Antiplatelet efficacy of prasugrel in patients with high on-clopidogrel treatment platelet reactivity and a history of coronary stenting

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Summary
Little is known about the antiplatelet action of the 3rd generation thienopyridine prasugrel in patients showing high platelet reactivity (PR) levels on clopidogrel. Thus, we aimed to determine the antiplatelet efficacy of prasugrel loading (LD) and maintenance dose (MD) treatment in a registry of patients with high PR levels on clopidogrel and a consecutive switch over to prasugrel in a setting of routine platelet function testing. In our registry of patients treated by percutaneous coronary intervention (n=73) with high levels of PR on clopidogrel, the ADP-induced platelet aggregation (PA, in AU x min) was assessed on a Multiplate analyser 1) after clopidogrel LD, 2) after prasugrel LD and 3) on prasugrel MD (5 vs. 10 mg/day). In patients with high PR levels on clopidogrel, prasugrel LD resulted in significantly lower PA values (574 [462–698] vs. 156 [89–234] AU x min; p<0.0001). Only 2.7% of patients showed high PR (HPR, ≥468 AU x min) following prasugrel LD. On prasugrel MD, PA was significantly higher as compared to prasugrel LD (248 [145–406] vs. 156 [89–234] AU x min; p<0.0001) with more patients showing HPR on MD vs. LD (16.4% vs. 2.7%; p=0.009).

For prasugrel MD, HPR rates were higher in 5 vs. 10 mg/day treated patients (46.2% vs. 10.0%; p=0.006). In conclusion, for patients with high PR levels on clopidogrel, prasugrel LD abolished this status in the majority of patients. However, prasugrel response variability was detected, being more pronounced on prasugrel MD vs. LD treatment. The clinical impact of these findings warrants further investigation.

Keywords
Clopidogrel, high platelet reactivity, prasugrel, response variability

Introduction
P2Y12 receptor inhibition with the 2nd generation thienopyridine clopidogrel in combination with aspirin is established for patients undergoing percutaneous coronary intervention (PCI) and has significantly improved patients’ outcome (1, 2). However, interindividual response variability as well as an insufficient level of platelet inhibition, termed high platelet reactivity (HPR), are major shortcomings associated with clopidogrel therapy (3, 4). Patients with high levels of platelet reactivity (PR) on clopidogrel exhibit a high risk for suffering from post-PCI ischaemic events including stent thrombosis (5-7). The wish to optimise the efficacy of oral platelet inhibition resulted in the advent of novel antiplatelet drugs including the 3rd generation thienopyridine prasugrel that achieves more potent and rapid P2Y12 receptor inhibition as compared to clopidogrel (8-11). The clinical efficacy of prasugrel was demonstrated in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) by showing a significant reduction of ischaemic events for prasugrel as compared to clopidogrel; however, at the cost of a higher bleeding risk (12).

Besides this proven clinical efficacy, the ex vivo antiplatelet action of prasugrel was investigated in numerous studies enrolling healthy volunteers or patients with coronary artery disease (9-11, 13). Just recently, the phenomenon of HPR was also reported in PCI-treated patients receiving prasugrel as well as the association of HPR on prasugrel with a worse clinical outcome (14). With regard to their blood platelets and responsiveness to antiplatelet treatment, patients already showing HPR on clopidogrel constitute a distinct and high-risk cohort in terms of drug responsiveness and data is limited in these patients on the antiplatelet action of prasugrel. It can be hypothesised that especially patients with HPR on clopidogrel may also show insufficient platelet inhibition on prasugrel treatment. The latter may be attributed to a general status of platelet hyperreactivity or to insufficient cytochrome P450 (CYP) -dependent in vivo bioactivation of orally administered antiplatelet agents.

At present, data and clinical experience is limited with regard to a personalised and platelet function testing guided approach of...
P2Y12 receptor directed antiplatelet treatment. Current guidelines have now included platelet function testing (class IIb recommendation) as a means to guide antiplatelet treatment in selected cases when clopidogrel is used (2, 15, 16).

