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Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel

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Summary

Patients receiving dual antiplatelet treatment with aspirin and clopidogrel are commonly treated with proton pump inhibitors (PPIs). Attenuating effects on platelet response to clopidogrel have been reported solely for the PPI omeprazole. PPIs differ in their metabolisation properties as well as their potential for drug-drug interactions. The aim of this study was to investigate the impact of different PPIs (pantoprazole, omeprazole, esomeprazole) on platelet response to clopidogrel in patients with previous coronary stent placement under chronic clopidogrel treatment. In a cross-sectional observational study, consecutive patients under clopidogrel maintenance treatment (n=1,000) scheduled for a control coronary angiography were enrolled. Adenosine diphosphate (ADP)-induced platelet aggregation (in AU*min) was measured with multiple electrode platelet aggregometry (MEA). From the entire study population, 268 (26.8%) patients were under PPI treatment at the time point of platelet function testing (pantoprazole, n=162; omeprazole, n=64; esomeprazole, n=42). Platelet aggregation (median [interquartile range]) was significantly higher in patients with omeprazole treatment (295.5 [193.5–571.2] AU*min) compared to patients without PPI treatment (220.0 [143.8–388.8] AU*min; p=0.001). Platelet aggregation was similar in patients with pantoprazole (226.0 [150.0–401.5] AU*min) or esomeprazole (209.0 [134.8–384.8] AU*min) treatment compared to patients without PPI treatment (p=0.69 and p=0.88, respectively). Attenuating effects of concomitant PPI treatment on platelet response to clopidogrel were restricted to the use of omeprazole. No attenuating effects on platelet response to clopidogrel were observed for pantoprazole or esomeprazole. Specifically designed and randomized clinical studies are needed to define the impact of concomitant PPI treatment on adverse events after percutaneous coronary intervention.

Keywords

Clopidogrel, proton pump inhibitors, platelet aggregation

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Introduction

For patients undergoing coronary stent placement, dual antiplatelet treatment with aspirin and clopidogrel is the therapy of choice to prevent thrombosis of the treated vessels and subsequent ischemic events (1). 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 (ADP) P2Y12 receptor (2, 3). The hepatic isoenzymes involved in this two-step metabolisation process of clopidogrel include CYP2C19, 3A4/5, 1A2, 2B6 and 2C9 (4). Platelet response to clopidogrel treatment is highly variable (5) and clinical (6), cellular (7) as well as genetic factors (8–10) have been declared causative for a low-response to clopidogrel. Low-response to clopidogrel loading (11–13) or maintenance treatment (14, 15) has been associated with adverse events following percutaneous coronary intervention (PCI) including stent thrombosis.

For the time period after PCI, patients receiving dual antiplatelet treatment with aspirin and clopidogrel are commonly treated with proton pump inhibitors (PPIs) with the objective of minimising the risk of gastrointestinal bleeding complications. Current guidelines recommend prescription of a PPI in all patients under dual antiplatelet treatment (16). Recently, it was reported in the randomized and double-blind OCLA (Omeprazole CLopidogrel Aspirin) study (17), that in clopidogrel-treated patients the PPI omeprazole was associated with significantly

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higher platelet P2Y12 reactivity. Hepatic metabolization of PPIs is CYP-dependent and it has been hypothesised that a potential drug-drug interaction at the level of the hepatic CYP system exists (17) causing an attenuated response to clopidogrel under concomitant omeprazole treatment due to diminished CYP-dependent metabolisation of clopidogrel into its active thiol metabolite.

Importantly, PPIs differ in their metabolisation properties as well as their potential for drug-drug interactions (18). From the currently available PPIs, only pantoprazole is metabolised to a significant extent by a conjugating enzyme, a cytosolic sulfotransferase, and therefore has by far the lowest potential for drug-drug interactions (19).

In the OCLA study (17), an interaction of PPI treatment on platelet response to clopidogrel has been investigated solely for the PPI omeprazole. A comparative analysis of omeprazole and other PPIs such as pantoprazole or esomeprazole regarding their interaction potential with clopidogrel has never been undertaken. Possible differences of the currently available PPI agents regarding their potential interactions with clopidogrel would have important clinical implications in terms of choosing one or the other PPI agent in the setting of antiplatelet treatment with clopidogrel.

