Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention


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Aims

Several studies have demonstrated that the mutant *2 allele of the CYP2C19 681G>A loss-of-function polymorphism is associated with diminished metabolization of clopidogrel into its active thiol metabolite and an attenuated platelet response to clopidogrel treatment. It is not known whether patients carrying the mutant CYP2C19*2 allele have a higher risk of stent thrombosis (ST) compared with homozygous CYP2C19*1 wild-type allele carriers following percutaneous coronary intervention (PCI). The aim of this study was to assess the impact of the CYP2C19 681G>A loss-of-function polymorphism on ST following PCI performed after pre-treatment with clopidogrel.

Methods and results

The study population included 2485 consecutive patients undergoing coronary stent placement after pre-treatment with 600 mg of clopidogrel. Genotypes were determined with a TaqMan assay. The primary endpoint of the study was the incidence of definite ST within 30 days following PCI. Of the patients studied, 1805 (73%) were CYP2C19 wild-type homozygotes (*1/*1) and 680 (27%) carried at least one *2 allele (*1/*2 or *2/*2). The cumulative 30-day incidence of ST was significantly higher in CYP2C19*2 allele carriers (*1/*2 or *2/*2) vs. CYP2C19 wild-type homozygotes (*1/*1), [10 patients (1.5%) in CYP2C19*2 allele carriers vs. 7 (0.4%) in CYP2C19 wild-type homozygotes (*1/*1), HR 3.81, 95% CI 1.45–10.02, \( P = 0.007; P = 0.006 \) after adjustment for confounding variables]. The risk of ST was highest (2.1%) in patients with the CYP2C19*2/*2 genotype (\( P = 0.002 \)).

Conclusion

CYP2C19*2 carrier status is significantly associated with an increased risk of ST following coronary stent placement.

Keywords

Clopidogrel • Genetics • CYP2C19 • Stent thrombosis

Introduction

In patients scheduled for percutaneous coronary intervention (PCI), dual antiplatelet treatment with aspirin and clopidogrel is routinely administered to prevent thrombotic events after coronary stent placement. Despite this treatment, stent thrombosis (ST), a life-threatening event with severe clinical consequences, is still feared to occur. Platelet response to clopidogrel treatment is highly variable and clinical, cellular, and genetic factors have been declared causative for this phenomenon. Persisting high platelet reactivity, despite adequate pre-treatment with clopidogrel, is associated with an increased risk of adverse cardiovascular events after PCI including ST. This has been demonstrated consistently by several prospective studies implementing different methods of platelet function testing. Clopidogrel, an inactive prodrug, requires two-step oxidation by the hepatic cytochrome P450 (CYP) system to generate its active compound, the thiol metabolite, which targets and irreversibly inhibits the adenosine diphosphate P2Y12 receptor. The hepatic enzymes involved in this two-step metabolization process of clopidogrel include CYP2C19, 3A4/5, 1A2, 2B6, and 2C9. Variability in catalytic activity of the hepatic CYP system affects the conversion of clopidogrel into its active compound, which further attenuates the pharmacodynamic action of the drug.
Such variability may arise from genetic alterations in genes encoding for constituent parts of the hepatic CYP system. In this context, pharmacokinetic studies have demonstrated that metabolization of clopidogrel into its active thiol metabolite is diminished in carriers of the CYP2C19 681G>A *2 allelic variant (*2 denotes the mutant 681A allele and *1 denotes the wild-type 681G allele),11,13 encoding for a cryptic splice site resulting in complete loss of CYP2C19 enzyme activity.14 Platelet function studies investigating healthy volunteers reported that the CYP2C19*2 allele is associated with higher levels of platelet aggregation after clopidogrel treatment.11,13,15 Subsequent studies investigating the influence of CYP2C19*2 carrier status in coronary artery disease (CAD) patients undergoing PCI and following clopidogrel treatment were able to confirm the negative impact of the mutant CYP2C19*2 allele on platelet response to clopidogrel.16–18 Recently, Trenk et al.17 investigated the impact of CYP2C19*2 carrier status on different platelet function parameters and on the 1-year incidence of death and myocardial infarction in a population of 797 consecutive patients undergoing PCI. Albeit confirming the influence of CYP2C19*2 carrier status on platelet response to clopidogrel, no significant influence of CYP2C19*2 carrier status on the 1-year incidence of death and myocardial infarction was observed in this study. However, the impact of CYP2C19*2 carrier status on the occurrence of ST was not reported separately.

