Antiplatelet Therapy

Clopidogrel Loading Dose Adjustment According to Platelet Reactivity Monitoring in Patients Carrying the 2C19*2 Loss of Function Polymorphism

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Objectives
We aimed to investigate the biological impact of a tailored clopidogrel loading dose (LD) according to platelet reactivity monitoring in carriers of the cytochrome (CYP) 2C19*2 loss-of-function polymorphism undergoing percutaneous coronary intervention for an acute coronary syndromes.

Background
CYP2C19*2 polymorphism is associated with reduced clopidogrel metabolism and a worse prognosis after percutaneous coronary intervention.

Method
A prospective multicenter study enrolling 411 patients with non–ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention was performed. Platelet reactivity was measured using the vasodilator-stimulated phosphoprotein (VASP) index, and a cutoff value of >50% was used to define high on-treatment platelet reactivity (HTPR). The genetic polymorphism of CYP2C19 was determined by allele-specific polymerase chain reaction. In patients carrying CYP2C19*2 and exhibiting HTPR after a first 600-mg LD of clopidogrel, dose adjustment was performed by using up to 3 additional 600 mg LDs to obtain a VASP index <50%.

Results
One hundred thirty-four patients (35.3%) carried at least one 2C19*2 allele (11 homozygotes [2.7%] and 123 heterozygotes [32.6%]). The VASP index in these patients was significantly higher than in homozygotic patients for the wild-type alleles (61.7 ± 18.4% vs. 49.2 ± 24.2%; p = 0.001). Of the 134 carriers of the loss-of-function polymorphism, 103 were considered to have HTPR. After a second clopidogrel LD, the VASP index was significantly decreased in these patients (69.7 ± 10.1% vs. 50.6 ± 17.6%; p < 0.0001). Finally, dose adjustment according to platelet reactivity monitoring, enabled 88% of 2C19*2 carriers exhibiting HTPR to reach a VASP index <50%.

Conclusions
Increased and tailored clopidogrel loading dose according to platelet reactivity monitoring overcome HTPR in carriers of the loss-of-function CYP2C19*2 polymorphism. (J Am Coll Cardiol 2010;56:1630–6) © 2010 by the American College of Cardiology Foundation

High on-treatment platelet reactivity (HTPR) after a clopidogrel loading dose (LD) has been shown to predict the short- and long-term prognoses in patients undergoing percutaneous coronary intervention (PCI) (1–3). It has been demonstrated that the level of platelet reactivity inhibition (PRI) after a clopidogrel LD strongly correlates with post-PCI outcome, particularly with early stent thrombosis (3).

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The vasodilator-stimulated phosphoprotein (VASP) index has been used in several studies to assess clopidogrel responsiveness (4–6). It is the most specific platelet assay to evaluate P2Y12 adenosine diphosphate (ADP) receptor activity and thus the effect of clopidogrel on platelets (7,8). Importantly studies have
constantly reported the same cutoff value of the VASP index to predict post-PCI thrombotic events of 50% (4–6). This cutoff value was shown to have a very high negative predictive value using receiver-operator characteristic curve analysis in several trials. In a recent consensus article on the definition of HTPR, this cutoff value (VASP index \( \geq 50\% \)) was suggested to be of clinical significance and could thus be used as a surrogate end point (9).

Clopidogrel is a prodrug that necessitates biotransformation by hepatic cytochromes (CYPs) into its active metabolites. Recent studies underlined the critical role of the CYP2C19*2 polymorphism in the biological response to clopidogrel and thus in the rate of patients with HTPR (10–14). Carriers of this loss-of-function polymorphism have reduced active metabolite generation and therefore suboptimal PRI, which in turn results in a higher rate of thrombotic events post-PCI, particularly early stent thrombosis (12,13).

We previously demonstrated that a tailored LD of clopidogrel according to PRI in patients with HTPR can improve the level of PRI, resulting in improved clinical outcomes (15,16). However, it remains unknown whether such a strategy is effective in carriers of the loss-of-function CYP2C19*2 polymorphism. In the present study, we aimed to evaluate a strategy of clopidogrel LD adjustment according to PRI monitoring in carriers of CYP2C19*2 loss-of-function polymorphism exhibiting HTPR.

Methods

A prospective multicenter study was performed. All patients undergoing PCI for non–ST-segment elevation acute coronary syndrome were eligible. Non–ST-segment elevation acute coronary syndrome was defined as clinical symptoms compatible with acute myocardial ischemia within 12 h before admission and at least 1 of the following: a new finding of ST-segment depression >0.05 mV, T-wave inversion >0.3 mV in at least 2 leads, or elevated levels of cardiac markers. The flow chart of the study is shown in Figure 1. All patients received oral LDs of 250 mg aspirin and 600 mg clopidogrel at least 6 h before the first VASP index measurement. Dose adjustment was performed before PCI in all patients.

