Should Genetic Testing Be Done in All Patients Treated With Clopidogrel and Undergoing Percutaneous Coronary Intervention?

Current Evidence for Genetic Testing in Clopidogrel-Treated Patients Undergoing Coronary Stenting

Dirk Sibbing, MD; Isabell Bernlochner, MD; Adnan Kastrati, MD

A combined dual antiplatelet treatment consisting of aspirin and the P2Y12 receptor inhibitor clopidogrel is still considered the standard of care treatment in most of the patients undergoing percutaneous coronary intervention (PCI). Numerous research studies during the last decade, however, have highlighted possible shortcomings of the oral antiplatelet agent clopidogrel, namely its large response variability resulting in an unpredictable response for the individual patient,1,2 the association of both a low3 or enhanced response4,5 with a worse clinical outcome and the dependency of individual responsiveness on nongenetic and genetic variables.6

Response by Paré and Eikelboom on p 513

Clopidogrel is a prodrug that requires bioactivation into its active thiol metabolite before it targets the P2Y12 receptor on blood platelets. In vivo bioactivation of the drug is a 2-step process that is closely linked to the cytochrome P450 (CYP) system. Different isoenzymes are responsible for clopidogrel bioactivation and among them the isoenzyme CYP2C19 was found to play a key role in this setting by contributing to both clopidogrel bioactivation steps.7 In this context, common genetic variants within the CYP2C19 gene have been the subject of considerable attention and have stimulated numerous research projects in recent years.8–14 Beyond CYP2C19, other genes involved in clopidogrel absorption, bioactivation or interplay with the blood platelet and their receptors have been associated with drug responsiveness and clinical outcome as well. Indeed, a growing body of evidence suggests a possible role of genotyping in patients undergoing coronary stenting with a view on optimizing response to P2Y12 receptor inhibitors during and after the procedure. We review available evidence on the need of individualizing antiplatelet treatment regimens in everyday clinical practice.

Genetic Determinants for Clopidogrel Response and Clinical Outcome

In recent years, multiple genetic factors within different candidate genes being involved in clopidogrel absorption, bioactivation, and platelet P2Y12 receptor interaction have been associated with both high and low platelet reactivity to this drug. Concordantly, in terms of clinical outcome measures, variants were linked to either ischemic8,13,15 or bleeding events16,17 after coronary stenting procedures. By far, the most prominent and best established genetic factor is located within the CYP2C19 gene. The polymorphically expressed isoenzyme CYP2C19 is involved in both metabolic steps of clopidogrel’s 2-step active metabolite generation.7,18 In 2006 and probably without anticipating the momentousness of their observation, Hulot et al
Table. CYP2C19*2 Genotype and Clinical Efficacy of Clopidogrel Therapy

<table>
<thead>
<tr>
<th>Study</th>
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<td>Mega et al</td>
<td>1477 (PCI ACS)</td>
<td>Death from CV causes, MI, stroke at 15 mo</td>
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CAD indicates coronary artery disease; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; PCI, percutaneous coronary intervention; and ST, stent thrombosis.

for the first time reported that a single-nucleotide polymorphism (SNP) located within the CYP2C19 gene is a major determinant of clopidogrel responsiveness in healthy subjects. Since then, several studies as well as their meta-analyses have demonstrated that the presence of this common CYP2C19*2 loss-of-function allelic variant, which is associated with a complete loss of enzyme function, comes along with an attenuated response to clopidogrel and with a higher risk for ischemic events including stent thrombosis in PCI-treated patients. Selected studies with clinical end points investigating CYP2C19*2 in clopidogrel-treated patients are highlighted in the Table. Our results in a large PCI cohort of patients have also been consistent with other studies in terms of CYP2C19*2 allele carriage and bleeding. In the study of 1524 PCI-treated patients this GOF variant was found to be associated with lower ADP-induced platelet aggregation values (enhanced response) and a substantially higher bleeding risk for CYP2C19*17 allele carriers, although a protective effect of *17 carriage on ischemic events was not observed. Later on, the association of *17 allele carriage and bleeding was confirmed by a genetic substudy of the PLATO trial, in which significantly more bleeding events were found in clopidogrel-treated patients. A similar association was found in a post hoc analyses of the CURE and ACTIVE trials, and a similar association was found in a group of patients with acute myocardial infarction. Overall, results for CYP2C19*17 remain conflicting, with some functional and clinical studies finding an impact on clopidogrel treatment efficacy or safety and others not finding an impact. Reasons for conflicting data on CYP2C19*17 remain unclear but could be related to the small sample size in some studies but also to the circumstance that the influence of this variant should be considered as modest when compared with CYP2C19*2. However, similar as for CYP2C19*2, carriage of the GOF variant may be the reason to shift certain patients toward threshold values for their platelet reactivity level. Ultimately, this may cause a bleeding event in one patient, whereas it may prevent thrombotic complications in another. Besides the common *2 and *17 variants located within the CYP2C19 gene, a number of uncommon variants (*3 to *8) exist as well. Their detailed description is beyond the scope of the present manuscript and is summarized elsewhere.

