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

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

CYP2C19 Genetic Testing Should Not Be Done in All Patients Treated With Clopidogrel Who Are Undergoing Percutaneous Coronary Intervention

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Clopidogrel when added to aspirin reduces major vascular events in patients undergoing percutaneous coronary intervention (PCI). Recent reports have suggested that common genetic variants involving hepatic cytochrome P450 system enzymes that convert clopidogrel to its active metabolite are associated with an increased risk of cardiovascular events. Specifically, patients who are carriers of 1 or more loss-of-function CYP2C19 alleles (including the *2 and *3 alleles) have reduced conversion of clopidogrel to its active metabolite, decreased platelet inhibition, and an increased risk of myocardial infarction, death, and stent thrombosis compared with noncarriers. Based on these findings and on related pharmacokinetic and pharmacodynamic data (NCT01123824), the United States Food and Drug Administration (FDA) has issued a “black box” warning of reduced effectiveness of clopidogrel in patients who are carriers of 2 loss-of-function alleles (so-called poor metabolizers) and has suggested that affected individuals receive a higher dose of clopidogrel or an alternative antiplatelet agent. This warning has led some investigators to conclude that all patients undergoing PCI with planned clopidogrel therapy should undergo CYP2C19 genetic testing.

Response by Sibbing, Bernlochner, and Kastrati on p 521

In this report, we critically review the evidence for routine CYP2C19 testing in patients undergoing PCI according to established criteria for the implementation of a screening test in clinical practice.

Summary of the Evidence Linking CYP2C19 Loss-of-Function Alleles to Clopidogrel Response and Cardiovascular Risk

Clopidogrel is a prodrug that must undergo 2-step hepatic metabolism by enzymes of the CYP system to form the active moiety that inhibits the platelet P2Y12 receptor. Common loss-of-function variants involving the CYP2C19 gene have been conclusively demonstrated to influence clopidogrel active metabolite levels and levels of platelet inhibition (Figure 1), and an increasing number of clinical reports link loss-of-function alleles with adverse clinical outcomes.

Estimates from a meta-analysis of observational studies of patients with coronary artery disease treated with clopidogrel (n=9685), most of whom were undergoing PCI, suggest that carriage of 1 loss-of-function CYP2C19 allele is
associated with a 1.55-fold increased risk of major adverse cardiovascular events (95% confidence interval, 1.11–2.17; \(P=0.01\)) and carriage of 2 alleles is associated with a 1.76-fold increase (95% confidence interval, 1.24–2.50; \(P=0.002\)). However, observational studies are subject to confounding, and because all of the patients included in the meta-analysis were treated with clopidogrel (ie, there was no untreated control group), these data cannot establish whether the increased risk of adverse outcomes linked with carriage of \(\text{CYP2C19}\) loss-of-function alleles is attributable to reduced clopidogrel metabolism or whether it might be mediated through alternative mechanisms that do not involve clopidogrel.

A possible association between \(\text{CYP2C19}\) loss-of-function alleles and cardiovascular risk has also been examined in the context of 3 randomized trials involving acute coronary syndrome (ACS) patients randomly assigned to receive clopidogrel versus placebo (CURE\(^{13}\)), prasugrel (TRITON\(^{7,14}\)), or ticagrelor (PLATO\(^{15}\)), respectively. The main advantage of evaluating the association in the context of a randomized trial is that the design “adjusts” for any impact of \(\text{CYP2C19}\) loss-of-function alleles on outcome that is unrelated to its effect on clopidogrel metabolism. None of the analyses from randomized, controlled trials demonstrated an association between \(\text{CYP2C19}\) loss-of-function alleles and outcome in control patients (ie, patients not treated with clopidogrel), thus providing no evidence that \(\text{CYP2C19}\) predicts outcome independent of its effect on clopidogrel metabolism. However, in analyses involving 5059 patients enrolled in the CURE trial, there was also no evidence that \(\text{CYP2C19}\) loss-of-function alleles modified the benefits of clopidogrel compared with placebo (\(P\) heterogeneity=0.84), including a separate analysis of 736 patients undergoing PCI with stent insertion (\(P\) heterogeneity=0.37). Likewise, the analyses from the PLATO trial involving 10 285 ACS patients failed to demonstrate a significant effect of \(\text{CYP2C19}\) loss-of-function alleles on the benefit of ticagrelor compared with clopidogrel (\(P\) heterogeneity=0.46). Results for patients undergoing PCI have not been separately reported. In contrast with the results of the CURE and PLATO trials, analyses from the TRITON trial demonstrated a nominally significant interaction between \(\text{CYP2C19}\) loss-of-function alleles and treatment with prasugrel compared with clopidogrel (\(P\) heterogeneity=0.046), a finding that is consistent with a modest impact of the \(\text{CYP2C19}\) loss-of-function allele on outcome in clopidogrel-treated patients.