Here, we present data from a registry of patients where antiplatelet treatment was altered based on platelet function testing results. For this specific analysis we aimed to assess the antiplatelet action of prasugrel in patients with HPR on clopidogrel after PCI in different clinical scenarios including prasugrel loading dose (LD) and different doses of prasugrel maintenance treatment (MD).

Materials and methods

Study population and design

Since 2009 we have started to perform platelet function monitoring on a routine basis in our institution. Obtained on-clopidogrel treatment aggregation values have been used since then for guidance of tailored P2Y12-receptor directed antiplatelet treatment. In this registry, 73 patients were included with (a) either HPR on clopidogrel (HPR defined per consensus [17] definition ≥468 AU x min) or (b) with comparatively high levels of PR on clopidogrel (range of 402-467 AU x min in this cohort). Of note, ADP-induced platelet aggregation (PA) values, clinical variables, comorbidities, the complexity of the performed PCI procedure of patients were considered for the decision when and how to intensify P2Y12 receptor directed antiplatelet treatment. The time point and mode of switching was always an individual decision of the treating physician. The decision for administration of prasugrel 5 mg was also individually driven by the treating physician and was primarily based on the patient’s age and co-morbidities. Of note, all patients who received prasugrel 5 mg MD were at the age of 70 years or older.

Due to their measured platelet function (PF) testing results on clopidogrel treatment, all patients within this registry were switched over to a prasugrel treatment regimen. Patients for this registry were recruited from June 2009 to September 2012 at the Deutsches Herzzentrum München or at the Klinikum der Technischen Universität München, Munich, Germany in a setting of routine PF testing for patients undergoing PCI. None of the patients in this registry had contraindications to prasugrel such as active pathological bleeding or a history of stroke.

Patients eligible for this registry required at least three PF measurements: 1) post-clopidogrel LD administration as well as 2) post-prasugrel LD administration during their index PCI visit and 3) a 3rd testing on prasugrel MD during a follow up visit. Figure 1 illustrates the flow of patients within this registry. In brief, during their index PCI visit, all patients received a clopidogrel 600 mg LD in preparation for the PCI procedure and the very first PF testing was performed following clopidogrel LD administration in the catheterisation laboratory directly before PCI or shortly after PCI. During their hospital stay post-PCI, the majority of patients received additional clopidogrel LDs in response to their individual PF testing results. In all patients with administration of additional clopidogrel LDs, PF testing was repeated with a sufficient time lag post-LD administration (up to three clopidogrel LDs were given in part of the patients). The time points of drug administration and blood sample collection with consecutive platelet function testing were documented. In general, as soon as measurement results of ADP-induced PA were available, it was promptly responded by an amendment of the antiplatelet treatment regimen.

The decision when to switch patients from clopidogrel over to prasugrel was made on an individual basis due to the attending physician’s choice. Once the decision was made, a prasugrel LD (high LD of 60 mg in all except for three patients that received a low LD) was administered and PF testing was repeated again with a time lag post prasugrel LD treatment. For prasugrel MD treatment in hospital and after discharge, a dose of 5 or 10 mg/day was administered, and PF testing on MD treatment was performed when patients returned to our hospital for a follow-up visit. At the follow-up visit, all patients were on prasugrel MD and the patient’s compliance was assessed at hospital admission through a medical history interview.

Blood sampling and platelet function testing

Whole blood for platelet function testing was collected into 4.5 ml plastic tubes containing lepirudin (25 µg/ml, Refludan, Dynabyte, Munich, Germany) and ADP (6.4 µM)-induced PA was assessed using multiple electrode platelet aggregometry (MEA) on the Multiplate analyser (Verum Diagnostica, Munich, Germany) as described previously (18). PA measured with MEA was quantified as area under the curve (AUC=AU x min) of aggregation units (AU). All material used for PF testing was obtained from the
manufacturer. Along with the index PCI, blood samples for PF testing were obtained in the laboratory from the arterial sheath of clopidogrel pre-loaded patients directly before PCI or shortly after PCI. For all other PF tests, blood samples were taken from patients in a steady-state condition with a loose tourniquet through a short venous catheter from an antecubital vein.