Exclusion criteria were persistent ST-segment elevation acute coronary syndrome, failed PCI, New York Heart Association functional class III or IV, cardiac arrest, contraindications to anti-platelet therapy, a platelet count <100 g/l, history of bleeding diathesis, and concurrent severe illness with expected survival of <1 month.

Blood samples for VASP index analysis were drawn by atraumatic venipuncture of the antecubital vein between 6 and 12 h after each clopidogrel LD. The initial blood drawn was discarded to avoid measuring platelet activation induced by needle puncture; blood was collected into a Vacutainer containing 3.8% trisodium citrate and filled to capacity. The platelet count pre-treatment was adjusted individually, before PCI, to 100 g/l, history of bleeding diathesis, and concurrent severe illness with expected survival of <1 month.

VASP index phosphorylation analysis was performed within 24 h of blood collection by an experienced investigator using Platelet VASP kits (Diagnostica Stago, Asnières, France) as previously described (4). Briefly, a citrated blood sample was incubated with prostaglandin E1 (PGE1) or with PGE1 and ADP 10 \( \mu \)mol/l for 10 min and fixed with paraformaldehyde, after which the platelets were permeabilized with nonionic detergent. Analyses were performed on an EPICS XL-MCL flow cytometer (Beckman Coultronics, Margency, France), the platelet population was identified from its forward and side scatter distribution, and 10,000 platelets were gated. A PRI VASP index was calculated from the median fluorescence intensity (MFI) of samples incubated with PGE1 or PGE1 and ADP according to the formula: PRI VASP index = \( \frac{MFI_{\text{PGE1}} - MFI_{\text{PGE1,ADP}}}{MFI_{\text{PGE1}}} \times 100 \). HTPR was defined as a VASP index \( \geq 50\% \) according to the consensus article (9).

Dose adjustment strategy. The VASP index was measured at least 6 h and within 12 h after the first 600-mg LD of clopidogrel. Patients with a VASP index <50% after the clopidogrel LD were considered good responders. Patients with a VASP index \( \geq 50\% \) despite the 600-mg LD were considered to have HTPR. For those patients, clopidogrel pre-treatment was adjusted individually, before PCI, to obtain a VASP index <50%, as previously described.
(15,16). Briefly, as many as 3 additional LDs of 600 mg were prescribed 24 h after the previous dose, and the VASP index was assessed 12 h after each administration until a VASP index <50% was obtained. If these 3 additional boluses were unable to decrease the VASP index to <50%, patients were considered to have a failed dose adjustment.

**Genetic polymorphisms.** Whole blood for genotyping was obtained from the arterial sheath of all patients directly after diagnostic angiography. Genomic DNA was extracted from peripheral blood lymphocytes by using standard procedures. The variant was genotyped in a reaction using amplification refractory mutation system polymerase chain reaction (PCR). The primers (Invitrogen, Carlsbad, California) are 2*: forward: CAg AGT TTg gCA TAT TgT ATC; 2* reverse: TAT CgC AAa CAg TCA CAT AAC; *2 G specific (sens): ACT ATC ATT gAT TAT TTC CCg; and 2* A specific (antisens): gTA ATT TgT TAT ggg TTC CT. The size of the PCR products generated are CYP2C19*2 forward/reverse: 373 pb, 2* G (normal allele): 283 pb, and 2* A (mutated) allele: 129 pb.

Reactions were made in a final volume of 12.5 μl, using 200 nM of primer except for 2* A primer (300 nM), 0.15 unit of Taq DNA polymerase (QBiopta, MP Biomedicals Inc., Cleveland, Ohio) in its accompanying buffer and 200 μM of accompanying deoxyribonucleoside triphosphate. Cycling conditions consisted of a touch down program: the first denaturing step was 1 min 30 s at 94°C, then 10 cycles of 30 s at 94°C, 30 s at 65°C, and 50 s at 72°C followed by 10 cycles with a decrease of 0.5°C per cycle for annealing temperature; then 15 cycles with an annealing temperature of 60°C (the rest of the program does not change); and then a final extension step of 3 min at 72°C and cooling to 15°C.

PCR products were run on 2% agarose gels, and genotypes were assigned according the PCR product sizes observed. The sequence variation c.681G>A in the CYP2C19 gene was screened to determine the presence of the wild-type allele or 2*. Base numbering and allele definitions follow the nomenclature of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee according to den Dunnen recommendations.

