



CYP2C19*2 allele: guiding medication choice after percutaneous coronary intervention

*"...a 'tailored treatment' (with clopidogrel) may not be the ideal solution for high platelet reactivity, at least in CYP2C19*2 carriers."*

KEYWORDS: clopidogrel ■ genetic ■ PCI ■ percutaneous coronary intervention ■ platelet

High platelet reactivity (HTPR) following clopidogrel treatment in patients undergoing percutaneous coronary intervention (PCI) has been associated with an increased rate of adverse events, including stent thrombosis [1]. These events have been particularly linked with the presence of the loss-of-function cytochrome (CYP) 2C19*2 allele [2–9]. The recent US FDA 'boxed warning' on clopidogrel addresses the need for pharmacogenomic testing to identify patients at risk for a suboptimal clinical response to clopidogrel and notes that tests are available to identify patients with genetic polymorphisms. Furthermore, the FDA suggests that alternative treatment strategies should be considered in clopidogrel-poor metabolizers [10]. However, CYP2C19*2 genotyping is an efficient predictive tool to guide antiplatelet treatment post-PCI and, specifically, to define who will require an adequate platelet inhibition following standard clopidogrel dose and who will need increased clopidogrel dose or an alternative P2Y₁₂ inhibitor? The answer to this question is unknown at this present time, with advocates and opponents of the role of CYP2C19*2 genotyping in everyday practice.

CYP2C19*2 allele & clopidogrel pharmacodynamic data

CYP2C19 is responsible for approximately 45% of the first metabolic step (the formation of 2-oxo-clopidogrel) and approximately 20% of the final step – the generation of the pharmacologically active thiol metabolite of clopidogrel. The three major CYP2C19 genetic polymorphisms are CYP2C19*1, corresponding to normal function, and CYP2C19*2 and CYP2C19*3, which are loss-of-function alleles. The CYP2C19*2 has an allelic frequency of 25–30% in the white population and accounts for 95% of the subjects classified as carriers of a reduced CYP2C19-function allele [4]. CYP2C19*2 is reproducibly associated

with variability in clopidogrel-active metabolite bioavailability, antiplatelet effects and clinical outcomes [2,3,6–9]. Among clopidogrel-treated patients in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 trial, carriers had a relative increase of 53% in the composite primary efficacy outcome of the risk of death from cardiovascular causes, myocardial infarction or stroke, compared with non-carriers, and a threefold increase in the risk of stent thrombosis [4].

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There are few pharmacodynamic data on the inhibitory effect of clopidogrel dosing regimens in CYP2C19*2 carriers. In a total of 134 non-ST elevation myocardial infarction (NSTEMI) carriers with PCI, 103 were considered to have HTPR after an initial 600-mg loading dose of clopidogrel. Following dose adjustment with up to three additional 600-mg loading doses, 88% of them became clopidogrel responsive [10]. In the Accelerated Platelet Inhibition by a Double Dose of Clopidogrel According to Gene Polymorphism (ACCEL-DOUBLE) study in patients receiving clopidogrel 150 mg/day for at least 1 month, CYP2C19*2 carriage predicted the risk of HTPR [11]. An improved platelet inhibition was reported in nine CYP2C19*2 allele carriers by increasing the clopidogrel dose from 75 to 150 mg/day, while in two small studies in patients with HTPR on a standard dose, clopidogrel 150 mg daily resulted in no significant difference in platelet reactivity change between carriers and noncarriers [12–14]. By contrast, in



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59 genotyped patients with HTPR, we demonstrated that doubling the standard clopidogrel dose resulted in a significantly smaller change in platelet reactivity in carriers than in non-carriers, with almost half of the carriers remaining hyporesponsive [15]. Our suggestion was that a 'tailored treatment' (with clopidogrel) may not be the ideal solution for HTPR, at least in *CYP2C19**2 carriers.

New, more potent P2Y₁₂ inhibitors & *CYP2C19**2

In contrast to clopidogrel, prasugrel has only one intrahepatic metabolic step and is much less dependent on *CYP2C19**2. Active drug metabolite levels, inhibition of platelet aggregation or clinical cardiovascular event rates in individuals treated with prasugrel are not influenced by *CYP2C19**2 carriage [16,17]. Ticagrelor – a direct P2Y₁₂ inhibitor – was tested in the Platelet Inhibition and Patient Outcomes (PLATO) trial versus clopidogrel in patients with acute coronary syndromes (ACS) who were treated in more than 60% of the cases with PCI and stenting. In the genetic substudy of 10,285 genotyped patients, the observed differences of ticagrelor versus clopidogrel (reduced composite outcome but increased noncoronary artery bypass grafting-related bleeding) were irrespective of *CYP2C19* polymorphisms [18,19]. In addition, in a series of seven patients with clinical resistance to clopidogrel manifesting as stent thrombosis, increasing the dose of clopidogrel did not override the effect of *CYP2C19**2, whereas 10 mg of prasugrel did, suggesting that a strategy of an incremental increase in the clopidogrel in such patients is both time consuming and minimally effective [20]. Clopidogrel-'resistant' patients respond mostly to prasugrel or invariably to ticagrelor [15,21]. Therefore, it seems that we may not need to conduct genotyping if prasugrel or ticagrelor are to be used. Alternatively, considering the lower cost of clopidogrel owing to its generic availability, prasugrel or ticagrelor may be better suited for those who are genetically poor responders or have failed clopidogrel therapy. The potential ischemic benefit of the more potent P2Y₁₂ inhibitors should be balanced against the increased risk of bleeding. In particular, prasugrel is contraindicated in patients with stroke and transient ischemic attack, and is of doubtful benefit in patients who weigh less than 60 kg or those who are older than 75 years [22].