The aim of this study was to investigate the impact of concomitant treatment with different PPIs (pantoprazole, omeprazole and esomeprazole) on platelet response to clopidogrel in patients with previous coronary stent placement under chronic antiplatelet treatment with clopidogrel and aspirin.

Materials and methods

Patients

A total of 1,000 consecutive coronary artery disease (CAD) patients admitted for a control coronary angiography scheduled per institution protocol were enrolled in this study at the Deutsches Herzzentrum München (Technische Universität München, Munich, Germany).

Patients eligible for this study were under dual antiplatelet treatment with aspirin and clopidogrel (75 mg/day) and had undergone a PCI a median of seven months [interquartile range=6–8] before study inclusion. Exclusion criteria were the presence of an acute coronary syndrome and treatment with GP IIb/IIIa inhibitors during the 10 days before platelet function testing.

The study of platelet function testing during angiography was approved by the institutional ethics committee, complies with the Declaration of Helsinki and all patients gave written informed consent for it.

Blood sampling

For all patients, peripheral venous blood samples were drawn directly at hospital admission in a fasting state and before any in-hospital drug administration with a loose tourniquet through a short venous catheter inserted into a forearm vein. The first tube drawn was labelled as a discard, and was not used for platelet function testing. Blood was placed in 4.0 ml plastic tubes containing the anticoagulant lepirudin (25 µg/ml, Refludan, Hirudin blood collection tubes, Dynabyte, Munich, Germany). Blood samples were kept at room temperature for at least 30 minutes (min) before platelet function testing.

Point-of-care platelet function testing

ADP-induced platelet aggregation in whole blood was assessed with multiple electrode platelet aggregometry (MEA) using a new generation impedance aggregometer called Multiplate® analyser (Dynabyte, Munich, Germany) as previously described (20–22). Aggregation measured with MEA is quantified as AU and area under the curve (AUC) of arbitrary units (AU*min). All material used including ADP was obtained from the manufacturer (Dynabyte). No centrifugation steps are needed for MEA and one measurement takes about 10 min.

Endpoints, definitions and sample size calculation

The primary endpoint of this study was ADP-induced platelet aggregation (in AU*min) in patients with concomitant pantoprazole treatment versus patients without PPI treatment. Sample size calculation for the present study was based on results of the OCLA study (17), in which an approximately 30% relative increase of P2Y12 reactivity was observed in the group of patients with concomitant omeprazole treatment. We sought to test whether the commonly prescribed PPI pantoprazole attenuates the clopidogrel response to a similar extent (relative increase of ADP-induced platelet aggregation by 30%) as observed for omeprazole in the OCLA study. The number of patients for the present study was therefore based on the assumption that co-administration of pantoprazole (compared to no PPI treatment) results in a 30% relative increase (from 300 ± 220 AU*min to 390 ± 220 AU*min) of ADP-induced platelet aggregation assessed with MEA. Under the assumption that approximately 15% of patients are under concomitant treatment with pantoprazole, which was based on medical records of our clinic, and choosing a power of 90% with a two-sided α-value of 0.017 (α-value corrected for the comparison of the 3 individual PPI groups against the non-PPI group), an overall sample size of at least 712 was required (nQuery advisor, version 5.0, Statistical Solutions, Cork, Ireland). In order to compensate for the other PPIs (omeprazole and esomeprazole) prescribed in our patients we aimed for the inclusion of a total of 1,000 patients.

The secondary endpoint of this study was ADP-induced platelet aggregation in patients with concomitant omeprazole or esomeprazole treatment versus patients without PPI treatment. Another secondary endpoint was the proportion of clopidogrel low-responders in patients with PPI treatment (for each PPI separately). Definition of low-response to clopidogrel varies from study to study and most of the studies investigating this issue have used the upper 5–44% of patients to define a cut-off value for low-response (23, 24). In the present study, we defined low-response to clopidogrel treatment by setting a cut-off point at the upper quintile (upper 20%) of patients according to MEA measurements. This cut-off point has been established in a large prospective study (n=1,608 patients) to define low-response to clopidogrel treatment(13), where we were able to demonstrate that low-response to clopidogrel assessed with MEA is significantly associated with an increased risk of stent thrombosis and other ischemic events following PCI.

