Inter-patient variability and impact of proton pump inhibitors on platelet reactivity after prasugrel

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**Summary**

Although there is considerable variability of platelet reactivity among patients treated with clopidogrel, little is known about inter-individual differences and possible role of proton pump inhibitors (PPIs) after prasugrel. We defined the extent of inter-patient variability, and evaluated the impact of PPI interaction in prasugrel-treated patients with acute coronary syndrome (ACS). Between January 2010 and May 2011, 104 prospective, high-risk patients with ACS were recruited into this multicentre, prospective, observational study. Twelve to 24 hours after receiving 60 mg loading dose of prasugrel, light transmission aggregometry (LTA) and whole blood impedance aggregometry (Multiplate) were used to assess platelet activity. Platelet function measurements were repeated during maintenance phase on reduced (5 mg) or on conventional (10 mg) doses of prasugrel. High platelet reactivity (HPR) was defined according to the consensus document of the Working Group on High On-Treatment Platelet Reactivity (LTA:>46%; Multiplate:>47U). Compared to maintenance doses, 60 mg loading dose of prasugrel provided significantly greater platelet reactivity inhibition (p<0.05). There were no significant differences between the conventional and reduced maintenance doses. Notably, a remarkable inter-patient variability was present in platelet reactivity after all doses of prasugrel, and the prevalence of HPR was significantly higher during the maintenance doses (p<0.05). Although median platelet reactivity values were consistently higher when prasugrel was used in combination with PPIs, these differences were not significant (p≥0.17). Despite potent platelet inhibition, inter-patient variability is present after all tested doses of prasugrel. The 60 mg loading dose is superior to conventional and reduced maintenance doses in terms of platelet reactivity inhibition and regarding the prevention of HPR.

**Keywords**

ADP receptors, antiplatelet agents, antiplatelet drugs, platelet pharmacology

**Introduction**

In spite of its potential limitations, clopidogrel is the most frequently used thienopyridine to prevent thrombotic events among patients with acute coronary syndromes and after percutaneous coronary intervention (PCI) (1, 2). Major shortcomings include delayed onset of action, relatively low level of platelet inhibition, large inter-patient variability in P2Y12-receptor inhibition and a potential for drug-drug interactions with the commonly co-prescribed proton pump inhibitors (PPIs), statins or calcium channel blockers (3). These drawbacks originate mostly from the poor bioavailability of clopidogrel: only 10–15% of the absorbed prodrug reaches the hepatic site for activation, because plasma esterases inactivate the majority of the absorbed clopidogrel in the portal circulation (3). Moreover, the activity of hepatic cytochromes catalysing the oxidation of clopidogrel is commonly decreased by genetic polymorphisms and drug interactions (4, 5).

Contrary to clopidogrel, prasugrel has a lot more efficient, two-step active metabolite generation, since the absorbed prodrug is not neutralised but activated by the esterases (6). In its initial studies among low-risk coronary artery disease patients, this pharmacokinetic benefit resulted in a more rapid, more potent and more predictable adenosine diphosphate (ADP)-receptor inhibition, and prasugrel virtually eliminated high platelet reactivity (7–9). In contrast, Bonello et al. recently showed that using the vasodilator stimulated phosphoprotein phosphorylation (VASP) assay in real-world patients with acute myocardial infarction, there is a large variability in platelet reactivity after prasugrel and those harbouring high platelet reactivity values continue to suffer ischaemic events after PCI (10). In the current study, we aimed to determine the extent of inter-individual variability in platelet reactivity after prasugrel and to analyse whether the concomitant administration of PPIs influence the degree of platelet inhibition in a high-risk cohort of patients with acute coronary syndromes.