Limitations of *CYP2C19**2 use to guide antiplatelet treatment choice

The value of *CYP2C19**2 genotyping for clinical use post-PCI is limited by several factors. The *CYP2C19**2 genotype accounts for only approximately 12% of variability in platelet response to clopidogrel [6]. A significant proportion of carriers do not have HTPR, while this is present in many patients with wild-type alleles [2]. The positive predictive value of *CYP2C19* polymorphisms for events is estimated to be between 12 and 20% in patients with ACS undergoing PCI [4,5]. The number of reduced-function alleles is important as individuals with two variant alleles (poor metabolizers) have lower exposure to the active metabolite of clopidogrel than individuals with one variant allele (intermediate metabolizers) [4,6]. Interestingly, the FDA boxed warning refers only to poor metabolizers. Other genetic polymorphisms, although much less common, are associated with impaired (*CYP2C19**3, *4, *5 and *8) or increased (*CYP2C19**17) activity, while a possible direct effect of genetic polymorphisms on platelet activity cannot be excluded. The proportion of risk attributed to the genomic profile varies over time in a given individual, depending on the specific clinical scenario including diabetes, obesity and ACS [6]. Finally, there is no prospective randomized evidence to support genotyping post-PCI. However, there are several ongoing studies using *CYP2C19**2 genotyping post-PCI with different outcomes, either clinical or pharmacodynamic: the Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes (GeCCO) study assesses the non-inferiority of clopidogrel in *CYP2C19* extensive metabolizers compared with prasugrel. The Reassessment of Anti-Platelet Therapy Using an Individualized Strategy Based on Genetic Evaluation (RAPID GENE) using a *CYP2C19**2 point-of-care genetic test tries to answer whether prasugrel is better than clopidogrel in carriers post-PCI. Identification of resistance and genotype is used in the Thrombocyte Activity Reassessment and Genotyping for PCI (TARGET-PCI), where treatment in clopidogrel-naïve subjects will be guided by the Verigene (Nanosphere, IL, USA) *CYP2C19* genotyping assay. Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment (GIANT) study tries to evaluate whether adjustment of treatment based on genetics (increase clopidogrel, switch to prasugrel or switch to clopidogrel) results in

differences between carriers and noncarriers. The Genotype Information and Functional Testing (GIFT) study looks for genes influencing residual platelet reactivity on a standard or high-maintenance dose of clopidogrel. Upon completion of these studies, a better understanding of the role of *CYP2C19* genotyping for post-PCI treatment choice is expected.

How can we use *CYP2C19**2 genotyping for antiplatelet treatment choice in clinical practice?

There are three frequently encountered clinical scenarios. The first scenario is if newer, potent P2Y₁₂ inhibitors are not available, contraindicated or not desired because of safety concerns, cost and so on, either platelet reactivity assessment or genotyping may be performed. If genotyping is performed and a patient is a *CYP2C19**2 carrier, assessment of platelet reactivity is mandatory, as doubling the clopidogrel dose is of only partial efficacy. The second scenario is willingness for prasugrel or ticagrelor to be used based on the TRITON and PLATO results. In this case, genotyping is not needed. However, if beyond the first period (e.g., either 1 week or 1 month) a clinician wants to switch to clopidogrel, then genotyping may be applied, and if a patient is found to be a carrier, he should insist on prasugrel or ticagrelor treatment. The third scenario applies if there is contraindication to prasugrel (in approximately 25% of patients). If ticagrelor is available, this might be a solution, although there has been no experience of such a situation. Otherwise, clopidogrel use may be followed by a platelet-reactivity assessment. In case of resistance (30%

of the patients), identification by genotyping of the carriage status defines a population with a low likelihood of achieving adequate platelet inhibition by increasing the clopidogrel dose. Needless to say, for genotyping to have a useful role in antiplatelet choice, the method used should be easy to perform, rapid, accurate, a point-of-care approach and of low cost.

“...platelet reactivity assessment appears complementary or even mandatory – if carriage is identified.”