Table

- **CYP2C19*2 Genotype and Clinical Efficacy of Clopidogrel Therapy**

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Similar as for the CYP2C19 GOF variant, available data are also conflicting for another genetic marker located within the ABCB1 gene, which encodes for the enteric multidrug resistance protein 1 (MDR 1). This protein is responsible for the absorption of clopidogrel in the intestine and an influence of an SNP within the ABCB1 gene (C3435T) was first described by Taubert et al in 2006.31 Whereas some studies20,32 reported on a positive association of the ABCB1 C3435T genotype with clopidogrel treatment efficacy, other studies failed to show a significant impact of this variant on the outcome of clopidogrel-treated patients.16,29 Further studies are surely needed to confirm or to refute an impact of this variant on clopidogrel treatment efficacy.

Just recently, a single genetic variant (Q192R) within the gene encoding for the paraoxonase-1 (PON1) enzyme was linked to clopidogrel bioactivation, response to clopidogrel therapy, and the risk for stent thrombosis in clopidogrel-treated patients.16,29 Further studies are surely needed to confirm or to refute an impact of this variant on clopidogrel treatment efficacy.24 In line with this, the recently completed Genotype Information and Functional Testing (GIFT) trial (NCT:00992420), a platelet substudy from the GRAVITAS trial36 reported at the American College of Cardiology 2011 Scientific Sessions, also failed to find any evidence for a relevant role of PON1 in clopidogrel-treated patients. Concordantly, the first and so far only genome-wide association study on clopidogrel treatment efficacy, only reported compelling evidence for 1 major locus on chromosome 10q24 that influences clopidogrel drug response.8 The reported locus encompasses the CYP2C19 gene locus, but other loci or specifically loci including the PON1 or ABCB1 genes were not reported by the authors to be associated with clopidogrel responsiveness.
In summary, a number of genetic factors are likely to act in concert on clopidogrel bioactivation and the clinical outcome of clopidogrel-treated patients. Further studies in large cohorts of patients are urgently needed to confirm or to refute a role of previously described variants in this setting and to explore new and yet unidentified genetic markers. Until then, one single genetic variant stands out in playing a key role in the setting of clopidogrel treatment; namely the CYP2C19*2 loss-of-function allele. This should be the first-choice SNP to be tested when it comes to the issue of what markers should be genotyped in the individual patient.