Pharmacogenetics as a Screening Test
Laboratory testing is often used to screen for conditions in individuals who do not have signs or symptoms of disease. Before any new screening strategy is adopted, the clinical usefulness of a new screening strategy can be evaluated using the WHO criteria first published by Wilson and Junger in 1968\(^{16}\) and recently adapted by Mosca.\(^{17}\) Key criteria are presented in Table 1. The goal of pharmacogenetic testing in patients undergoing PCI is to identify those who are at increased risk of major cardiovascular events and thus might benefit from an alternative antiplatelet treatment. In this respect, pharmacogenetic testing to identify patients who carry 1 or more \(\text{CYP2C19}\) loss-of-function polymorphisms is no different from screening for other conditions. We believe that it is instructive to evaluate \(\text{CYP2C19}\) testing by using the same rigorous criteria.

Critical Evaluation of the Clinical Usefulness of \(\text{CYP2C19}\) Screening in Patients Undergoing PCI
We evaluated the clinical usefulness of \(\text{CYP2C19}\) screening using the criteria presented in Table 1.

Is There a Convenient and Validated Test of \(\text{CYP2C19}\) Genotype?
Validated \(\text{CYP2C19}\) genotyping methods are well established and yield reproducible results with low error rates in the majority of patients. For the present, however, testing for the \(\text{CYP2C19}\) loss-of-function alleles is largely confined to research settings. New technologies that enable rapid testing in the clinic are being developed and could be made available at a reasonable cost if deemed necessary.

Does \(\text{CYP2C19}\) Testing Provide Clinically Significant Prognostic Value Above and Beyond That Provided by Traditional Risk Factors?
\(\text{CYP2C19}\) testing appears to provide prognostic value beyond that provided by traditional risk factors, but there is uncertainty about the strength of the association between genotype and clinical outcomes. Estimates of relative risk from individual studies are highly variable, ranging from a 1.5- to 5-fold\(^{8,11}\) increase in major cardiovascular events associated with carriage of a loss-of-function \(\text{CYP2C19}\) allele. It is unclear to what extent differences in patient presentation

<table>
<thead>
<tr>
<th>Table 1. Criteria for the Evaluation of (\text{CYP2C19}) Genotype as a Screening Test</th>
</tr>
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<tbody>
<tr>
<td>Is there a convenient and validated test of (\text{CYP2C19}) genotype?</td>
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<td>Does (\text{CYP2C19}) testing provide clinically significant prognostic value above and beyond that provided by traditional risk factors?</td>
</tr>
<tr>
<td>Do we know how to interpret the results of (\text{CYP2C19}) testing?</td>
</tr>
<tr>
<td>Does intervention that alters the risk factor lead to clinical benefit?</td>
</tr>
<tr>
<td>What are the direct and indirect risks of screening?</td>
</tr>
</tbody>
</table>
Because small trials are subject to greater potential for publication bias than large trials, and a fixed-effects model avoids a disproportionate effect of small studies on the overall estimate. Unadjusted analyses are more applicable to clinical practice than adjusted analyses because the impact of genotype is generally not adjusted for in clinical practice. It is unclear whether the weak association that we demonstrated between CYP2C19 loss-of-function alleles and cardiovascular risk is clinically important. Perhaps even more importantly, the lack of impact of the loss-of-function allele on the benefits of clopidogrel compared with placebo in the CURE trial and a similar lack of interaction in the PLATO trial raise questions about the relevance of the results of testing for patient care.

