Impact of Cytochrome P450 2C19 Loss-of-Function Polymorphism and of Major Demographic Characteristics on Residual Platelet Function After Loading and Maintenance Treatment With Clopidogrel in Patients Undergoing Elective Coronary Stent Placement

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Objectives

The aim of this study was to evaluate the relative impact of demographic and clinical variables versus the cytochrome P450 2C19 (CYP2C19) polymorphism on antiplatelet effects of clopidogrel.

Background

Platelet responses to clopidogrel show a marked interindividual variability with substantial impact on clinical outcome. Several demographic and clinical characteristics as well as a polymorphism of CYP2C19 have been described as predictors for a low response to clopidogrel.

Methods

This analysis enrolled 760 patients undergoing elective coronary stent implantation after loading with 600 mg of clopidogrel. Residual platelet aggregation was determined by optical aggregometry (adenosine diphosphate 5 μmol/l) before discharge. We analyzed the predictive value of the CYP2C19*2 polymorphism and baseline variables for an insufficient antiplatelet response by multivariable regression analysis and classification and regression trees analysis and determined the proportion responsible for the antiplatelet response of these predictors by multivariable linear regression analysis.

Results

Major independent predictors for an insufficient antiplatelet response to clopidogrel were CYP2C19*2 carrier status (odds ratio [OR]: 2.74; 95% confidence interval [CI]: 1.93 to 3.90) together with age (OR: 1.03; 95% CI: 1.01 to 1.05), diabetes mellitus (OR: 1.75; 95% CI: 1.19 to 2.56), and body mass index (OR: 1.06; 95% CI: 1.02 to 1.11). The classification and regression trees analysis demonstrated that CYP2C19*2 carrier status followed by diabetes mellitus was the best discriminator between a sufficient and an insufficient antiplatelet response to clopidogrel. The full linear regression model including all these parameters could only explain 11.5% of the antiplatelet response (5.2% by CYP2C19*2 carrier status alone).

Conclusions

Thus, our study does not suggest that, in patients critically dependent on adequate platelet inhibition, genotyping alone or in combination with clinical factors can replace phenotyping of platelet function. (Effect of Clopidogrel Loading and Risk of PCI [EXCELSIOR]; NCT00457236). (J Am Coll Cardiol 2010;55:2427–34) © 2010 by the American College of Cardiology Foundation

Dual antiplatelet therapy with aspirin and clopidogrel is the established treatment for prevention of stent thrombosis after percutaneous coronary interventions (PCI) (1,2). The efficacy of such treatment is hampered by the large variability of platelet inhibition by clopidogrel (3). Several independent clinical studies have demonstrated that patients with high residual platelet reactivity on clopidogrel were at increased risk for stent thrombosis and other car-
The variability of clopidogrel responses is a consequence of variable formation of the active metabolite (9,10). The highly polymorphic cytochrome P450 (CYP) system of the liver plays a key role in this respect (11,12). Specifically, carriers of the loss-of-function allele of CYP2C19 generate less amounts of the active metabolite of clopidogrel, resulting in a decreased antiplatelet effect, and therefore carry an increased risk of major adverse cardiac events after stent placement compared with wild-type homozygotes of this gene (8,13–17). After documentation of the impact of the variability of the clopidogrel effect on clinical outcome, there has been growing interest in platelet function testing to guide antiplatelet therapy (18). Alternatively, the development of means to predict responses to clopidogrel without performing platelet function assays is highly attractive. To this end, testing for CYP polymorphisms, specifically CYP2C19*2, has been suggested (17,19,20). Irrespective of genetic background, however, there are a number of demographic and clinical variables that interfere with clopidogrel responses, such as age, body mass index (BMI), and diabetes (6,8,21,22). The relative role of these demographic and clinical variables versus the on-clopidogrel residual platelet aggregation (RPA) at day 1 after PCI had a 3-fold increase in the 1-year incidence of death and myocardial infarction (MI) after elective stent placement as compared with patients with an intermediate or low RPA (8). The threshold for high on-clopidogrel RPA identified by this study was 14% after stimulation with 5-μmol/l adenosine diphosphate (ADP).