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Methods

Patients

Between January 2010 and May 2011, acute coronary syndrome (ACS) patients receiving prasugrel therapy for primary PCI were enrolled into this prospective, multicentre, observational study. Prasugrel was used according to the labelled indication: major exclusion criteria included prior stroke, active bleeding disorder and need for chronic oral anticoagulation. Patients who received a 300 or 600 mg clopidogrel loading dose less than seven days of the admission were also excluded. All patients received a 60 mg loading dose and 10 or 5 mg maintenance dose of prasugrel that was continued for one year. Five mg prasugrel was chosen in elderly (>75 years), and low bodyweight (<60 kg) patients. Twelve to 24 hours (h) after receiving the loading dose of prasugrel, light transmission aggregometry and whole-blood impedance aggregometry were performed to assess the inhibition of platelet aggregation. In case of glycoprotein IIb/IIIa inhibitor administration, the measurements were postponed 24 h after the cessation of the small-molecule infusion (tiroliban/eptifibatide) and six days after abciximab. Platelet reactivity was reassessed by both methods in maintenance phase treatment during an outpatient visit scheduled at 25–35 days after PCI. Patient recruitment and study design is depicted in Figure 1.

Figure 1: Flowchart of patient recruitment. CABG: coronary artery bypass grafting; LTA: light transmission aggregometry; PCI: percutaneous coronary intervention; TIA: transient ischaemic attack.
Table 1: Baseline clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=104)</th>
<th>PPI (n=61)</th>
<th>no PPI (n=43)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean ± SD)</td>
<td>59.8 ± 8.9</td>
<td>59.4 ± 9.5</td>
<td>60.4 ± 8.2</td>
<td>0.56</td>
</tr>
<tr>
<td>Male gender (n, %)</td>
<td>68 (65.4)</td>
<td>43 (70.5)</td>
<td>25 (58.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Caucasian</td>
<td>100 (96.2)</td>
<td>60 (98.4)</td>
<td>40 (93.0)</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Pakistani</td>
<td>3 (2.9)</td>
<td>1 (1.6)</td>
<td>2 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Type II diabetes (n, %)</td>
<td>51 (49.0)</td>
<td>28 (45.9)</td>
<td>23 (53.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>86 (82.7)</td>
<td>49 (80.3)</td>
<td>37 (86.1)</td>
<td>0.60</td>
</tr>
<tr>
<td>Dyslipidaemia (n, %)</td>
<td>61 (58.7)</td>
<td>28 (45.9)</td>
<td>33 (76.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Renal insufficiency (n, %)</td>
<td>19 (18.3)</td>
<td>9 (14.8)</td>
<td>10 (23.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Current smoker (n, %)</td>
<td>33 (31.7)</td>
<td>18 (29.5)</td>
<td>15 (34.9)</td>
<td>0.67</td>
</tr>
<tr>
<td>BMI (kg/m²; mean ± SD)</td>
<td>28.0 ± 3.8</td>
<td>27.5 ± 3.6</td>
<td>28.6 ± 3.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Enrolling diagnosis (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>STEMI</td>
<td>64 (61.5)</td>
<td>40 (65.6)</td>
<td>24 (55.8)</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>21 (20.2)</td>
<td>14 (22.9)</td>
<td>7 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>19 (18.3)</td>
<td>7 (11.5)</td>
<td>9 (20.9)</td>
<td></td>
</tr>
<tr>
<td>Prior MI (n, %)</td>
<td>37 (35.6)</td>
<td>19 (31.2)</td>
<td>18 (41.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Prior PCI (n, %)</td>
<td>38 (36.5)</td>
<td>22 (36.1)</td>
<td>16 (37.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Prior CABG (n, %)</td>
<td>19 (18.3)</td>
<td>6 (9.8)</td>
<td>13 (30.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Prior stroke (n, %)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>PPI (n, %)</td>
<td>61 (58.7)</td>
<td>61 (100.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>59 (56.7)</td>
<td>59 (96.7)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>2 (1.9)</td>
<td>2 (3.3)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>CCB (n, %)</td>
<td>51 (49.0)</td>
<td>27 (44.3)</td>
<td>24 (55.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Statin (n, %)</td>
<td>87 (83.7)</td>
<td>53 (86.9)</td>
<td>34 (79.1)</td>
<td>0.30</td>
</tr>
<tr>
<td>CYP3A4-met. statin (n, %)</td>
<td>53 (51.0)</td>
<td>31 (50.8)</td>
<td>22 (51.2)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

BMI: body mass index; CABG: coronary artery bypass grafting; CCB: calcium-channel blocker; CYP3A4: cytochrome 3A4 isoenzyme; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-segment elevation myocardial infarction. *: comparison between PPI vs. no PPI groups.

