Genetic variability in response to clopidogrel therapy: clinical implications

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This editorial refers to ‘CYP2C19*2 and CYP2C9*3 alleles are associated with stent thrombosis: a case–control study†, by A.M. Harmsze et al., on page 3046

Introduction

In the past few years, it has been realized that cardiovascular events under dual antiplatelet therapy (DAPT) might be associated with a poor response to clopidogrel. Based on different platelet function assays, ~20–25% of clopidogrel-treated patients undergoing percutaneous coronary intervention (PCI) and coronary stenting have been defined as poor responders and were prone to an increased risk of recurrent cardiovascular events.

Reasons for a diminished action of clopidogrel are multifactorial and include besides non-compliance, under-dosing, drug–drug interactions, and several co-morbidities (e.g. diabetes mellitus, hyperlipidaemia), also genetic disorders that interact with intestinal absorption, metabolic activation in the liver, and pharmacodynamics.

In the current issue of the journal Harmsze and co-workers have elegantly demonstrated in the so far biggest patient cohort (n=176) during DAPT after PCI and stent implantation that carriage of the loss-of-function alleles CYP2C19*2 and CYP2C9*3 increases the risk of stent thrombosis, while no effect of other investigated genetic variants for genes involved in clopidogrel absorption (ABCB1 C1236T, G2677T/A, C3435T), metabolism (CYP2C19*3, CYP2C9*2, CYP3A4*1B, and CYP3A5*3), or the P2Y1 receptor (P2Y1A1622G) was seen.

Gene polymorphisms and clopidogrel

Clopidogrel is an ADP receptor inhibitor prodrug. After intestinal absorption (ABCB1 gene), the majority (85%) of the prodrug is metabolized and inactivated by esterases and only the remaining 15% of clopidogrel is transformed into the intermediate 2-oxo-clopidogrel metabolite by three isoenzymes (CYP1A2, CYP2B6, and CYP2C19). This intermediate non-active metabolite is further hydrolysed into the highly unstable active thiol derivative R-130964 by involvement of four isoenzymes (CYP2B6, CYP2C9, CYP2C19, and CYP3A4) (Figure 1) and inhibits platelet aggregation through an irreversible blockade of the ADP P2Y12 receptors on the platelet surface.

Genetic disorders influencing absorption

ABCB1

Intestinal absorption is limited by the ABCB1 gene. Compared with non-carriers (CC genotype), the bioavailability of clopidogrel was significantly reduced among patients receiving a clopidogrel loading dose before elective PCI who have either one (CT genotype) or two (TT genotype) copies of the ABCB1 C3435T single nucleotide polymorphism.

Patients with acute myocardial infarction with the TT genotype had significantly higher event rates at 1 year than those with the ABCB1 wild-type (CC) genotype [15.5% vs. 10.7%; adjusted hazard ratio (HR) 1.72; 95% confidence interval (CI) 1.20–2.47]. The presence of any two CYP2C19 loss-of-function alleles (*2,*3,*4, or *5) and at least one ABCB1 variant allele was associated with the highest risk of primary cardiovascular events (HR 5.31; 95% CI 2.13–13.20), whereas the ABCB1 variant allele had no significant independent effect.

Genetic disorders influencing metabolism

CYP2C19

The CYP2C19 genetic polymorphism has a wide interethnic variability, ranging from 20–30% among Caucasians to 30–45% among African-Americans and ~50–65% in East Asians, whereby the CYP2C19*2 allele seems to be the most frequent defective allele (75–85% in Caucasians and East Asians).
Multiple studies have demonstrated a relationship between carriage of CYP2C19 loss-of-function alleles, especially of the CYP2C19*2 loss-of-function allele, or of any two CYP2C19 loss-of-function alleles (*2,*3,*4, or *5) and a higher rate of adverse cardiovascular events including a nearly three-fold increased risk of stent thrombosis than non-carriers (for review see Holmes et al.).