The variability of clopidogrel responses is a consequence of single-center study conducted in a referral center setting in Bad Krozingen, Germany. We did not include patients with acute MI according to the European Society of Cardiology/American College of Cardiology consensus document (23); patients taking chronic oral anticoagulation or thienopyridine treatment within the last 2 weeks before admission; patients with contraindications to aspirin, clopidogrel, or heparin; and patients with cancer or hemodialysis. The study was approved by the ethics committee of the medical faculty of the University of Freiburg, Germany. All patients gave written informed consent.

**Study protocol.** Before the intervention all patients received a loading dose of 600 mg of clopidogrel. Catheterization was timed according to the routine schedule of the catheterization laboratory. The PCI with stent placement was performed as described previously (3,6). The choice of stent type, bare-metal, paclitaxel-eluting, or sirolimus-eluting stent, was left to the operator’s discretion. All patients received an intra-arterial dose of 100 to 140 U/kg heparin; glycoprotein IIb/IIIa inhibitors were not allowed except for bail-out. After PCI, all patients received aspirin (≥100 mg/day), lifelong, and clopidogrel (75 mg/day) for 30 days after placement of bare-metal stents or for 6 months after placement of at least 1 drug-eluting stent.

**Platelet function assay.** As described previously (6,24), platelet aggregation was assessed by turbidimetric aggregometry with a 4-channel Bio/Data PAP4 aggregometer (Mölab, Langenfeld, Germany). Blood samples for platelet function testing were drawn before discharge at day 1 after loading with clopidogrel, 2 to 4 h after intake of the first maintenance dose (in the vast majority of patients between 16 and 24 h after loading dose). Samples were drawn into tubes containing 3.8% sodium-citrate (Sarstedt, Nuembrecht, Germany) and processed within 1 h after blood-drawing. We prepared platelet-rich plasma by centrifugation of citrated venous blood at 750 g for 2 min and adjusted to 275 to 325 × 10^9 thrombocytes/l by dilution with platelet-poor plasma from the same patient. We used ADP (Sigma-Aldrich, Munich, Germany) to induce aggregation. Light transmission in platelet-rich plasma was determined 5 min after addition of ADP at a final concentration of 5 μmol/l. Results were expressed as percentage of maximal light transmission with platelet-poor plasma from the same patient as reference (100% aggregation). The coefficient of variation of our optical aggregometry assay is 6.1% (3,6).

**Genotyping by TaqMan polymerase chain reaction.** Determination of genotype was performed as previously described (8). In brief, genomic deoxyribonucleic acid (DNA) was extracted from peripheral potassium ethylenediaminetetraacetic acid-anticoagulated blood with the Flexigene Kit (Qiagen, Hilden, Germany) according to the manufacturer's instruction. After extraction, the concentration of DNA was measured photometrically, and DNA was diluted to a concentration of 5 mg/l. The CYP2C19*2 (681G>A; rs4244285) was genotyped with a commercially available, validated Drug Metabolism Genotyping Assay
(Applied Biosystems, Frankfurt, Germany). After amplification (QPCR Master Mix, Abgene, Hamburg, Germany), reaction mixtures were loaded in an ABI Prism Sequence Detector 7900 (Applied Biosystems). After polymerase chain reaction, fluorescence yield for the 2 different dyes was measured and presented in a 2-dimensional graph.