Platelet function testing

Plasma light transmission aggregometry (LTA) and whole-blood impedance aggregometry were used to evaluate the antiplatelet effects of prasugrel. In case of LTA, 5 μM ADP-stimulated maximal (AGGmax) and 6-minute (min) late aggregation (AGGlate) values were calculated in every measurement from citrate-anticoagulated blood samples after centrifuging for platelet pure and platelet rich plasma. Calibration for aggregation measurements were established using light transmission percentage through platelet-rich plasma and platelet poor plasma. In case of whole-blood aggregometry, the Multiplate standardised impedance aggregometer (Verum Diagnostica GmbH, Munich, Germany) were used with 6.4 μM ADP-stimulated maximal (AGGmax) and 6-minute (min) late aggregation (AGGlate) values in case of LTA and >47 U (equal to 468 AU) in case of the Multiplate assay (3). Although less well established, the Multiplate device had a receiver-operating curve (ROC)-defined cut-off for bleeding that was used as a limit for low platelet reactivity (LPR): <18U (11). Although there were no exact recommendations regarding the HPR cut-off in case of AGGlate values, the 15% final aggregation limit was selected on the basis of the EXCELSIOR study (12).

Definition of low and high platelet reactivity values

The definition of high platelet reactivity (HPR) followed the consensus recommendations of the expert panel: >46% AGGmax values in case of LTA and >47 U (equal to 468 AU) in case of the Multiplate assay (3). Although less well established, the Multiplate device had a receiver-operating curve (ROC)-defined cut-off for bleeding that was used as a limit for low platelet reactivity (LPR): <18U (11). Although there were no exact recommendations regarding the HPR cut-off in case of AGGlate values, the 15% final aggregation limit was selected on the basis of the EXCELSIOR study (12).

Statistical analysis

Continuous variables are presented as means ± SD. Categorical variables are expressed as frequencies and percentages. Differences between groups were assessed with the Fisher’s exact test or chi-square test for categorical variables. Paired t-tests were used for comparison of normally distributed continuous variables in the same group between time points, while unpaired t-tests were used for comparison of normally distributed, continuous variables between other groups. Non-normally distributed, paired variables were compared using the Wilcoxon matched pairs test, while non-normally distributed variables between groups were analysed with the Mann-Whitney test. Multivariate linear regression models were used to calculate the linear association between platelet reactivity values (dependent variables) and clinical characteristics (independent variables) using the stepwise method. The R² value was used to reflect the goodness of fit in the linear model. All statistical analyses were performed with SPSSv18.0 software (SPSS Inc. Chicago, IL, USA).

Sample size calculation

On designing the study, we calculated that approximately 20 patients are required to demonstrate a 10% difference in mean AGGmax values after 60 mg and 10 mg of prasugrel (20 ± 12% vs. 30 ± 12%) with a 90% power at a two-sided alpha level of 0.05 (7, 13, 14). Moreover, to be able to demonstrate a 10% difference (3% vs. 13%) in the proportion of high platelet reactivity between 60 mg and 10 mg doses of prasugrel with an 80% power at a two-sided alpha level of 0.05, 100 patients were required.
Results

Inter-individual differences after prasugrel

The basic clinical characteristics of the 104 recruited patients are described in Table 1. Notably, the patient group comprised a real high-risk subset of patients with 62% ST-segment elevation myocardial infarction, 49% with type 2 diabetes, 18% with renal insufficiency, and more than a third with prior myocardial infarction or prior PCI.