It is not known whether patients carrying the CYP2C19*2 allele have a higher risk of ST following PCI compared with homozygous CYP2C19*1 wild-type allele carriers. The aim of this study was to assess whether there is an association between CYP2C19*2 carrier status and ST in patients undergoing coronary stent placement after pre-treatment with clopidogrel.

**Methods**

**Patients**

A total of 2485 patients with CAD undergoing PCI were enrolled in this study. The flow chart of the study population is illustrated in Figure 1. Patients were consecutively recruited at Deutsches Herzcentrum München (Munich, Germany) in the setting of randomized trials. These trials were conducted between May 2000 and December 2005 and details of the trial designs including inclusion and exclusion criteria have been reported previously.19–22 In brief, all trials have assessed the value of the glycoprotein IIb/IIIa inhibitor abciximab in patients undergoing primary PCI. This assessment was performed in low-to-intermediate risk patients undergoing elective PCI in the ISAR-REACT trial,21 in patients undergoing PCI for lesions located in small vessels in the ISAR-SMART 2 trial,19 in diabetic patients undergoing elective PCI in the ISAR-SWEEt trial,22 and in patients with non-ST-segment elevation acute coronary syndromes undergoing PCI in the ISAR-REACT 2 trial.20 Before coronary intervention, all patients were uniformly pre-treated with a loading dose of 600 mg clopidogrel. Common exclusion criteria of these trials were: ST-segment elevation acute myocardial infarction, haemodynamic instability, malignancies, stroke within the previous 3 months, active bleeding or bleeding diathesis, recent trauma or major surgery in the last month, suspected aortic dissection, oral anticoagulation within 7 days, patients who received a glycoprotein IIb/IIIa inhibitor within 14 days, a haemoglobin level <100 g/L or haematocrit <34%, platelet count <100 × 10⁹/L or >600 × 10⁹/L⁻¹, known allergy to the study medication; and pregnancy (present or suspected).

The present study complies with the Declaration of Helsinki and was approved by the Institutional Ethics Committee. All patients gave written informed consent prior to study inclusion.

**Blood sampling and genotyping**

Whole blood for genotyping was obtained from the arterial sheath of all patients directly after diagnostic angiography and before PCI. Genomic DNA was extracted from 200 μL of blood using commercially available kits (Nucleo Spin Blood Quick Pure, Macherey-Nagel, Germany) according to manufacturer’s instructions. Genotypes were determined with a TaqMan assay on an ABI Prism Sequence Detector 7000 (Applied Biosystems) according to standard procedures. Primers 5’-GATATGCAATAATTTTCTTACTCTCCAAAATATCAC-3’ and 5’-FAM-TTATTTCCCGGGAACC-3’ were used to amplify a sequence of the CYP2C19 gene containing the single nucleotide polymorphism 681G>A (rs4244285) in exon 5. The sequence of the G allele-specific probe was 5’-FAM-ATTATTTTCTCCAAAAATATCAC-3’ and the sequence of the A allele-specific probe was 5’-VIC-ATTATTTTCTCCAAAAATATCAC-3’. To control for correct sample handling, genotyping was repeated in 20% of the patients. All repeated experiments revealed identical results when compared with the initial genotyping.

**Study endpoints and definitions**

The primary endpoint of this study was the cumulative incidence of definite ST during a 30-day follow-up period. Definite ST was defined according to the Academic Research Consortium (ARC) criteria23 as the occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. We also assessed the incidence of death, myocardial infarction, and ischaemic stroke. The diagnosis of myocardial infarction was made according to Thrombolysis in Myocardial Infarction (TIMI) criteria24 and based on new abnormal Q-wave appearance in the electrocardiogram and/or an increase in the CK-MB value to three or more times the upper limit of normal. The diagnosis of ischaemic stroke required confirmation by computed tomography or magnetic resonance imaging of the head. All events were adjudicated by an event adjudication committee blinded to the genotype of the patients.