**Statistical methods.** The sample size calculation based on the 30-day primary end point of EXCELSIOR was published previously (6). For all multivariable analyses, we chose the baseline demographic and clinical variables assessed on admission to hospital with a difference between the 2 strata defined by pre-discharge RPA (≤14% and >14%) at a p value ≤0.20 with or without CYP2C19*2 carrier status (8). For identification of possible predictors for a high on-clopidogrel RPA (RPA >14%) we used multivariable binary logistic regression models with RPA >14% as dependent variable. We also entered all identified variables in a classification and regression trees (CART) analysis to determine the best discriminators for high on-clopidogrel RPA (chi-square automatic interaction detector algorithm, p value adjustment by Bonferroni method). The percentage of variability of on-clopidogrel RPA that could attribute to the variability in independent variables was derived from partial $\eta^2$ calculated by multivariable linear regression analysis with RPA as dependent variable and entering dichotomous variables as fixed factors. To evaluate the improvement in our binary model by adding the CYP2C19*2 carrier status to the model, including only clinical variables, we calculated the net reclassification improvement (based on the methods from Frank Harrell, run in R, Version 2.10.1, R Development Core Team, Vienna, Austria). For all other statistical analyses, we used the SPSS software package, version 18 (SPSS, Inc., Chicago, Illinois). In general, discrete variables are reported as counts (percentages), and continuous variables are reported as mean ± SD. For discrete variables, we tested differences between groups with the chi-square test or Fisher exact test when expected cell sizes were <5. We used the 2-tailed t test to compare continuous variables or the Kruskal-Wallis test between strata. Dashed line displays threshold for high RPA (14%). The p value by Kruskal-Wallis test between strata. The boxes show medians and upper and lower quartiles of the data, whereas the whiskers indicate the minimum and maximum values. ADP = adenosine diphosphate; wt = wild-type.

**Results**

The entire cohort of the EXCELSIOR study comprised 802 patients, of which CYP2C19 genotype as well as pre-discharge RPA results were available from 760 patients. A table of baseline characteristics has previously been published (8). The mean age in our population was 66 years, the proportion of men was 72%, drug-eluting stents were used in 37% of patients, and no patient was treated with a glycoprotein IIb/IIIa inhibitor.

**Variability of on-clopidogrel RPA in strata defined by CYP2C19 genotype.** In the entire cohort, the proportion of patients with high on-clopidogrel RPA was 28.4%. Figure 1 shows a scatter plot of RPA in the 3 strata defined by CYP2C19 genotype: *2* homozygotes (n = 15, 2%), *2* heterozygotes (n = 218, 29%), and wild-type homozygotes (n = 527, 69%). Although there was a highly significant difference in RPA, depending on CYP2C19 genotype, the overlap was considerable. Accordingly, 22.4% of the wild-type homozygotes had to be classified as high on-clopidogrel RPA, whereas 58.7% of the *2* heterozygotes and 53.3% of the *2* homozygotes did not meet the criteria for high on-clopidogrel RPA. Thus, the sensitivity of CYP2C19*2 carrier status for detecting high on-clopidogrel RPA was only 45.1%, whereas the specificity was 75.0%.

**Contribution of CYP2C19 genotype and clinical characteristics to on-clopidogrel RPA.** The baseline demographic characteristics of our study cohort have been published (8). In univariable analyses, the clinical patient characteristics that showed the strongest association to high on-clopidogrel RPA were age, BMI, and diabetes mellitus. In addition, we found significant differences (p < 0.05)
between patients with high on-clopidogrel RPA and those with a low-to-intermediate on-clopidogrel RPA in arterial hypertension, treatment with a nondihydropyridine calcium antagonist (verapamil or diltiazem), and previous balloon angioplasty. Further potentially relevant but nonsignificant differences between the 2 strata (p \leq 0.20) defined by high on-clopidogrel RPA were found in platelet count as well as in treatment with angiotensin-converting enzyme inhibitor and nitrates, previous coronary artery bypass grafting, impaired left ventricular function (ejection fraction <55%), and Canadian Cardiovascular Society angina class III or IV. These variables were included in a multivariable binary logistic regression model for prediction of high on-clopidogrel RPA. As shown in Table 1, this model confirmed that CYP2C19*2 carrier status was the strongest predictor of high on-clopidogrel RPA. Also, age, diabetes mellitus, and BMI prevailed as strong predictors in the multivariable analysis. Other clinical, procedural, and pharmacotherapeutic characteristics with a significant association with high on-clopidogrel RPA in the multivariable model were: treatment with a nondihydropyridine calcium antagonist (verapamil or diltiazem), and a previous balloon angioplasty. Addition of the clinical variables to a logistic regression model that contained only CYP2C19*2 carrier status as independent variable increased chi-square of model from 28.4 to 82.3.