**Food and Drug Administration Black Box Warning on Clopidogrel**

Discussions on the importance of genotyping in clopidogrel-treated patients undergoing PCI have been inspired by the action of US Food and Drug Administration (FDA) in March 2010. At that time, the FDA added a boxed warning to clopidogrel to alert patients and health care professionals to the fact “that the drug can be less effective in people who cannot metabolize the drug to convert it to its active form.” The FDA also stated that “Tests are available to identify a patient’s CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.” Moreover, it was stated that one should “consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.” The term “poor metabolizer status” was defined by the FDA as a subject being homozygous for the CYP2C19*2 allele. Defining only homozygous *2 allele carriers as poor metabolizers with advice for a change in treatment would narrow the population at risk to approximately 2%. However, data from numerous trials as well as their meta-analyses suggest that carriage of even one single *2 allele is enough to put a patient at a significantly higher risk for ischemic events including the occurrence of stent thrombosis. Although the FDA warning was therefore justified based on the overwhelming evidence for a relevant role of CYP2C19*2 in the setting of clopidogrel treated patients (see also summary of studies in the Table), for the attending physician it is difficult to translate this advice into clinical practice. This is due to a number of reasons, including (1) genotyping assays are not available in all situations; (2) algorithms are missing and are even lacking in the FDA statement commenting on how to improve treatment in CYP2C19*2 allele carriers; and (3) that numerous genetic and nongenetic variables act in concert on clopidogrel treatment efficacy, with CYP2C19*2 being only a single part of the entire puzzle the treating physician must deal with.

**Genetic Factors and Newer Antiplatelet Agents**

Prasugrel and ticagrelor, two newer antiplatelet agents, are now available, with a more rapid and predictable mode of action. The latter characteristics are related to the pharmacological properties of both drugs, and it is vitally important to recognize that prasugrel bioactivation is less dependent on CYP system bioactivating capacities and that ticagrelor is already absorbed in its active form without any need for in vivo bioactivation. Thus, for ticagrelor, it does not come as a surprise that different studies did not observe any influence of genetic markers including CYP2C19 and ABCB1 on either the pharmacodynamic effect of the drug or the clinical outcome of ticagrelor-treated patients. Similar observations were reported for prasugrel, with no influence of common functional CYP genetic variants (including CYP2C19*2) on active metabolite generation, inhibition of platelet aggregation, or the clinical outcome of prasugrel-treated patients. Thus, current data available do not provide a rationale for routine genotyping in prasugrel- or ticagrelor-treated patients. However, it may well be that yet unknown genetic factors significantly influence prasugrel bioactivation or the interaction of prasugrel and ticagrelor with the P2Y12 receptor on blood platelets. Other clinical scenarios where genotyping in patients on prasugrel or ticagrelor may provide important information are outlined later on.

**Available Assays Allowing Bedside Genotyping**

For reliable genotyping of genetic variants (especially CYP2C19*2) in clopidogrel-treated patients, conventional use of laboratory-based methods such as DNA sequencing or TaqMan genotyping will be best suited primarily for research purposes. These laboratory-based methods are time consuming and require a separate step of DNA isolation beforehand. A widespread adoption of genotyping in clinical routine can only be realized in the future.
with the utilization of genotyping assays that allow point-of-care testing without any need for prior separate DNA isolation step. Requirements for these assays are that they are easy to use, provide reliable results rapidly, and are reproducible and in terms of costs that they are affordable to be used in clinical practice. At present, only two point-of-care assays are available for CYP2C19*2 genotyping: the Verigene CYP2C19 XP system (Nanosphere, Northbrook, IL) and the Spartan RX CYP2C19 system (Spartan Bioscience Inc, Ottawa, Ontario). The Verigene system uses whole blood, with a detection technology based on gold nanoparticles. It allows the genotyping of different CYP2C19 allelic variants in parallel, but the time from probe sampling to results takes about 3 hours. The Spartan system uses a buccal swab with a detection technology based on end-point PCR. In its present form, this system allows for genotyping of CYP2C19*2 only, but results are available with 1 hour after probe sampling. Further assays are under development and await introduction in research projects and clinical routine.

Predictive Value for Estimates of Clopidogrel Response

Undoubtedly, both genotyping and platelet function testing (that is, phenotyping) can be considered as estimates of clopidogrel response. It is a crucial point to note that numerous studies and meta-analyses have clearly demonstrated a predictive value for both genotyping\(^1\) and numerous studies and meta-analyses have clearly demonstrated a predictive value for both genotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) and or phenotyping\(^1\) 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riers of the CYP2C19*2 allele (9.9% versus 8.0%, respectively). A similar risk relationship was observed for the occurrence of stent thrombosis in TRITON-TIMI 38 and the genetic substudy (1.1% in the prasugrel cohort37 versus 0.8% in clopidogrel-treated *2 noncarriers11). In other words, and from a more provocative point of view, knowing the CYP2C19*2 genotype of an individual patient may render it unnecessary to use a more potent antiplatelet agent such as prasugrel when keeping in mind the bleeding risk associated with the drug.