**Figure 1** Study flow chart. For the four ISAR studies, see Hausleiter et al.19 Kastrati et al.,20,21 and Mehilli et al.22 DNA, deoxy-ribonucleic acid; PTCA, conventional balloon angioplasty.
Table 1 Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n = 2485)</th>
<th>CYP2C19 *1/*1 (n = 1805)</th>
<th>CYP2C19 *1/*2 or *2/*2 (n = 680)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.5 ± 10.2</td>
<td>66.4 ± 10.2</td>
<td>66.7 ± 10.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Woman, n (%)</td>
<td>539 (22.0)</td>
<td>384 (21.3)</td>
<td>155 (22.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.2 ± 3.9</td>
<td>27.2 ± 3.8</td>
<td>27.2 ± 4.3</td>
<td>0.86</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55.4 ± 13.2</td>
<td>55.5 ± 13.3</td>
<td>55.1 ± 13.1</td>
<td>0.39</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>881 (35.0)</td>
<td>637 (35.2)</td>
<td>244 (35.9)</td>
<td>0.78</td>
</tr>
<tr>
<td>Active smokers, n (%)</td>
<td>402 (16.0)</td>
<td>282 (15.6)</td>
<td>120 (17.6)</td>
<td>0.22</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>1563 (63.0)</td>
<td>1130 (62.6)</td>
<td>433 (63.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>1204 (48.0)</td>
<td>898 (50.0)</td>
<td>306 (45.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>801 (32.0)</td>
<td>570 (31.6)</td>
<td>231 (34.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Previous bypass surgery, n (%)</td>
<td>325 (13.0)</td>
<td>235 (13.0)</td>
<td>90 (13.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>2006 (81.0)</td>
<td>1458 (80.8)</td>
<td>548 (80.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>ACS, n (%)</td>
<td>846 (34.0)</td>
<td>632 (35.0)</td>
<td>214 (31.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Platelet count, (× 10^9 µL⁻¹)</td>
<td>224 ± 60</td>
<td>223 ± 59</td>
<td>226 ± 62</td>
<td>0.30</td>
</tr>
<tr>
<td>Time from loading (h)</td>
<td>5.1 [3.0–14.0]</td>
<td>5.0 [3.0–13.1]</td>
<td>5.1 [3.0–15.5]</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Data presented are means ± SDs or numbers of patients (percentages). Time from clopidogrel loading (hours) to blood sampling is expressed as median [inter-quartile range]. ACS, acute coronary syndrome; MI, myocardial infarction.

Follow up
Patients stayed in hospital for at least 2 days after study inclusion and following PCI. Patients were interviewed by telephone call after 30 days (± 7 days). Those patients with cardiac symptoms were seen in the outpatient clinic for complete clinical, electrocardiographic, and laboratory check-up. Data of patients were collected and entered into a computer database by specialized personnel. All possible information from referring physicians, relatives, and from hospital re-admissions was entered as well. Source documentations were checked to ensure high quality data.

Statistical methods
Variables are presented as mean ± standard deviation (SD), counts (percentages), or median with inter-quartile range (IQR). Categorical variables were compared using χ² test. Kolmogorov–Smirnov test was used to check for normal distribution of continuous data. Normally distributed continuous variables were compared with two-sided unpaired t-test and not normally distributed data were compared with two-sided Wilcoxon test. We tested for a possible deviation of CYP2C19 genotype distribution from Hardy–Weinberg equilibrium proportions using the Pearson’s goodness-of-fit χ² test.

We assumed a dominant model for the majority of our analyses. Calculations for the endpoints of interest were therefore based on the comparison between CYP2C19 wild-type homozygotes (*1/*1) and carriers of the CYP2C19*2 allele (combined *1/*2 or *2/*2). A dominant model was chosen because the mutant *2 allele results in a complete loss of enzyme function, which means that one mutant allele exerts a relevant effect on overall enzyme activity.²⁴

Differences between CYP2C19*1/*1 patients vs. CYP2C19*1/*2 or *2/*2 patients in respect to clinical events were assessed by unadjusted Cox proportional hazards model, which allowed the calculation of hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). The independence of the association between CYP2C19*2 allele carriage and the primary outcome, definite ST (defined as the dependent variable), was assessed by a multivariable Cox proportional hazards model, with the inclusion of age, diabetes, acute coronary syndrome, type of stent (drug-eluting or bare-metal stent), the ISAR study in which the patient was enrolled, and the use of abciximab. Selection of variables included in the multivariable model was based on a previous report on predictors of ST.²⁵ Information was complete for all variables included in the multivariable model. In all cases of the use of the Cox proportional hazards model, the proportional hazards assumption was met as demonstrated by the method of Grambsch and Therneau.²⁶ Age was entered as a continuous variable because it fulfilled the linearity assumption. This was proved by the use of cubic spline function,²⁷ which showed that the relation between the continuous variable and the primary outcome of interest did not deviate significantly from the linear form. Power calculation for the primary end point was done with nQuery advisor version 7.0 (Statistical Solutions, Cork, Ireland). For all statistical analyses, P < 0.05 was considered statistically significant. All analyses were performed using the software package S-PLUS version 4.5 (Insightful Corp., Seattle, USA).