After the administration of 60 mg loading dose of prasugrel, both LTA and Multiplate showed low mean ADP-reactivity values reflecting potent P2Y12 receptor blockade; however, there were detectable inter-patient variations within the potency of P2Y12-receptor inhibition according to the individual values (range in Multiplate values, 60 mg: 5–75 U; 10 mg: 10–73 U; 5 mg: 13–108 U) (Figs. 2, 3). Interestingly, while 6-min late aggregation values were relatively insensitive to show these differences, the Multiplate-derived values showed a considerable inter-patient variability. As a result, a low proportion of the studied patients were found to have high on-treatment platelet reactivity in spite of 60 mg loading dose of prasugrel (Fig. 4). When patients were reassessed on maintenance phase (median time: 33 days, inter-quartile range: 26–35 days), a significantly lower level of platelet inhibition was discovered both after the conventional (10 mg) and the reduced (5 mg) maintenance doses (Figs. 2, 3). Notably, the extent of inter-patient variability and the proportion of patients with high platelet reactivity was higher with the maintenance doses as compared to 60 mg (p<0.05 for comparisons of 5 or 10 mg with 60 mg prasugrel, Fig. 4). In contrast, the proportion of patients having low platelet reactivity values with a potentially elevated risk for bleeding decreased inversely from 60 mg to 5 mg based on the results of the Multiplate analyzer (60 mg: 37%; 10 mg: 21%; 5 mg: 15%; p=0.03). As a result, approximately 55% (range: 53–58%) of the patients were within the hypothesised therapeutic window for optimal platelet reactivity in the tested doses of prasugrel.

Prasugrel-PPI interactions

To evaluate possible determinants of platelet reactivity after prasugrel, various clinical parameters as well as the prescribed medications (from Table 1) were used in multivariable linear regres-
sion analysis. As a result, age, chronic renal insufficiency and PPIs were found to alter ADP-reactivity after 60 mg prasugrel; however, none of these variables were found to influence maintenance-phase findings (Table 2). As a pre-specified analysis, platelet reactivity was compared between patients with and without PPI administration (PFIg. 5). Although the PPI and non-PPI groups were comparable except for the higher prevalence of dyslipidaemia in the PPI group (Table 1), there were only a slight difference according to PPI exposure or to the usage of high-dose PPI between patients; however, these differences were not significant (p>0.17).

Discussion

The main findings of the current prospective observational study can be summarised as follows:

1. Prasugrel achieves a potent, dose-dependent inhibition of platelet aggregation with significant differences between the loading and the maintenance doses in post-PCI ACS patients.
2. Although smaller than described with clopidogrel, there is a considerable inter-patient variability after all doses of prasugrel; the observed variability is higher during the maintenance phase as compared to the loading dose.
3. Compared to prior studies that used non-standardised definitions for HPR, the current study suggests that high platelet reactivity may be present in 1–8% after 60 mg, 9–21% after 10 mg and in 23–31% after 5 mg of prasugrel in a real-world, high-risk patient-population. The rate of HPR increases with the conventional (10 mg) and reduced (5 mg) maintenance doses as compared to the loading dose.
4. Based on the study results, most of the observed variability after prasugrel is not attributable to known determinants of clopidogrel response; PPIs induce only a slight, non-significant difference regarding the potency of ADP-receptor inhibition.