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Statistical analysis

Variables are presented as mean ± standard deviation (SD), counts (percentages) or median with interquartile range [IQR]. For statistical analysis, categorical variables were compared using Chi^2-test. Kolmogorov-Smirnov test was used to test for normal distribution of continuous data. Normally distributed continuous data were compared between groups with the one-way analysis of variance test. Non-normally distributed continuous data were compared between groups by the Kruskal-Wallis test. Platelet function data obtained with MEA were not normally distributed, are presented as median [IQR], were compared across all groups with the Kruskal-Wallis test and were compared between two groups with two-sided unpaired Wilcoxon test. For the multivariate analysis, a multiple linear regression model was used with ADP-induced platelet aggregation (in AU*min) as the dependent variable and PPI treatment (with pantoprazole, omeprazole or esomeprazole) as well as all variables shown in Table 1 as independent variables. Overall tests across the four study groups were considered significant for a p-value <0.05. In the presence of a significant overall test, we proceeded with two-group comparisons, with individual PPI groups against the non-PPI group. In this case, p-values <0.017 were considered to indicate statistical significance (after application of the Bonferroni's correction for the presence of 3 PPI drugs). Analyses were performed using the software package S-PLUS version 4.5 (Insightful Corp, Seattle, WA, USA).

Results

Patients

From the entire study population, 268 (26.8%) patients were under PPI treatment at the time point of platelet function testing. Among them, 162 patients were under pantoprazole treatment, 64 patients were under omeprazole treatment and 42 patients were under esomeprazole treatment. A total of 732 patients in this study were therefore not treated with any PPI. The baseline characteristics of the study population according to PPI treatment (per group) are shown in Table 1. Baseline characteristics were well balanced between the different groups.

Platelet aggregation and PPI treatment

For the entire study population (n=1,000), ADP-induced platelet aggregation (median [IQR]) assessed with MEA was 227.0 AU*min [145.8–401.0]. ADP-induced platelet aggregation was significantly different between the four investigated groups (p=0.01). Figure 1 demonstrates box-blot analyses of ADP-induced platelet aggregation according to the different PPIs (pantoprazole, omeprazole, esomeprazole) and compared to patients without PPI treatment: Platelet aggregation was significantly higher in patients with omeprazole treatment compared to patients without PPI treatment (p=0.001). Platelet aggregation was similar in patients with pantoprazole or esomeprazole treatment compared to patients without PPI treatment (p=0.69 and p=0.88, respectively).

Multivariate analysis

Multivariate analysis revealed that co-administration of omeprazole is associated with an attenuated platelet response to chronic clopidogrel treatment. The other PPIs (pantoprazole and esomeprazole) were not independently associated with platelet response to clopidogrel. Other variables that showed an independent association with an attenuated platelet response to clopidogrel were diabetes mellitus, body mass index, renal insufficiency, active smoking, previous myocardial infarction and platelet count. Detailed results of the multivariate analysis are shown in Table 2.

Table 1: Data presented are means ± SD or numbers of patients (percentages). Body mass index is expressed as median [interquartile range, IQR]. CABG, coronary artery bypass grafting; MI, myocardial infarction; PPI, proton pump inhibitor.