The study protocol was approved by the ethics committee of our institution, and patients gave written informed consent for participation.

**Statistical analysis.** All statistical analyses were performed using SPSS version 17.0 software (SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD. Categorical variables are expressed as frequencies and percentages. The usual 2-sided tests were used to compare continuous characteristics (Student t test) and qualitative characteristics (chi-square test) between patients carrying or not carrying the CYP2C19*2 allele and between patients with a good response to clopidogrel and those with HTPR.

After univariate analyses, forward stepwise logistic regression models were constructed to identify factors independently associated with HTPR. This forward approach was based on the log-likelihood ratio test (entry threshold: p < 0.05). Age, sex, body mass index (BMI), and 2C19*2 allele carriage (homozygotic for wild-type alleles vs. 2C19*2 carriers) when appropriate were considered eligible to enter in the multiple logistic regression models.

**Results**

**Study population.** Between January 2009 and January 2010, 411 patients met the inclusion criteria. The baseline characteristics of the study population are summarized in Table 1. The vast majority were men (78.1%) with an age of 62.9 ± 12.2 years. The prevalence of cardiovascular risk factors was high, including diabetes mellitus (34.8%) and current smoking (37.5%).

The VASP index after the 600-mg clopidogrel LD was 53.2 ± 23.2%. Using the 50% cutoff value for HTPR, 62.5% of patients were considered to have HTPR.

**Genotyping and PR.** Among the 411 patients, 134 (35.3%) carried at least 1 loss-of-function 2C19*2 allele. There were 11 homozygotic (2.7%) and 123 heterozygotic (32.6%) patients (Table 2). The genotype distributions were in Hardy-Weinberg equilibrium.

The VASP index in patients carrying at least 1 mutant allele was significantly higher than that of wild-type allele homozygotes (61.7 ± 18.4% vs. 49.2 ± 24.2%; p < 0.001). The prevalence of HTPR among carriers of the CYP2C19*2 allele was 77% (79% for heterozygotes [97 of 123] and 54% for homozygotes [6 of 11]) compared with 55.6% for patients carrying the wild-type genotype (154 of 277) (p < 0.0001).

In multivariate analysis, factors associated with HTPR in the overall population were age (odds ratio [OR]: 0.97, 95% CI: 0.95 to 0.99; p = 0.001) per 1-year decrease, BMI (OR: 1.09, 95% CI: 1.03 to 1.14; p = 0.001) per a 1-U increase, and 2C19*2 allele carriage (OR: 2.69, 95% CI: 1.66 to 4.36; p < 0.0001).

In carriers of the loss-of-function polymorphism, the only independent predictor of HTPR was BMI with an OR of 1.15 (95% CI: 1.04 to 1.28; p = 0.007).

**Impact of dose adjustment in patients homozygotic for the wild-type alleles.** Among the 277 patients carrying no loss-of-function alleles, 123 were good responders and 154 were considered to have HTPR (55.6%). After as many as 3 additional 600-mg LDs of clopidogrel, 137 patients (89%) reached a PRI <50%. Dose adjustment according to PRI monitoring failed in 17 patients (11%) (Fig. 3C).

In multivariate analysis, the only independent predictors of failed dose adjustment was BMI with an OR of 1.12 (95% CI: 1.03 to 1.22; p = 0.009) per a 1-U increase.

**Impact of repeat clopidogrel LDs on HTPR patients carrying the 2C19*2 loss-of-function allele.** Among the 103 patients carrying at least 1 2C19*2 allele and who had HTPR (VASP index ≥50%), all underwent a second LD of clopidogrel. The VASP index was significantly decreased after this second clopidogrel bolus (69.7 ± 10.1% vs. 50.6 ± 17.6%; p < 0.0001) (Fig. 3).

Four patients dropped out of the study because they could not follow the therapeutic protocol (2 withdrew consent...
after the second LD and 2 had nausea related to clopidogrel intake).

Among the remaining 99 patients carrying at least 1 mutant allele and exhibiting HTPR after the first clopidogrel LD, 87 patients (88%) reached a PR <50% with as many as 3 additional 600-mg LDs of clopidogrel. Twelve patients (12%) failed to reach this level of PRI despite 2,400 mg clopidogrel in 4 days (1 homozygotic [1 of 6] and 11 heterozygotic [11 of 93]) (Fig. 2).

The dose required in these patients was 1,400 ± 600 mg in both homozygotes and heterozygotes.