Results
Study population and CYP2C19 genotyping
Thirty-day follow-up was complete in all patients (100%). Baseline characteristics of the study population according to CYP2C19 genotype are demonstrated in Table 1. Variables were well balanced between the two groups except for the proportion of patients with hypercholesterolaemia, which was significantly higher in CYP2C19 *1/*1 patients. Angiographic and procedural characteristics are shown in Table 2 and were well balanced between the two groups.

Of the 2485 patients included in this study, 1805 (73%) were CYP2C19 wild-type homozygotes (*1/*1), 633 (25%) were
CYP2C19*2 heterozygotes (*1/*2), and 47 (2%) were homozygous (*2/*2) for the mutant CYP2C19 *2 allele. This genotype distribution results in the following allele frequencies: 85.4% for CYP2C19*1 vs. 14.6% for CYP2C19*2. No significant deviation from Hardy–Weinberg equilibrium was observed (P = 0.32).

The majority of our analyses were based on the comparison between CYP2C19 wild-type homozygotes (*1/*1) and carriers of the CYP2C19*2 allele (*1/*2 or *2/*2) as we assumed a dominant model and due to the rare occurrence of the *2/*2 genotype.

### Genotyping and outcomes

The primary endpoint (definite ST) within 30 days occurred in 17 (0.7%) patients of the study population. The cumulative 30-day incidence of ST was significantly higher in CYP2C19*2 allele carriers (*1/*2 or *2/*2) vs. CYP2C19 wild-type homozygotes (*1/*1) [10 patients (1.5%) in CYP2C19*2 allele carriers vs. 7 (0.4%) in CYP2C19 wild-type homozygotes (*1/*1), HR 3.81, 95% CI 1.45–10.02, P = 0.007].

Figure 2 shows the cumulative incidence of definite ST according to CYP2C19 genotypes. The risk of ST was highest in patients carrying two of the mutant CYP2C19 alleles (*2/*2 genotype) (P = 0.002; χ² test for trend). Table 3 shows the entire clinical outcome data according to the CYP2C19*2 carrier status. Besides ST, the cumulative incidence of ST-segment elevation myocardial infarction and ischaemic stroke was significantly higher in CYP2C19*2 allele carriers vs. CYP2C19 wild-type homozygotes.

For the entire study population, the proportion of patients with the use of abciximab was identical (50%) in patients with and without a positive CYP2C19*2 carrier status (Table 2). The time [median (IQR)] for the occurrence of ST in relation to the primary procedure was 5.9 (2.3–8.2) days in patients without the use of abciximab vs. 6.6 (3.2–10.9) days in patients with the use of abciximab during the procedure.

The results of the multivariable Cox proportional hazards model demonstrated that carriage of the CYP2C19*2 allele was found to be an independent predictor of 30-day ST (HR 3.86, 95% CI 1.47–10.14; P = 0.006). The ISAR study in which the patients were enrolled did not correlate significantly with 30-day ST (P = 0.44). Detailed results of the multivariable analysis are shown in Table 4.

### Discussion

To the best of our knowledge, this is the first study reporting on the impact of the cytochrome P450 2C19 loss-of-function...
polymorphism and the occurrence of ST in a large population of patients undergoing coronary stent placement. Although several studies have convincingly demonstrated the influence of this common genetic variant on platelet response to clopidogrel,6,8,28 in the present study population, we observed no significant association of CYP2C19*2 carrier status with the incidence of death or myocardial infarction. This finding is in line with the results of Trenk et al. Analysing the 1-year incidence of death and MI with respect to the CYP2C19*2 allele in a study population of 797 patients undergoing PCI, no significant differences were observed for the incidence of death or MI among carriers and non-carriers of the CYP2C19*2 allele (P = 0.371).

The 30-day incidence of definite ST according to ARC criteria in our study (0.7%) is low. However, the observed incidence is consistent with a large meta-analysis investigating the clinical outcome after bare-metal or drug-eluting stenting in 12 973 patients, where definite ST during the first 30 days after PCI was reported to occur at a rate of 0.7%. The majority of patients included in our study received a bare-metal stent. In this subgroup of patients, antiplatelet treatment with clopidogrel was prescribed in accordance with the current guidelines for at least 30 days following the procedure. Thus, choosing a 30-day endpoint is favourable in this setting, in order to avoid an influence on the results due to non-prescription of clopidogrel or poor compliance in the time period after 30 days post-PCI.

