assay, and the Multiplate analyzer).[3,4]

## GENETIC TESTING

The mechanisms leading to the large interindividual variability in the antiplatelet effect of clopidogrel are not fully understood, but steps have been made to unravel the mechanism behind this variability. As mentioned previously, clopidogrel must be converted to its active state using multiple cytochrome P450 liver enzymes, such as CYP2C19, 3A4/5, 1A2, 2B6 and 2C9.[1] Evidence points toward CYP2C19 as the most important enzyme involved in those bioactivation steps. Single nucleotide polymorphisms of the *CYP2C19* gene with partial or total loss of function are related to differences in exposure to the active metabolite of clopidogrel in patients.[5] In particular, the *2 gene polymorphism (the most common one) is related to diminished enzyme function and reduced clopidogrel effectiveness, as is the less common *3 gene polymorphism. In a study performed in healthy subjects receiving a loading dose of clopidogrel the maximum concentration and the area under the curve of the active metabolite were 40% and 46% lower, respectively, in CYP2C19*2 carriers.[6] The loss-of-function allele is not a rare phenomenon as about one third to two thirds of Caucasian and Asian populations, respectively, are carriers of at least one loss-of-function allele.

In March 2010 the American Food and Drug Administration issued a boxed warning to the clopidogrel label: "Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategies. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers." The American College of Cardiology Foundation and the American Heart Association, however, released a clinical alert on approaches to this Food and Drug Administration warning. The alert provides nuanced guidance for clinicians on how to deal with the clopidogrel label's boxed warning and is reticent about routine genotyping to assist clinical judgment,[7] mainly because a genotype-guided antiplatelet therapy has not been studied in a large scale randomized clinical trial.

## CLINICAL SIGNIFICANCE

The important question is how relevant *CYP2C19* genetic polymorphisms are for daily clinical practice. A meta-analysis of the association between *CYP2C19* loss-of-function alleles and

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major adverse cardiovascular events (MACE) in patients receiving clopidogrel and predominantly treated with PCI (9 studies containing 9685 patients) showed that patients carrying 1 or 2 loss-of-function allele(s), mostly the *2 gene polymorphism, had a higher risk of MACE compared to noncarriers with hazard ratios (HR) of 1.55 (*P*=.01) and 1.76 (*P*=.002), respectively. Furthermore, the HR for stent thrombosis for carriers of one or two loss-of-function function allele(s) were 2.67 (*P*<.0001) and 3.97 (*P*=.01), respectively.[8]

However, the genetic post hoc analyses of the PLATO, CURE and ACTIVE-A trials[9,10] were not included in the meta-analysis performed by Mega et al.[8] Representing a population of which 64% underwent PCI, PLATO only showed an effect of the *CYP2C19* loss-of-function allele on MACE at 30 days (HR 1.37, *P*=.028). In the ACTIVE-A and CURE trials no significant correlations where found.

If *CYP2C19* genetic polymorphisms do play a major role in the antiplatelet effect of clopidogrel, why is this result not found in those major clinical trials? In the study by Tello-Montoliu et al.[11] published in *Revista Española de Cardiología*, 40 stable ACS patients under dual antiplatelet therapy where tested for CYP2C19 *2 and *17 genotype and on-treatment platelet reactivity, using light transmittance aggregometry and vasodilator-stimulated phosphoprotein tests. For light transmittance aggregometry, no significant differences where found between wild-type and polymorphic subjects. For the vasodilator-stimulated phosphoprotein test, *2-carrying patients showed an increase in platelet reactivity index (72.3% [11.9%] vs 56.1% [18.8%], *P*=.02) and *17-carrying patients showed a decrease in platelet reactivity index (51.3% [17.8]% vs 63.8% [18.0%], *P*=.048).

Subsequently, 6-month follow-up data was obtained for a group of 426 unselected non-ST segment elevation myocardial infarction (non-STEMI) patients on dual antiplatelet therapy. No significant association was found between *CYP2C19* carrier status and the combined clinical endpoint, consisting of cardiovascular death or recurrent ACS requiring hospital admission. Rivera et al. conclude there is an association between CYP2C19 *2 and *17 genotype and on-treatment platelet reactivity, but this association could not be found for genotyping and clinical events in this non-STEMI patient group.

As mentioned in the article published by Tello-Montoliu et al.[11] the patient group studied seems to be crucial. Until today no correlation has been demonstrated between *CYP2C19* genetic polymorphisms and clinical endpoints in low-risk patients. Only trials containing a high number of high-risk patients, ie, STEMI and PCI patient groups, show an increased rate of MACE for *CYP2C19* loss-of-function allele carriers. Therefore the effect might have been missed in the ACTIVE-A and CURE trials because of the relatively low-risk population and the low proportion of patients that underwent PCI (18%). The significant results in the PLATO study at 30 days might be related to the increased risk for procedure-related events in the first days after PCI.

## BLEEDING RISK

On the opposite side of the antiplatelet spectrum in which the *2 and *3 polymorphisms play their loss-of-function role, patients who carry the CYP2C19*17 gene variant have an increased clopidogrel metabolism compared to noncarriers. In those patients CYP2C19*17 acts as a gain-of-function allele, which might result in lower atherothrombotic event rates but also in an increased bleeding risk. For STEMI patients a relationship between *17 carrier status and reduced MACE was found, but for other subgroups of patients the effect is still not clear.[12] More research is needed to determine if *17 genotyping would be useful in daily clinical practice.