Among patients carrying the 2C19*2 loss of function allele, the only factor associated with failed dose adjustment (inability of as many as four 600-mg LDs of clopidogrel to achieve a VASP index <50%) was BMI (OR: 1.12, 95% CI: 1.01 to 1.24; p = 0.025) per a 1-U increase.

**In-hospital outcome.** In-hospital outcomes are described in Table 3. Two thrombotic events were recorded: 1 stroke after PCI (in a wild-type allele carrier with successful dose adjustment) and 1 subacute stent thrombosis (in a patients heterozygotic for the CYP2C19*2 polymorphism in whom dose adjustment failed). There were 4 occurrences of minor Thrombolysis In Myocardial Infarction noncoronary artery bypass graft-related bleeding. It occurred in 4 patients homozygotic for the wild-type genotype, among whom 3 were good responders and 1 had successful dose adjustment. No patient had coronary artery bypass surgery.

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### Table 1 Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 411)</th>
<th>Wild-Type Genotype (n = 277)</th>
<th>Mutant Carriers (n = 134)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62.9 ± 12.2</td>
<td>63.2 ± 12.2</td>
<td>62.4 ± 12.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Men</td>
<td>321 (78.1)</td>
<td>223 (80.5)</td>
<td>98 (73.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 ± 4.5</td>
<td>27.1 ± 4.4</td>
<td>27.6 ± 4.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>66 (16.1)</td>
<td>44 (15.9)</td>
<td>22 (16.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Smoker</td>
<td>154 (37.5)</td>
<td>102 (36.8)</td>
<td>52 (38.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>218 (53)</td>
<td>148 (53.4)</td>
<td>70 (50.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>143 (34.8)</td>
<td>90 (32.5)</td>
<td>53 (39.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>243 (59.1)</td>
<td>160 (57.8)</td>
<td>83 (61.9)</td>
<td>0.4</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>65 (15.8)</td>
<td>42 (15.2)</td>
<td>23 (17.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>65 (15.8)</td>
<td>38 (13.7)</td>
<td>27 (20.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>1.8 ± 0.8</td>
<td>1.8 ± 0.8</td>
<td>1.9 ± 0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>VASP-1, %</td>
<td>53.2 ± 23.2</td>
<td>49.2 ± 24.2</td>
<td>61.7 ± 18.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leukocytes, g/l</td>
<td>8.5 ± 2.6</td>
<td>8.4 ± 2.6</td>
<td>8.7 ± 2.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>13.3 ± 2</td>
<td>13.3 ± 2</td>
<td>13.3 ± 1.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Platelets, 10⁹/μl</td>
<td>228 ± 68</td>
<td>226 ± 66</td>
<td>233 ± 73</td>
<td>0.1</td>
</tr>
<tr>
<td>Fibrinogen, g/l</td>
<td>3.8 ± 1.1</td>
<td>3.8 ± 1.1</td>
<td>3.8 ± 1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Creatinine, μmol/l</td>
<td>92 ± 47</td>
<td>93 ± 53</td>
<td>89 ± 30</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). *Includes patients with a previously documented diagnosis of hypercholesterolemia. Patients may be treated with diet or medication. A new diagnosis can be made during hospitalization, with an elevated total cholesterol >250 mg/dl. Does not include patients with elevated triglycerides. †Includes patients with a previously documented diagnosis of hypercholesterolemia. A new diagnosis can be made during hospitalization, with an elevated blood pressure >140/90 mm Hg at rest.

BMI = body mass index; CAD = coronary artery disease; VASP = vasodilator-stimulated phosphoprotein.

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### Table 2 Repartition of Genetic Polymorphisms of Cytochrome 2C19*2 According to Their Response to the First Loading Dose of Clopidogrel

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n = 411)</th>
<th>Wild-Type Genotype (n = 277)</th>
<th>Mutant Carriers (n = 134)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19*2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2*/2+</td>
<td>11 (2.7%)</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>wt/2+</td>
<td>123 (29.9%)</td>
<td>26</td>
<td>97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>wt/wt</td>
<td>277 (67.4%)</td>
<td>123</td>
<td>154</td>
<td></td>
</tr>
</tbody>
</table>

p Value calculated for the prevalence of HTPR in wild-type homozygotes versus carriers of the CYP2C19*2 polymorphism.

GR = good responder; HTPR = high on-treatment reactivity; wt = wild type.