Study definitions
The definition of HPR (≥468 AU x min) was based on prior studies (5, 19) and the consensus document (17) of the Working Group on High On-Treatment Platelet Reactivity. Low platelet reactivity (LPR, ≤188 AU x min) and normal platelet reactivity (NPR, 189-467 AU x min) were also defined on the basis of prior studies (19, 20).

Statistical analysis
Variables are presented as mean ± standard deviation (SD), numbers (percentages) or median with interquartile range (IQR). Kolmogorov-Smirnov test was used to test for normal distribution of continuous data. PF data were non-normally distributed and dependent data were compared across groups with two-sided paired and unpaired Wilcoxon-test, as appropriate. Categorical variables were compared using Chi²-test for unpaired data and McNemar test for comparison of paired data, as appropriate. Spearman rank correlation was used to test for the correlation of PA values after prasugrel LD vs. MD treatment. A multiple linear regression model was used to test for independent predictors of PA under steady-state conditions of prasugrel treatment (=MD treatment). Thus, this model included the ADP-induced PA (in AU x min) on prasugrel MD treatment as the dependent variable. Independent variables included age, gender, renal function, acute coronary syndrome (ACS) at admission for follow-up visit, a low prior NPR, 189-467 AU x min), and diabetes mellitus (41.1%) and a history of myocardial infarction (52.1%) were high in this cohort. For their index PCI

Results
Patients and baseline characteristics
A total of 73 patients with a history of PCI were included in this registry. Baseline characteristics of these patients are described in Table 1. The mean (± SD) age of patients was 67.9 (± 11.6) years, of the 73 patients received an additional clopidogrel 600 mg LD treatment (clopidogrel LD,) was 620 [509-760] AU x min. Sixty-four patients (87.7%) exhibited a status of HPR per consensus definition (≥468 AU x min) (17), while the remaining patients (n=9) showed high levels of PR (range of 402-467 AU x min). Fifteen patients were already on clopidogrel MD treatment (75 mg/day) prior to their index PCI visit, while the remaining patients were P2Y12 receptor inhibitor naive before clopidogrel LD₁ administration. For post clopidogrel LD₁ testing results, PA values were numerically lower in these 15 patients as compared to the remaining patients (n=58) without prior clopidogrel MD treatment (523 [496-651] vs. 648 [528-779] AU x min; p=0.07).

On-clopidogrel treatment PA measurements
The ADP-induced PA (median [IQR]) of patients (n=73) after the first clopidogrel 600 mg LD treatment (clopidogrel LD₁) was 620 [509-760] AU x min. Sixty-four patients (87.7%) exhibited a status of HPR per consensus definition (≥468 AU x min) (17), while the remaining patients (n=9) showed high levels of PR (range of 402-467 AU x min). Fifteen patients were already on clopidogrel MD treatment (75 mg/day) prior to their index PCI visit, while the remaining patients were P2Y12 receptor inhibitor naive before clopidogrel LD₁ administration. For post clopidogrel LD₁ testing results, PA values were numerically lower in these 15 patients as compared to the remaining patients (n=58) without prior clopidogrel MD treatment (523 [496-651] vs. 648 [528-779] AU x min; p=0.07).

Forty-two of the 73 patients received an additional clopidogrel 600 mg LD (clopidogrel LD₂) resulting in a moderate but significant reduction of ADP-induced PA values (607 [523-756] vs. 511 [452-627] AU x min; p=0.005). However, all patients remained in a range (408-1034 AU x min) of high PA values with 28 patients still