Do We Know How to Interpret the Results of CYP2C19 Testing?
To be useful for clinicians and patients, the results of a screening test must lend itself to nonambiguous interpretation. In the case of pharmacogenetic testing for clopidogrel, there is still uncertainty as to the genotype at risk. This uncertainty stems in part from the observation that CYP2C19 loss-of-function allele carriers (ie, individuals carrying either 1 or 2 loss-of-function alleles) are quite frequent in the population but have only modestly increased risk. Poor metabolizers (ie, individuals carrying 2 loss-of-function alleles) have a higher risk but are uncommon, at least in Caucasian populations, where they comprise an estimated 2% of individuals.11,13,15

There is also uncertainty on which loss-of-function variants to test. The most common CYP2C19 loss-of-function polymorphism is the *2 allele, which comprises >99% of all loss-of-function alleles in Europeans. The *3 allele is found in <1% of Europeans but represents >5% of all CYP2C19 alleles in Asian populations.21,22 Up to 14% of Chinese have the *2/*2 genotype,

<table>
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<tr>
<th>Study</th>
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<th>No. of Events</th>
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<td>5</td>
<td>243</td>
<td>7</td>
<td>554</td>
<td>1.65 (0.47–5.36)</td>
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</tr>
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<td>TRITON15</td>
<td>100</td>
<td>46</td>
<td>395</td>
<td>83</td>
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<td>FAST–MI10</td>
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<td>63</td>
<td>635</td>
<td>193</td>
<td>1573</td>
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<td>PLATO15</td>
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<td>149</td>
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<td>CURE13</td>
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<tr>
<td>Overall</td>
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<td>453</td>
<td>4583</td>
<td>1068</td>
<td>11 829</td>
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<td>0.06</td>
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<tr>
<td>Overall w/o CURE</td>
<td>83</td>
<td>401</td>
<td>3932</td>
<td>889</td>
<td>9943</td>
<td>1.17 (1.04–1.33)</td>
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PCI indicates percutaneous coronary intervention; LOF, loss of function; OR, odds ratio; and CI, confidence interval.

ORs are unadjusted for clinical covariables. Meta-analysis ORs and P values were derived using a fixed-effect model.

Adapted with permission from Mega JL et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA. 2010;304:1821–1830. Copyright 2010 American Medical Association. All rights reserved.11

Collectively, the available data demonstrate a statistically significant association between CYP2C19 loss-of-function alleles and cardiovascular risk, but the strength of the association is modest and varies according to outcome. A pooled analysis unadjusted for baseline characteristics, restricted to observational cohorts involving at least 500 patients and using a fixed-effects model, yielded an even weaker 1.12-fold increased risk associated with carriage of 1 CYP2C19 loss-of-function allele and a 1.22-fold increase in those who carry 2 alleles (Tables 2 and 3). We believe that these estimates are more reliable than those obtained from previous meta-analyses because small trials are subject to greater potential for publication bias than large trials, and a fixed-effects model avoids a disproportionate effect of small studies on the overall estimate. Unadjusted analyses are more applicable to clinical practice than adjusted analyses because the impact of genotype is generally not adjusted for in clinical practice. It is unclear whether the weak association that we demonstrated between CYP2C19 loss-of-function alleles and cardiovascular risk is clinically important. Perhaps even more importantly, the lack of impact of the loss-of-function allele on the benefits of clopidogrel compared with placebo in the CURE trial and a similar lack of interaction in the PLATO trial raise questions about the relevance of the results of testing for patient care.

Table 2. Meta-Analysis of Effect of Loss-of-Function Carriage on Cardiovascular Death, Myocardial Infarction, or Ischemic Stroke in Studies With >500 Participants

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<th>Study</th>
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but outcomes after PCI do not appear to differ markedly in Asian as compared with Caucasian populations.23

Furthermore, an effect of the CYP2C19 gain-of-function allele (*17) on ischemic13,24 and bleeding25 end points has recently been described. The effect of this allele in conjunction with loss-of-function alleles requires further evaluation before the results of CYP2C19 testing can be properly interpreted.