From CART analysis, CYP2C19*2 carrier status again emerged as the strongest variable for classification (Fig. 2). The second most relevant variable was diabetes mellitus, followed by BMI. The frequency of high on-clopidogrel RPA in the classes derived from this CART model varied from 48% in CYP2C19*2 carriers with BMI \geq 26 kg/m² to 16% in nondiabetic CYP2C19 wild-type homozygotes with a BMI <30 kg/m².

Table 1

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19* polymorphism</td>
<td>2.738</td>
<td>1.925–3.895</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>1.031</td>
<td>1.010–1.052</td>
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<tr>
<td>Arterial hypertension</td>
<td>1.348</td>
<td>0.830–2.190</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1.745</td>
<td>1.189–2.562</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.061</td>
<td>1.016–1.109</td>
</tr>
<tr>
<td>Platelets (×10⁹/l)</td>
<td>0.997</td>
<td>0.994–1.000</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>1.065</td>
<td>0.751–1.511</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1.095</td>
<td>0.754–1.590</td>
</tr>
<tr>
<td>Verapamil/diltiazem</td>
<td>2.569</td>
<td>1.185–5.572</td>
</tr>
<tr>
<td>Previous balloon angioplasty</td>
<td>1.509</td>
<td>1.058–2.184</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>1.282</td>
<td>0.783–2.101</td>
</tr>
<tr>
<td>Impaired LV function†</td>
<td>1.100</td>
<td>0.768–1.575</td>
</tr>
<tr>
<td>CCS angina class III or IV</td>
<td>0.667</td>
<td>0.443–1.003</td>
</tr>
</tbody>
</table>

Residual platelet aggregation \geq 14%. *Cytochrome P450 2C19 681G>A; †impaired left ventricular (LV) function (ejection fraction <55%). ACE = angiotensin converting enzyme; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society.
We also analyzed on-clopidogrel RPA as a continuous variable and estimated the individual contribution of the same variables as in the logistic model to the variation of on-clopidogrel RPA in a linear regression model. A linear regression model that only comprises CYP2C19*2 carrier status could explain 4.6% of the variability in on-clopidogrel RPA, whereas the full model comprising CYP2C19*2 carrier status and the clinical variables could explain 11.5%. In the full model (Table 2), we found that 5.2% of the observed variability in RPA could be attributed to CYP2C19*2 carrier status (p < 0.001), 1.0% to age (p = 0.006), 1.0% to BMI (p = 0.008), and 1.2% to the presence or absence of diabetes (p = 0.003).

Classification of the probability of high on-clopidogrel RPA based on clinical characteristics alone. Figure 3 illustrates the interaction of age, BMI, and diabetes in their impact on the percentage of patients with high on-clopidogrel RPA. In nondiabetic subjects, the increase in the proportion of patients with high on-clopidogrel RPA with age and BMI was conspicuous, ranging from 9% in lean (BMI <25 kg/m²), young (age <60 years) patients to 50% in obese (BMI >30 kg/m²), elderly (age >70 years) patients. By contrast, diabetic patients, in general, comprised more patients with high on-clopidogrel RPA than nondiabetic patients, but the effect of age and BMI was less prominent. With a chi-square of 50.7, a logistic regression model that included only clinical variables was less predictive than the full model comprising also CYP2C19*2 carrier status (see the preceding text). The addition of the CYP2C19*2 carrier status significantly improved both reclassification (net reclassification improvement = 0.403, p < 0.001) and the discrimination as calculated by the integrated discrimination improvement (p < 0.001).

When CYP2C19*2 carrier status was not entered (Fig. 4), the CART model identified diabetes mellitus, age, and hypertension as variables with statistically significant relevance to classification. The frequency of high on-clopidogrel RPA varied from 38% in diabetic patients to 16% in nondiabetic patients without hypertension.

In the multivariable linear regression model, the clinical variables without CYP2C19*2 carrier status could explain 6.7% of the variability in on-clopidogrel RPA.