Table 1: Baseline characteristics of registry patients. The table shows the baseline characteristics of patients recorded during their follow-up visit. Data presented are means SD or numbers of patients (percentages). ACS, acute coronary syndrome; MI, myocardial infarction; PCI, percutaneous coronary intervention.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=73)</th>
</tr>
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<tbody>
<tr>
<td>Age – years</td>
<td>67.9 ± 11.6</td>
</tr>
<tr>
<td>Woman – no. (%)</td>
<td>20 (27.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.1 ± 4.7</td>
</tr>
<tr>
<td>Diabetes mellitus – no. (%)</td>
<td>30 (41.1)</td>
</tr>
<tr>
<td>Active smokers – no. (%)</td>
<td>11 (15.1)</td>
</tr>
<tr>
<td>Hypertension – no. (%)</td>
<td>68 (93.2)</td>
</tr>
<tr>
<td>Hypercholesterolaemia – no. (%)</td>
<td>58 (79.5)</td>
</tr>
<tr>
<td>Previous bypass surgery – no. (%)</td>
<td>10 (13.7)</td>
</tr>
<tr>
<td>History of MI – no. (%)</td>
<td>38 (52.1)</td>
</tr>
<tr>
<td>History of PCI – no. (%)</td>
<td>73 (100)</td>
</tr>
<tr>
<td>No. of diseased coronary vessels – no. (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6 (8.2)</td>
</tr>
<tr>
<td>2</td>
<td>16 (21.9)</td>
</tr>
<tr>
<td>3</td>
<td>51 (69.9)</td>
</tr>
<tr>
<td>ACS at admission for follow-up – no. (%)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Creatinine level (mg/dl)</td>
<td>1.0 ± 0.3</td>
</tr>
</tbody>
</table>
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Values after prasugrel LD administration. ADP, adenosine diphosphate; AU, aggregation units; LD, loading dose.

Figure 2: Platelet aggregation in response to clopidogrel LD treatment. The figure shows the ADP-induced platelet aggregation values after repeated clopidogrel 600 mg LD administrations. Patients received either one clopidogrel LD (n=73, clopidogrel LD1), two clopidogrel LDs (n=42, clopidogrel LD2) or three consecutive clopidogrel LDs (n=2, clopidogrel LD3) before switching over to prasugrel treatment. Time intervals (median [IQR]) between clopidogrel administration and platelet function testing were 7.3 [4.9-13.1] hours for clopidogrel LD1, 5.5 [4.0-12.0] hours for clopidogrel LD2 and 9.0 [8.0-19.0] hours for clopidogrel LD3. The blue lines represent median values. Blue dots denote individual platelet aggregation measurements. ADP, adenosine diphosphate; AU, aggregation units; LD, loading dose.

Figure 3: Platelet aggregation following clopidogrel vs. prasugrel LD. The figure shows the ADP-induced platelet aggregation values after clopidogrel LD treatment in comparison to post prasugrel LD measurements. The time interval (median [IQR]) between prasugrel administration and platelet function testing was 7.0 [4.7-11.6] hours. The blue lines represent median values. Blue dots represent individual platelet aggregation values for the clopidogrel LD measurement (LD1 or LD2 or LD3) proximate to prasugrel switch. Red dots represent individual platelet aggregation values after prasugrel LD administration. ADP, adenosine diphosphate; AU, aggregation units; LD, loading dose.

On-prasugrel treatment PA measurements

After prasugrel LD administration, the ADP-induced PA was significantly lower as compared to the PF testing after the clopidogrel LD administration (LD1 or LD2 or LD3) proximate to prasugrel switch (156 [89-234] vs. 574 [462-698] AU x min; p<0.0001, Figure 3). Two patients received a low prasugrel LD of 30 mg resulting in PA values of 79 and 109 AU x min. One patient received only 10 mg LD resulting in a PA value of 408 AU x min.

After prasugrel LD administration, only 2/73 patients (2.7%) continued to show HPR (≥468 AU x min) (17) (Figure 3). These patients received an additional prasugrel LD resulting in a reduction of their ADP-induced PA from 494 AU x min to 279 AU x min in one patient, and from 908 to 97 AU x min in the other patient. A third patient with a high on-prasugrel PR level of 408 AU x min was given an additional prasugrel LD resulting in a reduction of the ADP-induced PA to 127 AU x min.