Concerning the pathogenesis of ST, the present study provides further evidence that its occurrence following PCI is to a significant proportion related to an attenuated metabolism of clopidogrel into its active thiol metabolite. Our findings corroborate previous observations showing that conversion of clopidogrel into its active compound is significantly diminished in ST patients compared with healthy controls following administration of a 600 mg clopidogrel loading dose.30,31 Thus, it must be assumed that in ST patients decreased generation of the active metabolite is at least in part caused by the CYP2C19*2 allelic variant, encoding for a cryptic splice site resulting in complete loss of enzyme activity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19*2 allele carriage</td>
<td>3.86 (1.47–10.14)</td>
<td>0.006</td>
</tr>
<tr>
<td>Agea</td>
<td>1.10 (0.69–1.77)</td>
<td>0.69</td>
</tr>
<tr>
<td>ACS</td>
<td>2.18 (0.69–6.84)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.13 (0.82–5.58)</td>
<td>0.12</td>
</tr>
<tr>
<td>Type of stent</td>
<td>0.79 (0.23–2.76)</td>
<td>0.71</td>
</tr>
<tr>
<td>Use of abciximab</td>
<td>0.71 (0.27–1.87)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome.

**Table 3 Clinical outcome**

<table>
<thead>
<tr>
<th>Ischaemic events, n (%)</th>
<th>CYP2C19 *1/*1 (n = 1805)</th>
<th>CYP2C19 *1/*2 or *2/*2 (n = 680)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite ST</td>
<td>7 (0.4)</td>
<td>10 (1.5)</td>
<td>3.81 (1.45–10.02)</td>
<td>0.007</td>
</tr>
<tr>
<td>Death</td>
<td>16 (0.9)</td>
<td>5 (0.7)</td>
<td>0.83 (0.30–2.26)</td>
<td>0.71</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>111 (6.1)</td>
<td>48 (7.1)</td>
<td>1.15 (0.82–1.61)</td>
<td>0.42</td>
</tr>
<tr>
<td>STEMI</td>
<td>9 (0.5)</td>
<td>10 (1.5)</td>
<td>2.96 (1.20–7.28)</td>
<td>0.02</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>102 (5.6)</td>
<td>38 (5.6)</td>
<td>0.99 (0.68–1.44)</td>
<td>0.96</td>
</tr>
<tr>
<td>Combined death/MI</td>
<td>121 (6.7)</td>
<td>52 (7.6)</td>
<td>1.14 (0.83–1.58)</td>
<td>0.42</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>0 (0.0)</td>
<td>4 (0.6)</td>
<td>-</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; ST, stent thrombosis; STEMI, ST-segment elevation myocardial infarction.

**Table 4 Results of a multivariable Cox proportional hazards model**

- Calculated for a 10-year increase in age.
activity. Whether other genetic variants in- or outside the hepatic CYP system play a role in this setting as well warrants further investigation. In this context, a significant influence on clopidogrel response variability has also been reported for the IVS10+12G>A polymorphism of the CYP3A4 gene. The results of the present study identify patients at high risk for ST and provide a rationale for administration of an intensiﬁed antiplatelet treatment in patients scheduled for coronary stent placement. Genetic determination of the CYP2C19 loss-of-function polymorphism may be beneﬁcial in this setting as high-risk patients can be identiﬁed prior to the planned procedure. High clopidogrel maintenance dosing or the use of novel and more potent P2Y12 receptor antagonists, such as prasugrel, may be potential treatment options for tailored antiplatelet therapy in CYP2C19*2 carriers.

Limitations

The present study has limitations that merit mention. Although being in line with the expected event rate for deﬁnite ST, the number of events for the primary endpoint of interest was small, despite the large number of patients included in this study. This reﬂects the increased safety associated with current PCI but also underscores the need for further studies to corroborate the present results. The study had 64% power to detect the observed increase for the occurrence of ST from 0.4% in CYP2C19*2 non-carriers to 1.5% in CYP2C19*2 carriers at a two-sided a-level of 0.05. In addition, an inﬂuence of abciximab treatment on the results of the present study cannot be excluded. However, the proportion of patients with abciximab treatment was identical in both groups and the large majority of stent thromboses in patients treated with abciximab occurred at a time point (median = 6.6 days; IQR = 3.2–10.9) when the effect of the drug was suspected to be marginal or absent.

Conclusion

CYP2C19*2 carrier status is signiﬁcantly associated with an increased risk of ST following coronary stent placement.

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