### Does Intervention That Alters the Risk Factor Lead to Clinical Benefit?

Even if a convenient, validated, and readily interpretable test exists that provides clinically significant prognostic value above and beyond that provided by traditional risk factors, it is unlikely to be of value if there are no interventions that can overcome the increased risk of cardiovascular disease associated with a positive test result. Pharmacological studies have shown that a higher dose of clopidogrel or alternative antiplatelet therapies such as prasugrel and ticagrelor provide enhanced platelet P2Y12 receptor inhibition in patients who are poorly responsive to standard doses of clopidogrel14,15,26,27 and improved clinical outcomes.7,8,28–30 However, enhanced platelet inhibition was also observed in clopidogrel responders, and there is no evidence that a management strategy based on the results of pharmacogenetic or pharmacodynamic testing compared with usual care (without testing) will lead to a benefit for patients.

Several randomized, controlled trials are examining the potential benefits of a management strategy based on the results of routine pharmacogenetic or pharmacodynamic testing compared with usual care (Table 4). The recently completed GRAVITAS trial32 involved 2214 patients who had undergone PCI with placement of 1 or more drug-eluting stents and failed to demonstrate a benefit of modifying antiplatelet therapy, based on the results of routine pharmacodynamic testing compared with usual care. The trial was powered to demonstrate a 50% reduction in death, myocardial infarction, or stent thrombosis with high-dose compared with standard-dose clopidogrel in patients with high on-treatment platelet reactivity but had unexpectedly low event rates. The TRIGGER-PCI had a planned enrolment of 2150 patients with ACS undergoing PCI but was stopped early because of lower than expected event rates (NCT00910299). If there is a clinical benefit of tailored antiplatelet therapy based on the results of CYP2C19 testing, it is likely to be evident in patients undergoing PCI who are at high risk of stent thrombosis. However, such patients have multiple other risk factors for stent thrombosis (Table 515), each of which appears to be at least as important as carriage of a CYP2C19 loss-of-function allele. Premature discontinuation of clopidogrel is the most important potentially modifiable risk factor, associated with a >40-fold increase in risk of stent thrombosis.33

An approach that is likely to be more effective and cost-efficient than routine CYP2C19 testing is to use a newer antiplatelet drug that has been shown in randomized trials to be more effective than standard-dose clopidogrel irrespective of genotype. The PLATO trial15 showed that ticagrelor is superior to clopidogrel for the prevention of major cardiovascular events, including mortality, in a broad cross section of patients with ACS. There was no net increase in major bleeding with ticagrelor compared with clopidogrel, although ticagrelor increased non–coronary artery bypass graft–related major bleeding. Ticagrelor has already been approved in Europe and could replace clopidogrel across the spectrum of patients with ACS and those undergoing PCI with stent insertion, thereby eliminating the need to consider CYP2C19 pharmacogenetic testing. There is no need for genotyping if the alternative treatment is superior to standard care irrespec-

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<tr>
<td>TRITON</td>
<td>100</td>
<td>4</td>
<td>38</td>
<td>83</td>
<td>1064</td>
<td>1.44 (0.41–3.73)</td>
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<tr>
<td>FAST-MI</td>
<td>70</td>
<td>10</td>
<td>58</td>
<td>193</td>
<td>1573</td>
<td>1.51 (0.71–2.91)</td>
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<tr>
<td>RECLOSE</td>
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<td>2</td>
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<td>14</td>
<td>525</td>
<td>3.21 (0.44–12.6)</td>
<td>0.17</td>
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<tr>
<td>ISAR</td>
<td>100</td>
<td>3</td>
<td>47</td>
<td>119</td>
<td>1805</td>
<td>1.01 (0.23–2.83)</td>
<td>1</td>
</tr>
<tr>
<td>Intermountain</td>
<td>100</td>
<td>3</td>
<td>14</td>
<td>141</td>
<td>906</td>
<td>1.53 (0.33–5.07)</td>
<td>0.47</td>
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<tr>
<td>CURE</td>
<td>15</td>
<td>4</td>
<td>61</td>
<td>178</td>
<td>1880</td>
<td>0.70 (0.20–1.72)</td>
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<tr>
<td>Overall</td>
<td>73</td>
<td>26</td>
<td>244</td>
<td>728</td>
<td>7753</td>
<td>1.22 (0.80–1.85)</td>
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<tr>
<td>Overall w/o CURE</td>
<td>91</td>
<td>22</td>
<td>183</td>
<td>550</td>
<td>5873</td>
<td>1.43 (0.90–2.27)</td>
<td>0.13</td>
</tr>
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</table>
A case for genotyping can only be made if the choice of therapy—standard clopidogrel or an alternative antiplatelet strategy—will differ depending on genotype (Figure 2).