Patients were assessed on prasugrel MD therapy at a median time of six months [IQR 4-7 months] after their index PCI procedure. As demonstrated in Figure 4, the ADP-induced PA was significantly higher on prasugrel MD as compared to measurements post prasugrel LD (248 [145-406] vs. 156 [89-234] AU x min; p<0.0001). Of note, a remarkable response variability (10th to 90th percentile: 113-701 AU x min) was observed in patients on prasugrel MD. Five patients (6.8%) presented with an ACS (troponin positive non ST-elevation myocardial infarction [NSTEMI] in all five patients) at the time point of the follow-up visit. Four of these patients were on prasugrel 10 mg MD and one patient was on prasugrel 5 mg MD. The ADP-induced PA (PA, median [IQR]) on prasugrel MD in patients with ACS did not differ from the PA of patients who presented without ACS (246 [114-436] vs. 250 [153-407] AU x min; p=0.75).

No significant correlation of PA values for prasugrel LD vs. MD treatment measurements was observed (Spearman rank correlation coefficient=-0.07; p=0.58). Figure 5 shows the responder phenotype in patients for prasugrel LD vs. MD treatment. Rates of HPR were significantly higher on prasugrel MD as compared to prasugrel LD (16.4% vs. 2.7%; p=0.009), whereas vice versa rates of LPR (≤188 AU x min) were significantly higher after prasugrel LD administration compared to prasugrel MD (60.3% vs. 37.0%; p=0.008).

Maintenance treatment with a low dose of 5 mg/day prasugrel (n=13) resulted in significantly higher ADP-induced PA values as compared to 10 mg/day MD (n=60) therapy (408 [233-803] vs. 227 [134-324]; p=0.006, Figure 6). The proportion of HPR patients (per consensus definition, ≥468 AU x min) was significantly showing a status of HPR (≥468 AU x min) per consensus definition (17). Two of these patients received a third clopidogrel 600 mg LD (clopidogrel LD3). These patients showed PA values of 1070 and 556 AU x min post-clopidogrel LD3. All individual on-clopidogrel treatment PA values as well as the respective clopidogrel loading intervals between the different time points of PF testing are shown in Figure 2.
higher in 5 vs. 10 mg/day treated patients (46.2% vs. 10.0%; p=0.006).

Using a multiple linear regression model, we tested for variables that were independently associated with PA on prasugrel MD treatment. Multivariate analysis revealed that a low prasugrel MD of 5 mg/day (p=0.014) was independently associated with PA values on prasugrel MD treatment. There was also a trend for an association between BMI and PA values on prasugrel MD treatment (p=0.07). Other variables (age, gender, diabetes mellitus, renal function, ACS and smoking) included in the model were not independently associated with PA values (p ≥ 0.27) on prasugrel MD treatment.

Concerning the clinical follow up data, there were six TIMI major bleedings (8.2%), all of which occurred in hospital during the index PCI visit and after switch from clopidogrel over to prasugrel. Thus all patients were on prasugrel treatment when the bleeding event occurred. Two of these patients showed the phenotype of low platelet reactivity with ADP values of 60 and 122 AU x min. There were two patients (2.7%) with post-PCI myocardial infarction. Neither cases of stent thrombosis nor ischaemic or haemorrhagic stroke were reported.

Discussion

To the best of our knowledge this is the first report of a registry of patients recruited in a real-life clinical setting with high levels of platelet reactivity on clopidogrel being switched over to prasugrel, where the antiplatelet action of prasugrel was evaluated in different scenarios including prasugrel LD and MD treatment. With this approach present data provides important information on the antiplatelet action of prasugrel in a cohort of patients that failed to show sufficient platelet inhibition on clopidogrel treatment even following repeated clopidogrel LDs.

The key findings of this study are that (1) in this high-risk cohort of patients, prasugrel LD administration eliminated the phenotype of high platelet reactivity with ADP values of 60 and 122 AU x min.

Figure 4: Platelet aggregation following prasugrel LD vs. MD treatment. The figure shows the ADP-induced platelet aggregation values in response to prasugrel LD vs. prasugrel MD (5 mg or 10 mg/day). The blue lines represent median values. Red dots denote individual measurements on prasugrel LD and MD treatment. The black line illustrates the cut-off value for HPR (>468 AU x min per consensus definition). ADP, adenosine diphosphate; AU, aggregation units; HPR, high platelet reactivity; LD, loading dose; MD, maintenance dose.