**Discussion**

**Genetic impact on platelet function.** The central message of our analysis of the interaction of genomic and clinical factors with on-clopidogrel platelet function in a large cohort of patients undergoing elective PCI is that the CYP2C19*2 loss-of-function polymorphism and several clinical variables show a statistical highly significant association with high on-clopidogrel RPA. Nevertheless, these

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**Table 2** Multivariable Linear Regression Model for RPA After Stimulation With 5 μmol/l ADP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial η²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19* polymorphism</td>
<td>0.052</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>0.010</td>
<td>0.006</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.001</td>
<td>0.386</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.012</td>
<td>0.003</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.010</td>
<td>0.008</td>
</tr>
<tr>
<td>Platelets (× 10⁹/l)</td>
<td>0.010</td>
<td>0.006</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>0.001</td>
<td>0.403</td>
</tr>
<tr>
<td>Nitrates</td>
<td>&lt;0.001</td>
<td>0.890</td>
</tr>
<tr>
<td>Verapamil/diltiazem</td>
<td>0.010</td>
<td>0.006</td>
</tr>
<tr>
<td>Previous balloon angioplasty</td>
<td>0.007</td>
<td>0.026</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>0.001</td>
<td>0.435</td>
</tr>
<tr>
<td>Impaired LV function†</td>
<td>&lt;0.001</td>
<td>0.945</td>
</tr>
<tr>
<td>CCS angina class III or IV</td>
<td>0.004</td>
<td>0.081</td>
</tr>
</tbody>
</table>

*Cytochrome P450 2C19 681G>A; †impaired LV function (ejection fraction <55%). ADP = adenosine diphosphate; RPA = residual platelet aggregation; other abbreviations as in Table 1.*
variables do not suffice to predict high on-clopidogrel RPA with the precision needed for clinical decision-making. This message is based on 4 key observations: 1) the \textit{CYP2C19*2} loss-of-function polymorphism was the strongest predictor of high on-clopidogrel RPA; 2) diabetes mellitus, age, and BMI were the clinical patient characteristics most strongly associated with high on-clopidogrel RPA; 3) a \textit{CYP2C19*2} carrier status together with all demographic and clinical predictors for high on-clopidogrel could only explain 11.5% of residual platelet reactivity; and 4) the CART derived from these variables did not identify any subgroup in which more than 48% or <16% of the patients showed high on-clopidogrel RPA.

Despite a statistically robust association of \textit{CYP2C19*2} carrier status with high on-clopidogrel RPA, \textit{CYP2C19*2} carrier status accounted for only 4.6% of the variability in on-clopidogrel RPA. A possible explanation for this finding might be that other genomic conditions could play a role as well. However, other CYP polymorphisms that several groups including ourselves previously investigated either had little impact on platelet function during clopidogrel treatment or were too rare to play a role in the given sample size (14,15,25,26). Likewise, we and others did not detect a relevant contribution of known polymorphisms of genes encoding for transporter proteins high on-clopidogrel RPA (26–28), although 1 study reported an association of \textit{ABCB1} polymorphism with clinical outcome in patients taking clopidogrel (29). Thus, according to the current knowledge, we were able to include the most relevant genetic polymorphism. Apart from genetic background, clinical conditions and concomitant drug therapy might interfere with on-clopidogrel RPA. We found that consideration of the clinical conditions in conjunction with \textit{CYP2C19*2} carrier status improved the prediction of high on-clopidogrel RPA, and 11.5% of the variability in on-clopidogrel RPA could be explained by a combination of clinical variables and \textit{CYP2C19*2} carrier status. The strongest clinical patient characteristics to predict high on-clopidogrel RPA were diabetes mellitus, age, and BMI. Considered together, these clinical factors are more relevant for prediction of high on-clopidogrel RPA than \textit{CYP2C19*2} carrier status alone, and addition of \textit{CYP2C19*2} carrier status to these factors could not improve the prediction substantially.

**Impact of medication and patient characteristics on platelet function.** Our findings on diabetes mellitus, age, and BMI are consistent with some but not all clinical studies that investigated factors affecting response to clopidogrel without assessment of the genetic background (21,30,31). Diabetes has also been associated with low response to clopidogrel in patients after coronary intervention (21,30). The impact of age on the response to many drugs is well-known (32). Surprisingly, little is known regarding the interaction of age with clopidogrel response. Only 1 trial has identified an age above 65 years as a possible but not strong predictor for a low antiplatelet response (21).
Data regarding BMI, so far, were inconsistent, because only one analysis could detect an impact of the BMI on the effect of clopidogrel (31). Another multivariable analysis did not confirm BMI as predictive for an insufficient response to clopidogrel (21).