What Are the Direct and Indirect Risks of Screening?

All of the potential costs and consequences of pharmacogenetic testing should be taken into account when considering the potential benefits and risks of CYP2C19 screening.

The most obvious costs are related to genotyping, which includes the laboratory infrastructure and personnel to provide genetic results with a fast turnaround time, switching to an alternative antiplatelet strategy in affected individuals, and the costs of cardiovascular events prevented and bleeding.
caused by the change in treatment. Pharmacoeconomic considerations are even more important when the risk conferred by carriage of 1 or more CYP2C19 loss-of-function alleles is small. The cost-effectiveness of implementing routine CYP2C19 screening is likely to compare unfavorably with alternative strategies such as measures to increase compliance with antiplatelet therapy, the single most important risk factor for stent thrombosis.33

The results of testing could also have adverse consequences. For example, an individual labeled as “unresponsive to clopidogrel, based on genes” who is unable to afford the alternative treatment might be tempted to forgo antiplatelet therapy altogether, thereby further increasing the risk of major cardiovascular events.

What Are the Implications for Future Research?
The results of clinical trials comparing management strategies based on the results of routine CYP2C19 genetic testing with usual care that are currently underway will provide additional insights into the potential benefits and risks of routine testing. In parallel with these studies, however, we urgently require further studies to identify other genetic determinants of response to clopidogrel. Best estimates suggest that the CYP2C19 loss-of-function alleles account for only 12% of the variability in response to clopidogrel,9 whereas 72% of the variability is heritable. This implies that most of the variability is accounted for by other as-yet undiscovered genetic factors. We also need reliable estimates of the effect of genetic determinants of response to clopidogrel on different types of ischemic events and on bleeding. Among patients with ACS and/or those undergoing PCI, stent thrombosis is less common but more sensitive to clopidogrel treatment and the potential impact of CYP2C19 loss-of-function alleles than other outcomes such as myocardial infarction or death. Most cases of stent thrombosis result in myocardial infarction or death, which are counted as major adverse cardiovascular events, but the limitation of using this composite is that the effects of a loss-of-function allele on stent thrombosis could be masked by myocardial infarctions and deaths that are unrelated to stent thrombosis (Figure 3). Even if an effect of CYP2C19 loss-of-function alleles on stent thrombosis is evident, we also need information on bleeding because it is possible that the increase in stent thrombosis is more than compensated for by a reduction in bleeding.

The highest-quality evidence concerning the impact of genetic testing on patient outcomes is likely to be obtained from appropriately designed, randomized, controlled trials that compare a strategy of modifying treatment, based on the results of genetic screening with standard care. Such trials will not only provide reliable estimates of the effect of genotype on drug response but will also take into account the potential impact of the testing procedure itself on patient outcomes. For example, implementation of genetic testing in real-life settings (as opposed to retroactive analysis of stored samples) could delay administration of effective antiplatelet therapies and thereby compromise patient outcomes.

Conclusion
The role of CYP2C19 loss-of-function alleles in determining the pharmacokinetics and pharmacodynamics of clopidogrel has been clearly demonstrated, and there is convincing evidence that CYP2C19 loss-of-function alleles are associated with adverse outcomes. However, uncertainty remains about the strength of association and the impact of CYP2C19 loss-of-function alleles on the net clinical benefit of clopidogrel treatment. Perhaps, most importantly, we do not know whether a treatment strategy based on the results of routine laboratory screening for CYP2C19 loss-of-function alleles improves patient outcome compared with usual care. In the absence of this information, we cannot support recommendations for mandatory testing of patients undergoing PCI.