Figure 5: Responder phenotype on prasugrel LD vs. MD. The figure shows the proportion of patients (in %) with LPR, NPR and HPR following prasugrel LD vs. prasugrel MD treatment. HPR, high platelet reactivity; LD, loading dose; LPR, low platelet reactivity; MD, maintenance dose; NPR, normal platelet reactivity.

Figure 6: Platelet aggregation measurements on prasugrel MD. The figure shows the ADP-induced platelet aggregation values in response to prasugrel 10 vs. 5 mg/day MD. The blue lines represent median values. Red dots denote individual measurements on prasugrel MD treatment. The black line illustrates the cut-off value for HPR (>468 AU x min) per consensus definition. ADP, adenosine diphosphate; AU, aggregation units; HPR, high platelet reactivity; MD, maintenance dose.
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Prasugrel loading dose administration eliminated the high rate of patients showing HPR on prasugrel.

Information about the antiplatelet action of prasugrel LD in patients with high PR levels on clopidogrel is limited despite the circumstance that these patients constitute a particular high risk cohort of patients who may benefit most from an intensified antiplatelet treatment (24). Results of our study showed that prasugrel LD administration – at least temporarily abolished HPR in the majority of patients and is thereby highly effective in lowering high on-clopidogrel PR values in the acute phase surrounding the PCI procedure.

The Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI) study (25) investigated the efficacy, safety and antiplatelet action of prasugrel compared to clopidogrel in stable patients with high PR levels on clopidogrel after elective PCI but was stopped early due to futility. Key results of TRIGGER-PCI were that prasugrel MD was assessed as three months post-PCI eliminated high PR levels on clopidogrel in the majority of patients. Despite that there was a trend towards a higher incidence of bleeding seen with prasugrel, results of TRIGGER-PCI cannot be used to draw conclusions on the clinical outcome of patients as the overall event rates were very low in the trial. With regard to the study design and in contrast to our registry here, the pharmacodynamic effect of prasugrel LD was not investigated in TRIGGER-PCI. Moreover, in comparison to TRIGGER-PCI we investigated a high-risk cohort of patients with a high rate of multivessel disease, prior MI and diabetes mellitus, who failed to show a sufficient response to clopidogrel even after repeated loading doses. In our cohort we found a considerable number of patients showing HPR on prasugrel MD treatment, especially for patients on the low prasugrel MD. In addition, we were able to compare the pharmacodynamic efficacy of prasugrel LD vs. prasugrel MD in these patients, data which is lacking in the TRIGGER-PCI study. Results of our study show that in high-risk patients with HPR on clopidogrel the platelet function phenotype is subject to change in the individual patient when comparing LD vs. MD treatment and that no correlation for platelet response to prasugrel LD vs. MD treatment exists in these patients. These findings, as well as prior pharmacodynamic studies demonstrating lower levels of platelet inhibition on prasugrel MD as compared to prasugrel LD (8, 26, 27) may argue for a platelet function monitoring strategy of antiplatelet drug responsiveness even beyond the acute phase and after discharge of PCI-treated patients.

Pharmacodynamic and clinical data on the antiplatelet action and the efficacy of a low prasugrel MD (5 mg/day) is limited with regard to patients showing high PR levels on clopidogrel. Aradi et al. assessed the antiplatelet efficacy of a prasugrel 5 vs. 10 mg/day MD therapy in ACS patients scheduled for PCI and these authors found HPR rates of >20% in patients receiving the low prasugrel MD (28). The large scale TaRgeted platelet Inhibition to Clarify the Optimal straGe to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial (29) and its platelet function substudy (30) assessed the pharmacodynamics and the clinical efficacy and safety of prasugrel (10 mg or 5 mg vs. clopidogrel 75 mg MD daily) in medically managed patients with unstable angina or NSTEMI ACS. In line with our findings, Gurbel et al. found that PA values were significantly higher in patients treated with prasugrel 5 mg daily as compared to prasugrel 10 mg daily (30). However, despite the greater P2Y12 receptor inhibition with prasugrel than with clopidogrel, prasugrel treatment was not associated with a reduction of the combined primary endpoint of myocardial infarction, stroke or cardiovascular death in ACS patients being medically managed without coronary stent placement (29, 30). Of importance, these studies did not focus on patients with high PR levels on clopidogrel and did not investigate PCI treated patients. Our study closes this gap of knowledge by focusing on PCI-treated patients with high PR levels on clopidogrel.