## ALTERNATIVE TREATMENT STRATEGIES

Are there alternative treatment strategies in patients demonstrating HPR despite acetylsalicylic acid and clopidogrel therapy? Doubling the dose of clopidogrel in patients was proposed, but a doubled dose did not show benefit in the low-risk PCI population of GRAVITAS.[13] An alternative would be to use a stronger antiplatelet agent like prasugrel or ticagrelor which are not effected by CYP genetics. In the new ACS guideline, presented at the 2011 European Society of Cardiology Congress, indeed a I-B recommendation is given to the use of ticagrelor for moderate- to high-risk patients (eg, elevated troponin) and prasugrel for $P2Y_{12}$ inhibitor-naïve patients in whom coronary anatomy is known and who are proceeding to PCI, unless there is a high risk of life-threatening bleeding or other contraindications. Clopidogrel is only recommended for patients who cannot receive prasugrel or ticagrelor.[14]

Where does the evidence come from? In the TRITON-TIMI 38 study of patients presenting with ACS (including unstable angina, non-STEMI, and STEMI), all scheduled for PCI, prasugrel was more effective compared to clopidogrel in the prevention of cardiovascular death, myocardial infarction, or stroke with an HR of 0.81 (95% confidence interval 0.73–0.90). However, prasugrel significantly increased the risk of non coronary artery bypass grafting related TIMI major bleeding compared to clopidogrel (HR 1.32, 2.4% vs 1.8%), as well as life-threatening bleeding (HR 1.52, 1.4% vs 0.9%) and fatal bleeding (HR 4.19, 0.4% vs 0.1%). In a post hoc analysis in STEMI patients, however, bleeding complications were not more frequent in prasugrel-treated patients.[15]

Ticagrelor belongs to a novel biochemical class, cyclopentyltriazolopyrimidine. The new drug is a reversible $P2Y_{12}$ inhibitor with a plasma half-life of approximately 12 h. The drug acts faster and has a stronger antiplatelet effect compared to clopidogrel, reducing the combined endpoint of cardiovascular death, myocardial infarction, or stroke from 11.7% to 9.8% in the PLATO trial. Total mortality was also significantly reduced (5.9% vs 4.5%). The incidence of noncoronary artery bypass grafting major bleeding and minor bleeding was increased and a higher rate of fatal intracranial hemorrhage was found in the ticagrelor group. Another disadvantage was the occurrence of dyspnea in up to 15% of patients using ticagrelor.[16]

## TAILORING ANTIPLATELET MEDICINE

Knowing that the antiplatelet response to prasugrel and ticagrelor is not influenced by *CYP2C19* gene polymorphisms and that these drugs were more effective in a head-to-head comparison with clopidogrel, why should we not prescribe one of those new drugs for every patient in need of dual antiplatelet therapy? Platelet function tests have been shown to have a very high negative predictive value (>93%) which means that those patients with normal platelet reactivity on clopidogrel have a very low risk for recurrent atherothrombotic events.[3] Administration of stronger antiplatelet drugs in these low-risk patients would probably not reduce the thrombotic risk but on the other hand would increase the risk of bleedings. Also, with the availability of generic clopidogrel the general use of prasugrel or ticagrelor would imply an enormous increase in drug costs.

The old "one size fits all" regime seems to come to its end and tailored antiplatelet therapy is taking over, based on the patient's individual risk factors for atherothrombotic events such as HPR, diabetes, ACS, and *CYP2C19* carrier status. Prescribing prasugrel or ticagrelor only to the high-risk patients could add to a new era of personalized medicine. However, no studies have been published so far to test this hypothesis in sufficiently powered

randomized clinical trials. Currently one trial testing this strategy has been completed (RAPID GENE Study, NCT01184300, in stable angina or non-STEMI patients) and one trial is recruiting patients (GIANT-trial, NCT01134380, in STEMI patients). In The Netherlands, a multicenter trial (POPular Genetics) has been started in which 2500 STEMI patients will be randomized to genotyping or routine care. In the genotyping arm, patients carrying a loss-of-function allele will be prescribed prasugrel or ticagrelor; in patients without loss-of-function, allele clopidogrel will be prescribed.

## CONCLUSIONS

Carrying a *CYP2C19* loss-of-function allele when using clopidogrel results in diminished antiplatelet effect and a higher risk for atherothrombotic events compared to patients who do not carry a loss-of-function allele.

In our opinion it seems to be a promising strategy to tailor antiplatelet therapy in high-risk patients after STEMI or PCI, based on factors such as *CYP2C19* carrier status, using clopidogrel in low-risk patients and prasugrel or ticagrelor in high-risk patients. Prescribing prasugrel or ticagrelor to high-risk patients could reduce event rates in those patients, without putting low-risk patients at an increased bleeding risk. However, large randomized clinical trials testing individualized antiplatelet therapy are urgently needed to confirm this hypothesis.

## CONFLICTS OF INTEREST

None declared.

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