We accept that it is not realistic to mandate a randomized, controlled trial for every genetic variant that is implicated as a modulator of drug action.34 However, in the case of CYP2C19 loss-of-function alleles, the best estimates that are currently available suggest that the effect of these alleles is so small that their impact can only be reliably quantified by using randomization to minimize the impact of potential confounders. If such trials are deemed worthwhile, it is imperative that they are adequately powered to avoid inconclusive results such as those obtained in the recently completed GRAVITAS trial and the prematurely discontinued TRIGGER-PCI trial.

Additional studies are also required to identify as-yet undiscovered genetic variants that could play a much more important role than CYP2C19 in determining response to clopidogrel. Any future genetic treatment algorithms must
also take into account the role of “traditional” risk factors in determining whether patients who are carriers of a CYP2C19 loss-of-function allele will benefit from alternative platelet therapies.

Despite our cautionary tone concerning the routine implementation of CYP2C19 for patients undergoing PCI, we believe that the future is bright for genetic testing. First, additional trials that are underway will help to resolve uncertainly about the clinical usefulness of CYP2C19 testing and will also serve to define the optimal approach to addressing questions of this nature in the future. Second, as the genetic architecture of clopidogrel response is elucidated and a higher fraction of the predicted heritability is accounted for, genetic testing that incorporates CYP2C19 testing will almost certainly gain in importance among patients who will be treated with clopidogrel. Finally, advances in testing technologies and informatics are expected to make the results of complete genetic testing more widely available in the general population, thereby assisting physicians to select the most appropriate antiplatelet therapy for individual patients without awaiting the results of additional laboratory testing.

Disclosures
Dr Paré is a member of the Thrombosis and Atherosclerosis Research Institute and has received honoraria from Sanofi and Bristol-Myers Squibb. Dr Eikelboom has received honoraria and research support from companies that develop and market existing and new antiplatelet drugs including Astra-Zeneca, Bayer, Bristol-Myers-Squibb, Eli-Lilly, and Sanofi.

References


Response to Paré and Eikelboom

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

Drs Paré and Eikelboom provide a very contemplative commentary and sound a note of caution in relation to CYP2C19 genetic testing in clopidogrel-treated patients. They present the results of their own meta-analysis on the effect of CYP2C19*2 allele carriage on cardiovascular death, myocardial infarction, or stroke. While finding only a modest association for this combined end point, they state that the strongest association of *2 appears to be with stent thrombosis, an end point that Paré and Eikelboom did not analyze. The authors’ assertion that the advent of ticagrelor may deem genotyping unnecessary is debatable. High-potency P2Y12 receptor blockers such as prasugrel or ticagrelor have been evaluated for their safety and efficacy profiles only in acute coronary syndrome patients thus far. However, the majority of patients undergoing coronary stenting are in a stable condition, and it may well be that in these patients, the balance between the reduction of ischemic events and the induction of bleeding is unfavorable. Moreover, the history of clopidogrel, with about a decade needed after its approval to really understand the pharmacokinetic and pharmacodynamic properties, has taught us to show a healthy mistrust when new and promising drugs are introduced. In this context, just recently, a first report on high on-treatment platelet reactivity with prasugrel has set the stage to study these newer drugs more thoroughly. A short while ago, when clopidogrel was the single choice of treatment available to sufficiently inhibit platelets with an acceptable safety profile, there was much less need for genotyping or phenotyping to individualize treatment regimens. Nowadays, however, the armamentarium of drugs that target the P2Y12 platelet receptor is rapidly increasing. With different treatment options available now, more guidance to tailor antiplatelet therapy is certainly necessary. Genotyping alone or, even better, in combination with platelet function testing to assess the level of P2Y12 receptor inhibition, will help us to sort out the best drug for the individual patient.
CYP2C19 Genetic Testing Should Not Be Done in All Patients Treated With Clopidogrel Who Are Undergoing Percutaneous Coronary Intervention
Guillaume Paré and John W. Eikelboom

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