Prasugrel is a third-generation thienopyridine derivative that has been shown to achieve approximately 10 times more potent ADP-receptor inhibition than clopidogrel in preclinical studies (15). Although the large variability in platelet inhibition after clopidogrel has been reported by many studies using various platelet function assays and studying diverse patient groups, little was known about inter-patient differences after prasugrel treatment (16, 17). First, Jernberg et al. reported that both 40 and 60 mg loading doses as well as the 10 and 15 mg maintenance doses of prasugrel achieved lower proportion of pharmacodynamic low responders than the 300/75 mg clopidogrel (7). Although the study has presented inhibition of platelet aggregation (IPA) values instead of post-treatment reactivity, the plots comparing the various doses of clopidogrel and prasugrel nicely suggested that inter-patient variability is not exclusively attributable to clopidogrel. Using non-recommended criteria for defining HPR, they observed a dose-dependent increase in the rate of HPR ranging from 3% after 60 mg up to 33% after 5 mg of prasugrel. Two major limitations to this study are...
the non-ACS patient population and the non-consensus defined cutoffs for HPR that is well detectable on the 45% clopidogrel non-responder rate in an elective subset. Although it was not the main aim of the study, Erlinge et al. also showed that a variable platelet aggregation is present not only after 2 h of clopidogrel loading, but also during loading and maintenance phase of prasugrel treatment (18). The first pharmacodynamic study that compared clopidogrel and prasugrel in the setting of ACS was the platelet function substudy of the TRITON TIMI38 trial that showed significantly greater platelet inhibition with prasugrel compared to 500 mg plus 75 mg clopidogrel (13). Although the inter-patient variability after prasugrel was still not emphasised in the conclusion, it is well detectable both after VASP assessment and using conventional aggregometry. After these studies, Bonello et al. were the first who clearly demonstrated that P2Y12-dependent platelet activity is greatly variable after 60 mg prasugrel loading dose in a real-world population comprising high-risk acute myocardial infarction patients (10). Although the VASP assay might be a bit oversensitive with this regard, 25% of the patients had high platelet reactivity values despite 60 mg prasugrel. More importantly, these patients were found to have a higher risk for ischaemic events after PCI that underscores the clinical importance of HPR, even in case of prasugrel. In line with these findings, our analysis is the first report that describes the presence of a substantial variability in platelet reactivity after prasugrel in a real-world ACS patient population with two independent, ADP-specific assays. Together with Bonello, our results emphasise that pharmacodynamic measurements of P2Y12 receptor antagonists should be performed among the patient ‘on label’ group in that the drug is intended to be used or indicated; healthy volunteers and stable coronary disease subjects might have completely different baseline platelet reactivity and drug response compared to an ACS patient. The differences in platelet reactivity were well detectable with the Multiplate assay, while final aggregation values of LTA were less sensitive to discriminate between patients with high levels of P2Y12 receptor inhibition. Our results show that HPR increases from 60 mg loading dose to maintenance doses; while HPR was common after the reduced maintenance dose of 5 mg (23–38%), it was infrequent after 60 mg prasugrel (2–8%). Although there is uncertainty about the association of bleeding events and low platelet reactivity values, based on the ROC-defined cutoff from a previous study (11), our results might implicate that a uniform administration of 60 mg loading dose and 10 mg maintenance dose of prasugrel results in an excessive ADP-receptor inhibition in approximately one third and one fifth of patients, respectively. This characteristic was also apparent in the Bonello study, in that 34% of the patients had excessive (VASP-PRI < 20%) ADP-receptor inhibition values. Whether the higher risk of bleeding in such patients can be tackled with a tailored approach on the basis of a platelet function testing, remains to be established.

Evidence is also scant regarding possible determinants of inter-patient differences after prasugrel. Compared to clopidogrel, cytochrome 2C19 and ABCB1 single nucleotide polymorphisms were shown to not affect the biological and clinical efficacy of prasugrel (19). In a recently published sub-study of the TIMI44 trial, Frelinger et al. demonstrated that the extent of baseline ADP-reactivity might be an important determinant of post-treatment values both after clopidogrel and prasugrel treatment (20). In another work from the same study, O’Donoghue et al. have found that platelet inhibition was reduced and the rate of HPR was increased in patients receiving PPIs together with prasugrel (21). Our results also show that some extent of the variability might be dedicated to the coadministration of PPIs; however, there was only a numeric trend towards higher platelet aggregation values in the PPI group compared to PPI-naïve patients that was not statistically significant. These relatively small pharmacodynamic differences are pre-