There are 2 previous studies that investigated the relevance of genetic and nongenetic factors for clopidogrel responses (33,34). Aleil et al. (33) identified body weight and CYP2C19*2 carrier status but not diabetes mellitus as independent predictors for a low response to clopidogrel and showed that an increase in maintenance dose can overcome this effect. In the analysis of Geisler et al. (34), nongenetic factors were less-relevant compared with our current study, but age and diabetes mellitus were also identified as significant predictors of clopidogrel response. We attribute the discrepancies with our results to substantially smaller sample sizes (n = 153 and n = 237, respectively) and the inclusion of both stable and unstable patients in the second study.

We identified, apart from the patient characteristics to predict high on-clopidogrel RPA, interaction of nondihydropyridine calcium antagonists (verapamil and diltiazem) with the effect of clopidogrel—most likely due to common metabolism via hepatic cytochromes. Our findings are partially in line with a recent study (35). In this study, however, nearly all patients were treated with dihydropyridine calcium-channel blockers, whereas in our dataset this type of calcium antagonist had no significant effect on clopidogrel response. Because only a minority of our patients (4.1%) received nondihydropyridine calcium-channel blockers, the relevance of this treatment to the overall on-clopidogrel RPA was limited. Nevertheless, our data suggest avoiding nondihydropyridine calcium-channel blockers in patients needing treatment with clopidogrel.

**Study limitations.** Our findings can only explain a small part of the observed variability in on-clopidogrel RPA. This means that there are still some relevant factors interfering with clopidogrel responses that are yet unknown. These might include novel gene polymorphisms that, so far, have not been identified or investigated as well as clinical and demographic factors or noncompliance, which were not considered. We cannot exclude that the prediction of clopidogrel responses might become better as further factors emerge.

All patients in our cohort receiving a proton pump inhibitor (8%) were treated with pantoprazole, which has not been associated with increased platelet reactivity in patients treated with clopidogrel—in contrast to omeprazole or esomeprazole (36). Therefore, our analysis could not evaluate the impact of this drug class.

We also need to consider that some of the observed variability was introduced by variations in sampling conditions, timing of the clopidogrel maintenance dose, and scatter of the platelet assay. To minimize these confounders we implemented a strict protocol for drug intake and blood sampling. In addition, we could verify a low coefficient of variation (6%) for our optical aggregometry method. Our findings only apply to stable patients undergoing elective PCI. We purposely excluded the influence of overt heart failure and MI, which have been shown to modify the acute responses to clopidogrel substantially.

**Clinical implications.** Given the risks associated with poor suppression of platelet function, identification of patients with high on-clopidogrel platelet reactivity is of major clinical interest. In these patients, alternative, more potent antiplatelet regimens have to be instituted or they might be ineligible for high-risk interventions such as the placement of multiple stents or left main interventions. Nevertheless, platelet function assays have not entered routine clinical practice in most centers, because they are technically demanding, poorly standardized, or expensive. Large-scale studies assessing easy-to-use point-of-care assays are under way. Until these assays have found their way into clinical practice, clinical or laboratory predictors of a low response to clopidogrel are highly desirable.

A potentially attractive candidate in this respect is the CYP2C19*2 polymorphism (8,13,14). Independent of clopidogrel intake, determination of this genetic trait might give an estimate of the probability of a low response to clopidogrel. Our current data, despite confirming the strong impact of the CYP2C19 loss-of-function polymorphism on antiplatelet effect of clopidogrel, suggest that genotyping for CYP2C19 is insufficient for clinical decision-making without platelet function testing. Addition of clinical variables could not fully correct this shortcoming.

Thus, our study does not suggest that, in patients critically dependent on adequate platelet inhibition, genotyping alone or in combination with clinical factors can replace phenotyping of platelet function.

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**REFERENCES**


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