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### Figure 2 Impact of Repeated Clopidogrel LD on PRI in Mutant Allele Carriers

Reduction of platelet reactivity in 2C19*2 carriers exhibiting high on-treatment platelet reactivity after a second 600-mg LD of clopidogrel. PRI = platelet reactivity inhibition; other abbreviations as in Figure 1.
Discussion

The present study is the first to demonstrate that, despite having reduced clopidogrel metabolism, most carriers of the loss-of-function CYP2C19*2 polymorphism can reach optimal PRI using a strategy of tailored LD according to PRI monitoring. These data reinforce the potential of PRI monitoring to improve the outcome of patients undergoing PCI for an acute coronary syndrome.

Several reports highlighted the critical role of peri-PCI PRI (1–4). Blindt et al. (5) prospectively demonstrated that patients exhibiting a PRI ≥50% after a clopidogrel LD and undergoing PCI more often presented with early stent thrombosis. Consistently, we and others have confirmed the high negative predictive value of this cutoff value of the VASP index to predict thrombotic events after PCI. This value was recently validated in a consensus definition of HTPR and proposed as a surrogate end point (4–6,9).

Clopidogrel is a prodrug that requires hepatic conversion to an active metabolite to exert its antiplatelet properties. The majority of absorbed clopidogrel (85% to 90%) is hydrolyzed by carboxylase to an inactive metabolite, whereas the remaining 10% to 15% is metabolized by hepatic CYP P-450 isoenzymes in a 2-step process (17–19). Studies indicate that CYP2C19, CYP1A2, and CYP2B6 participate in the first metabolic step, whereas CYP2C19, CYP2C9, CYP2B6, and CYP3A are responsible for the second step (17,18). This metabolic activation pathway is consistent with the time-dependent cumulative inhibition of ADP-induced platelet aggregation as observed with repeated daily dosing of clopidogrel (20–22). Previous research strongly suggests that variable and insufficient active metabolite generation is the main explanation for clopidogrel response variability and HTPR (23). Importantly, CYP2C19 is involved in both steps of clopidogrel metabolism. The 2* loss-of-function polymorphism of this enzyme has been shown to be associated with HTPR.

Hulot et al. (10) demonstrated that the 2C19*2 loss-of-function polymorphism was associated with decreased clopidogrel metabolism and thus reduced antiplatelet effect of the drug. Furthermore, several studies have not only confirmed the negative impact of this polymorphism on the biological effect of the drug but also its association with a poor outcome after PCI (11–14). In the genetic substudy of the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) trial (12), carriers of these mutant alleles receiving clopidogrel had a 5-fold increase in their risk of stent thrombosis and major adverse cardiovascular events compared with carriers of the wild-type genotype. More recently, Collet et al. (11) confirmed in young patients admitted for a first myocardial infarction the negative impact of CYP2C19*2 allele carriage. In a retrospective analysis, Simon et al. (14) observed a worse outcome in homozygotic but not in heterozygotic patients compared with patients carrying 2
wild-type alleles. Altogether recent data suggest that both heterozygotic and homozygotic patients have reduced clopidogrel metabolism and a poor prognosis after PCI.

In the present study, we observed that an increased or tailored LD of clopidogrel according to PRI monitoring resulted in improved PRI and reduced the rate of patients with HTPPR for patients carrying the loss-of-function polymorphism. In fact, a strategy of clopidogrel LD adjustment according to PRI was efficient in approximately 90% of the studied population. Although the number of patients homozygous for the loss-of-function polymorphism is small, the present study further suggests that this therapeutic strategy may be efficient in this population as well as in heterozygotic patients. Our findings also suggest that the strategy may be efficient in this population as well as in the present study further suggests that this therapeutic strategy, may be of clinical benefit.

Study limitations. This study is relatively small and did not assess the prognostic impact of the therapeutic strategy. However, previous studies have already demonstrated that dose adjustment is clinically beneficial and thus PRI can be used as a surrogate end point. We did not assess other genetic polymorphisms that could be involved in the biological response to clopidogrel. However, a therapeutic strategy that would be based on >1 genetic polymorphism would be very complex to perform.

Conclusions

An increased or tailored clopidogrel LD according to platelet reactivity monitoring can overcome HTPPR in most carriers of CYP2C19*2 loss-of-function polymorphism, which may result in reduced thrombotic risk post-PCI.

Acknowledgments

The authors are grateful to Soraya Moulay for her help in data management and to Marie-Christine Alessi, Andrée Robaglia, Karine Berthaux, and Mouradian Cecile for their technical assistance. They are also grateful to Dr. Probal Roy for his comments and help with this study.

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REFERENCES


Key Words: cytochrome 2C19 polymorphism • P2Y12 adenosine diphosphate receptor blocker • percutaneous coronary intervention • stent thrombosis • vasodilator-stimulated phosphoprotein.