### Table 2: Multivariate linear regression model for platelet aggregation after 60 mg prasugrel.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardised coefficient with 95% CI</th>
<th>Standardised coefficient</th>
<th>Percentage in variability explained (R²)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age (years)</td>
<td>0.87 (0.36–1.38)</td>
<td>0.47</td>
<td>12.9%</td>
<td>0.001</td>
</tr>
<tr>
<td>2. PPI</td>
<td>10.89 (2.30–19.48)</td>
<td>0.35</td>
<td>21.5%</td>
<td>0.014</td>
</tr>
<tr>
<td>3. Chronic renal insufficiency</td>
<td>12.14 (1.54–22.74)</td>
<td>0.31</td>
<td>30.7%</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Whole blood platelet aggregation values were obtained with the Multiplate analyzer. *: Model 1: Age; Model 2: Age+PPI; Model 3: Age+PPI+chronic renal insufficiency.

What is known about this topic?
- There is considerable inter-individual variability of platelet reactivity after clopidogrel due to clinical effects, genetic factors and drug interactions.
- Initial studies including healthy volunteers and stable coronary disease patients suggested that prasugrel achieves a more reliable and more potent platelet inhibition with low inter-patient variabilities compared to clopidogrel.

What does this paper add?
- Although prasugrel generally produces potent platelet inhibition, there are substantial differences in the achieved platelet reactivity between patients with acute coronary syndromes.
- The potency of platelet reactivity inhibition is greater in case of 60 mg loading dose compared to reduced and conventional maintenance doses.
- The prevalence of high platelet reactivity is higher with 10 or 5 mg prasugrel than after the 60 mg loading dose.
sumably not clinically meaningful, giving that the subanalysis of the TRITON TIMI38 trial did not confirm any interaction with PPIs in prasugrel-treated patients (21).

It is uncertain, whether age and renal insufficiency might be real predictors of response to 60 mg loading dose of prasugrel; however, these factors are known determinants of HPR in case of clopidogrel administration (22). Since age is also a risk factor for bleeding, balancing between safety and efficacy without a tailored approach using prasugrel might be really difficult among the elderly patients.

**Limitations**

Our study has some obvious limitations. First, it would have been desirable to include a clopidogrel arm in the study to better compare the observed inter-individual differences and the rate of HPR to prasugrel. Second, the study recruited patients from three different sites: although the Multiplate assay is standardised and the observed results are comparable, there might be some differences in LTA results due to the poor standardization of the assay. Third, it would have been extremely valuable to match clinical outcome data with the observed platelet function results after prasugrel. However, the study was designed and planned as a pharmacodynamic analysis, and there were no strict clinical follow-up that prevented us from registering ischaemic and bleeding events precisely in the cohort. Finally, the majority of our PPI-treated patients (97%) received pantoprazole. Since the impact of PPIs on the antiplatelet effect of clopidogrel is not a “class effect”, other PPIs, like the strong cytochrome 2C19 inhibitor omeprazole, might have had a different influence on the antiplatelet effect of prasugrel.

Despite potent platelet inhibition, intrapatient variability is present after all tested doses of prasugrel. The 60 mg loading dose is superior to conventional and reduced maintenance doses in terms of platelet reactivity inhibition and regarding the prevention of HPR.

**Conclusions**

Despite potent platelet inhibition, inter-patient variability is present after all tested doses of prasugrel. The 60 mg loading dose is superior to conventional and reduced maintenance doses in terms of platelet reactivity inhibition and regarding the prevention of HPR. PPI coadministration explained a small extent of the observed variability after prasugrel. Although less well pronounced than in case of clopidogrel, the inter-patient variability and the interaction at the site of cytochrome isoenzymes might be a class-effect for thienopyridines.

**Conflict of interest**

Dániel Aradi receives consulting fees from Verum Diagnostica. Wiktor Kuliczkowski and Dan Atar declare no conflict of interest.

Dr. Serebruany is listed as an inventor, and received compensation for the U.S. Patent Application P-17232 “Method for treating vascular diseases with prasugrel” assigned to Lilly. He received funding for research studies with both prasugrel and clopidogrel.

**References**