Data on predictors of prasugrel responsiveness are limited. Here we were able to provide initial evidence that a low prasugrel MD was found to be independently associated with PA values on prasugrel MD treatment. There was also a trend for an association between BMI and PA values on prasugrel MD treatment. Interestingly, this observation is in line with studies investigating predictors of clopidogrel responsiveness (21, 31) and might be explained by an increased distribution volume in obese patients requiring increased drug dosages. However, presence of a diabetes mellitus, age and sex were not associated with PA values on prasugrel MD treatment which is in contrast to studies focusing on the 2nd generation thienopyridine clopidogrel (23, 32, 33). Even in our high-risk cohort of patients the high potency of prasugrel seems to overcome the hyper-reactive state of blood platelets commonly seen in diabetic patients (34).

The value of an individualised antiplatelet treatment regimen in PCI-treated patients is still under investigation. In the recently published randomised open-label Double Randomisation of a

What is known about this topic?

- Patients with high levels of platelet reactivity on clopidogrel exhibit a high risk for ischaemic events after percutaneous coronary intervention.
- In general, prasugrel achieves superior platelet inhibition as compared to clopidogrel.

What does this paper add?

- Pharmacodynamic data on the antiplatelet action of prasugrel loading dose and maintenance dose in patients with high on clopidogrel treatment platelet is provided.
- Prasugrel loading dose administration eliminated the high platelet reactivity in the majority of patients.
- High platelet reactivity occurred in a considerable number of patients on prasugrel maintenance dose.
- Especially a low maintenance dose of prasugrel (5 mg/day) resulted in a high rate of patients showing high platelet reactivity.

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Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy (ARCTIC) trial (35), however, platelet function guided adjustment of antiplatelet treatment strategies in mostly elective patients treated with PCI and with HPR was not beneficial compared to standard clopidogrel therapy, which might support previous findings that platelet function guided adjustment of P2Y12 receptor inhibition appears to be more distinctive in ACS patients as compared to elective PCI patients (36).

The following limitations of our study merit mention: We only used one device (Multiplate analyser) for platelet function testing and it is unknown in how far our findings can be extrapolated to other platelet function assays. Our study lacks pharmacokinetic data since we did not measure plasma metabolites of clopidogrel or prasugrel. Besides, timing intervals between drug administration and platelet function testing were different in each group of assays but, importantly, they were long enough to assess the maximum antiplatelet effect as expected by the administered antiplatelet drug. In addition, we did not assess the antiplatelet efficacy of other potent antiplatelet drugs like ticagrelor in this high-risk cohort of patients with high levels of platelet reactivity on clopidogrel. A further limitation of the present study is that the sample size was too low to assess clinical outcome data. Finally, this analysis was a post-hoc analysis from a non-randomised study population and, therefore, it is subject to limitations inherent to all such analyses.

Conclusion

In a high-risk cohort of PCI-treated patients with high levels of platelet reactivity on clopidogrel, prasugrel LD resulted in sufficient platelet inhibition and abolished HPR in the majority of patients. However, the antiplatelet action of prasugrel was not uniform and response variability was more pronounced on prasugrel MD vs. LD treatment. The clinical impact of these findings warrants further investigation.

Conflicts of interest

Dr. Sibbing reported receiving speaker fees from Verum Diagnostica and fees for advisory board activities from Eli Lilly and Company and Astra Zeneca. Dr. Kastrati reported receiving speaker fees from Eli Lilly, Sanofi-Aventis and Bristol-Myers Squibb. None of the other authors declares any conflict of interest.

References

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