In healthy volunteers, carriers with a reduced function CYP2B6 allele had a 15.7% lower plasma exposure of the active metabolite of clopidogrel and less reduction of platelet aggregation in response to clopidogrel, while loss-of-function alleles in CYP1A2, CYP3A5, and CYP2C9 were not associated with pharmacokinetic and pharmacodynamic responses to clopidogrel.8,9

In contrast, as demonstrated in high-risk patients with stent thrombosis4 and in Korean patients undergoing PCI, 10 carriers of the CYP2C9*3A allele single-nucleotide polymorphism had more remaining platelet aggregation under constant DAPT compared with those without, thus underlying the potential importance of the CYP2C9*3 loss-of-function allele as an independent risk factor for a diminished response to clopidogrel in patients.4

P2Y12 receptor

Genetic variations in the gene encoding the P2Y12 receptor have been investigated and shown no association between clopidogrel responsiveness and the genetic polymorphism encoding the P2Y12 receptor.5,11

Prasugrel, ticagrelor and influences of genetic variants

Similar to clopidogrel, prasugrel has to be converted into its active metabolite by cytochrome P450 (CYP) enzymes after a first step, when the prodrug is hydrolysed by carboxylesterases into an intermediate metabolite, which is then catalysed to the active metabolite by five different isoenzymes (CYP3A4, CYP3A5, CYP2B6, CYP2C19, CYP2C9) (Figure 1). These isoenzymes can compensate each other, a reason why genetic polymorphisms of different CYP-enzyme alleles do not influence the generation of the active metabolite of prasugrel.12 Accordingly, prasugrel-treated carriers of the CYP2C19 loss-of-function allele were not at increased risk of stent thrombosis, myocardial infarction, stroke, or other cardiovascular complications.8,13

Prasugrel and ticagrelor, which are not affected by CYP2C19 genetic variants, have been demonstrated to be more effective than standard-dose clopidogrel. Accordingly, these agents should be used preferentially in high-risk clinical situations prone to atherothrombotic complications including stent thrombosis [e.g. acute coronary syndrome (ACS) patients referred for PCI and stenting] and in any patient suspected of treatment failure to standard-dose clopidogrel.14

Ongoing studies

At present, several studies with different study populations, endpoints, and follow-up periods are being performed or planned to evaluate the clinical role of pharmacogenetic testing (especially...
for CYP2C19 with respect to the patient’s exposure to active metabolite and to the response of platelet function assays to clopidogrel: SPICE (two trials), ACCEL-2C19, ACCELAM12C19, ACCEL2C19, GeCCO, PAPI-2 (for a review see Holmes et al.7). The clinical importance of pharmacogenetic testing in tailoring individual antiplatelet therapy depends on completion of these trials.

**Summary**

In their manuscript Harmsze et al.4 concluded that personalized therapy targeting patients who carry these genetic variants might help to improve clinical outcome after stent implantation. For the clinical role of genetic profiling multiple unknown factors still remain: while in the majority of trials CYP2C19 genetic polymorphisms and occasionally CYP2C9 genetic polymorphisms have been shown to reduce clopidogrel metabolism and its clinical effectiveness, there are no prospective studies demonstrating a clinical benefit of personalizing antiplatelet therapy based on genotyping. Commercially available genetic tests that can determine CYP2C19 genotype (and other) variants are not routinely reim-bursed and point of care assays (e.g. for patients with ACS) are lacking at present. Moreover, it is important to point out that CYP2C19 polymorphisms account for only ~12% of variability in clopidogrel platelet response,15 the positive predictive value of CYP2C19 loss-of-function polymorphisms for cardiovascular events in patients with ACS undergoing PCI is low, ~12–20%,8,15 and other clinical factors and risk constellations might be of greater clinical importance. Finally, it is not known whether a specific genetic polymorphism is capable of influencing outcome for the individual patient. Accordingly, genetic profiling should not be recommended for routine use at present but will remain of increased scientific interest.

**References**