Based upon our current knowledge, genotyping may be useful in antiplatelet treatment choice post-PCI if clopidogrel, but not prasugrel or ticagrelor, use is considered. Even if genetic tests are successfully developed, genotyping alone cannot be regarded as a substitute for platelet function testing in identifying clopidogrel nonresponders, and platelet reactivity assessment appears complementary or even mandatory – if carriage is identified. The exact role of *CYP2C19**2 genotyping in clinical practice post-PCI should be elucidated by appropriately designed prospective clinical trials.

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Bibliography

- Sofi F, Marcucci R, Gori AM *et al.*: Clopidogrel non-responsiveness and risk of cardiovascular morbidity: an updated meta-analysis. *Thromb. Haemost.* 103, 841–848 (2010).
- Trenk D, Hochholzer W, Fromm MF *et al.*: Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J. Am. Coll. Cardiol.* 51, 1925–1934 (2008).
- Simon T, Verstuyft C, Mary-Krause M *et al.*: Genetic determinants of response to clopidogrel and cardiovascular events. *N. Engl. J. Med.* 360, 363–375 (2009).
- Mega JL, Close SL, Wiviott SD *et al.*: Cytochrome p-450 polymorphisms and response to clopidogrel. *N. Engl. J. Med.* 360, 354–362 (2009).
- Collet JP, Hulot JS, Pena A *et al.*: Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet* 373, 309–317 (2009).
- Shuldiner AR, O’Connell JR, Bliden KP *et al.*: Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 302, 849–857 (2009).
- Giusti B, Gori AM, Marcucci R *et al.*: Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. *Am. J. Cardiol.* 103, 806–811 (2009).
- Sibbing D, Stegheer J, Latz W *et al.*: Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *Eur. Heart J.* 30, 916–922 (2009).
- Mega JL, Simon T, Collet JP *et al.*: Reduced-function *CYP2C19* genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 304, 1821–1830 (2010).
- Bonello L, Armero S, Ait Mokhtar O *et al.*: Clopidogrel loading dose adjustment according to platelet reactivity monitoring in patients carrying the *2C19**2 loss of function polymorphism. *J. Am. Coll. Cardiol.* 56, 1630–1636 (2010).

- 11 Jeong YH, Kim IS, Park Y *et al.*: Carriage of cytochrome 2C19 polymorphism is associated with risk of high post-treatment platelet reactivity on high maintenance-dose clopidogrel of 150 mg/day. Results of the ACCEL-DOUBLE (Accelerated Platelet Inhibition by a Double Dose of Clopidogrel According to Gene Polymorphism) study. *J. Am. Coll. Cardiol. Interv.* 3, 731–741 (2010).
- 12 Gladding P, White H, Voss J *et al.*: Pharmacogenetic testing for clopidogrel using the rapid INFINITI analyzer: a dose-escalation study. *J. Am. Coll. Cardiol. Interv.* 2, 1095–1101 (2009).
- 13 Barker CM, Murray SS, Teirstein SS, Kandzari DE, Topol EJ, Price MJ: Pilot study of the antiplatelet effect of increased clopidogrel maintenance dosing and its relationship to *CYP2C19* genotype in patients with high on-treatment reactivity. *J. Am. Coll. Cardiol. Interv.* 3, 1001–1007 (2010).
- 14 Aleil B, Léon C, Cazenave JP *et al.*: *CYP2C19**2 polymorphism is not the sole determinant of the response to clopidogrel: implications for its monitoring. *J. Thromb. Haemost.* 7, 1747–1749 (2009).
- 15 Alexopoulos D, Xanthopoulou I, Dimitropoulos G *et al.*: PRO-GR: a prospective, randomized, crossover study of maintenance high-dose clopidogrel vs prasugrel in clopidogrel resistant patients with and without the *CYP2C19**2 loss-of-function allele. Presented at: *Transcatheter Cardiovascular Therapeutics*. Washington DC, USA, 23–25 September, 2010.
- 16 Varenhorst C, James S, Erlinge D *et al.*: Genetic variation of *CYP2C19* affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. *Eur. Heart J.* 30, 1744–1752 (2009).
- 17 Mega JL, Close SL, Wiviott SD *et al.*: Cytochrome P450 genetic polymorphisms and the response to prasugrel relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation* 119, 2553–2560 (2009).
- 18 Wallentin L, Becker RC, Budaj A *et al.*: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 361, 1045–1057 (2009).
- 19 Wallentin L, James S, Storey RF *et al.*: Effect of *CYP2C19* and *ABCB1* single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* 376, 1320–1328 (2010).
- 20 Pena A, Collet JP, Hulot JS *et al.*: Can we override clopidogrel resistance? *Circulation* 119, 2854–2857 (2009).
- 21 Gurbel PA, Bliden KP, Butler K *et al.*: Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. *Circulation* 121, 1188–1199 (2010).
- 22 Wiviott SD, Braunwald E, McCabe CH *et al.*: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 357, 2001–2015 (2007).

Website

- 101 US FDA Drug Safety Communication: reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug www.fda.gov/Drugs/DrugSafety/