In certain clinical scenarios, genotyping alone may help guiding antiplatelet treatment of P2Y12 receptor targeting drugs. This could be the case in the run-up to high-risk coronary stenting procedures such as planned left-main stenting or multiple vessel stenting, in which genotyping beforehand may allow for roughly predicting the presumed response to standard clopidogrel treatment before intake of the drug. Patients could then be pretreated with an intensified antiplatelet treatment regimen in preparation to the procedure. Specifically for CYP2C19*2 homozygous patients, more potent drugs such as prasugrel or ticagrelor may be a better first choice treatment option because about 1 of 2 patients (see Figure 2) in this specific cohort exhibit a high on-clopidogrel treatment platelet reactivity, which cannot be overcome in all of them by just intensifying the dose of clopidogrel.42 In addition, when platelet function assays are unavailable or when patients are under the influence of GP IIb/IIIa receptor inhibitors, which obviates the possibility to assess clopidogrel response for most available assays, genotyping may provide prompt information on clopidogrel bioactivation capacities. Further clinical scenarios could be assumed in patients on ticagrelor or prasugrel treatment, also keeping in mind that their response to clopidogrel cannot be assessed with platelet function testing at that time. Regardless of whether their primary ischemic event was considered as an ACS or not some patients may have bleeding events or from clinically relevant side effects of the respective drug. In addition, contraindications may become obvious or may arise before or while being on drug treatment that preclude from continuing further drug administration. Latter aspects may directly affect morbidity and mortality risk but may also be a cause for noncompliance in the individual patient, and a clinical decision must be made whether or not to switch them over to clopidogrel. Non-CYP2C19*2 carriers would be excellent candidates to switch in such situations because their risk for HPR on clopidogrel is lowest (see also Figure 2). Moreover, genotyping could play a role during a clinical risk profile assessment for PCI-treated patients in general but specifically for patients with a history of prior stent thrombosis. In this instance, questions always arise in how far this event may have been related to technical shortcomings at the index procedure (eg, stent underexpansion) or to treatment failure of the prescribed antiplatelet treatment.

Finally, when considering the usefulness of genetic testing from an economic point-of-view, it is important to consider that clopidogrel is already available in a generic version in many countries now. This may play a role in selected cases when one considers the higher daily therapy costs for newer antiplatelet agents such as prasugrel or ticagrelor.

II. Scenarios Favoring a Combined Phenotyping/Genotyping Approach

One must be aware, however, of the circumstance that a major shortcoming of genotyping alone is surely the uncertainty with which the clopidogrel response is predicted as the determined genotype can never surely predict the clopidogrel responder phenotype.9 This means, for example, that patients across all CYP2C19*2 genotypes (wt/wt or wt/*2 or *2/*2) could end up as enhanced, normal, or low responders to clopidogrel. Thus, a combined approach of both genotyping and simultaneous platelet function testing may show the greatest promise and certainty for future guidance of tailored antiplatelet treatment. The Thrombocyte Activity Reassessment and GEnoTyping for PCI (TARGET-PCI) trial (ClinicalTrials.gov Identifier: NCT01177592) is currently addressing this issue with a combined approach of platelet function testing and genotyping (including the determination of CYP2C19*2 carrier status). Other ongoing studies that try to prove the concept in how far a genotyping-guided approach may improve the outcome of PCI-treated patients in need of sufficient P2Y12 receptor inhibition are the Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment (GIANT) trial (ClinicalTrials.gov Identifier: NCT01134380) and the Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes Study (GeCCO) (ClinicalTrials.gov Identifier: NCT00995514).

In general, it seems unlikely that genotyping could be expected to substitute for platelet function testing, as only the latter reflects the influence of all extrinsic (eg, com- dication) and intrinsic (eg, genetic variants) variables that act in concert on clopidogrel bioactivation and ultimately on the measured response to the drug. Moreover, it was shown that a CYP2C19*2 carrier status could only account for about 5% of the antiplatelet response to clopidogrel.34 However, genotyping can provide important confirmatory information for platelet function testing results when it comes to the question in how far an observed low responder status to clopidogrel is likely to be stable over time or not. Clinical scenarios may also exist, where platelet function testing only reflects a snapshot of the patient’s platelet reactivity, which is subject to change over time. In ACS patients, for example, platelets are highly activated during the event43 and are likely to settle to a more quiescent state later on. Genotyping may help to better distinguish durability or instability of a measured platelet response. Thus, in everyday clinical practice a
step-by-step approach may prove useful where the phenotype is determined contemporary to the PCI procedure by platelet function testing and genotyping could be performed later on before the patient is discharged. The combined information may help to find the best treatment for the individual patient during (a) the acute phase surrounding the procedure and (b) for the chronic phase of treatment that follows. It may well be that different time periods for the individual patient may long for different potency levels of the prescribed P2Y12 receptor inhibitor. A patient may need more potent drugs such as prasugrel or ticagrelor in the acute setting but may be efficiently treated with clopidogrel later on.

Reflecting the growing body of evidence for a predictive value of both genotyping and platelet function testing in clopidogrel-treated patients undergoing coronary stenting, recently updated “ACCF/AHA Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction” now include new class IIb recommendations for both approaches (level of evidence: B for platelet function testing, level of evidence: C for CYP2C19*2 genotyping). With randomized studies including genotyping-directed treatment options still lacking, these guideline recommendations offer the treating physician some reassurance in case one opts to change treatment, based on testing results. Clinical scenarios where genotyping or combined genotyping/phenotyping may help to guide antiplatelet treatment are summarized in Figure 3.

Concluding Remarks

It was in 1999 and 2 years after the approval of the second-generation thienopyridine clopidogrel by the FDA, when the first case of clopidogrel treatment failure was reported in the literature. Since then, it took more than a decade to elucidate the drug’s pharmacological and pharmacogenetic properties. Nowadays, we all know that the drug works well in most but not in all patients and the phenomenon of clopidogrel response variability as well as its association with genetic variants is well perceived. More potent drugs such as prasugrel or ticagrelor are available, and an individualized approach of antiplatelet treatment seems logical in this circumstance. Different clinical scenarios may favor a genotyping approach only, but in most scenarios the comprehensive information received from both phenotyping and genotyping will provide the perception necessary to build treatment decisions on.

Disclosures

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References


**Response to Sibbing, Bernlochner and Kastrati**

Guillaume Paré, MD, MSc; John W. Eikelboom, MBBS, MSc

We agree with Sibbing and colleagues that *CYP2C19* loss-of-function alleles are a determinant of pharmacodynamic response to clopidogrel and clinical outcome. Evidence of association is, however, insufficient to justify the introduction of a new laboratory test into routine clinical practice; we also need evidence that a therapeutic strategy based on the results of testing will yield worthwhile benefits for patients. In the case of *CYP2C19* genetic testing, there are strong grounds to expect that any benefit of testing will be modest and difficult to demonstrate. First, compared with clinical risk factors, genetic determinants of response are a relatively minor determinant of risk of cardiovascular events following PCI; for example, lack of compliance with clopidogrel therapy is far more important and is also potentially modifiable. Second, *CYP2C19* loss-of-function alleles account for only a small fraction of the heritability of clopidogrel response; other genetic polymorphisms appear to account for most of the response variability but are as yet undiscovered. Third, because any impact of *CYP2C19* polymorphisms is likely to be small, distinguishing their effects from those of potential confounders will require an adequately powered randomized controlled trial that will be costly and logistically challenging. We agree that individualizing antiplatelet therapy according to the results of laboratory testing is an attractive and exciting concept but the utility of this approach remains unproven and has not been supported by recent trial results (eg, GRAVITAS, TRIGGER PCI). Until such times, we believe that the best outcomes for patients will be obtained by basing treatment decisions on the overall results of large randomized controlled trials.
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