Variable	No PPI (n=732)	Pantoprazole (n=162)	Omeprazole (n=64)	Esomeprazole (n=42)	P-value
Age, (years)	67.2 ± 10.0	68.0 ± 10.4	68.3 ± 11.2	65.6 ± 10.3	0.48
Woman, n (%)	158 (21.6)	35 (21.6)	21 (32.8)	13 (31.0)	0.11
Body mass index, (kg/m^2)	27.2 [24.8–30.0]	26.7 [24.7–29.4]	27.5 [25.4–30.5]	26.7 [24.7–29.9]	0.34
Ejection fraction, (%)	55.2 ± 10.8	54.7 ± 10.2	53.9 ± 11.3	55.3 ± 10.2	0.77
Diabetes mellitus, n (%)	191 (26.1)	37 (22.8)	14 (21.9)	17 (40.5)	0.11
Active smokers, n (%)	71 (9.7)	24 (14.8)	9 (14.1)	6 (14.3)	0.19
Hypertension, n (%)	515 (70.4)	107 (66.0)	42 (65.6)	26 (61.9)	0.45
Hypercholesterolemia, n (%)	577 (78.8)	124 (76.5)	52 (81.2)	27 (64.3)	0.14
Family history, n (%)	318 (43.4)	77 (47.5)	26 (40.6)	24 (57.1)	0.26
Previous MI, n (%)	281 (38.4)	76 (46.9)	27 (42.2)	17 (40.5)	0.25
Previous CABG, n (%)	117 (16.0)	32 (19.8)	11 (17.2)	9 (21.4)	0.57
Multivessel disease, n (%)	615 (84.0)	138 (85.2)	52 (81.2)	36 (85.7)	0.89
Platelet count, $x10^3/\mu l$	214 ± 55	227 ± 55	221 ± 58	222 ± 60	0.08
Serum creatinine, mg/dl	1.0 ± 0.4	1.1 ± 0.3	1.0 ± 0.3	0.9 ± 0.4	0.26

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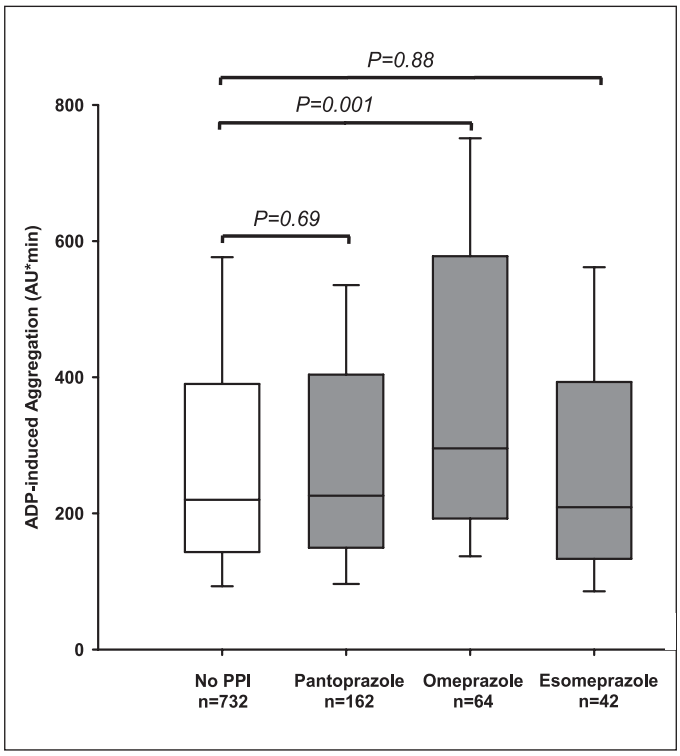

Figure 1: PPI treatment and platelet aggregation. Box plot analyses (n=1,000 patients) of multiple electrode platelet aggregometry (MEA) measurements for adenosine diphosphate (ADP)-induced platelet aggregation according to PPI treatment. Boxes indicate 25th and 75th percentiles and whiskers denote 10th and 90th percentiles. PPI, proton pump inhibitor.

Table 2: Multivariable linear regression model with adenosine diphosphate (ADP)-induced platelet aggregation assessed with MEA (in AU*min) as the dependent variable. BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PPI, proton pump inhibitor.

Variable	Regression coefficient		P-value
	Value	Standard error	
PPI treatment			
Omeprazole	86.60	26.12	0.001
Pantoprazole	–8.69	18.71	0.64
Esomeprazole	–10.00	34.49	0.77
Age, (years)	0.56	0.79	0.47
Woman, n (%)	24.50	18.47	0.18
BMI (kg/m^2)	4.73	1.71	0.006
Ejection fraction, (%)	–0.58	0.73	0.42
Diabetes mellitus, n (%)	51.37	16.33	0.002
Active smokers, n (%)	57.74	22.84	0.01
Arterial hypertension, n (%)	10.83	15.54	0.48
Hypercholesterolemia, n (%)	–22.93	16.32	0.16
Family history of CAD, n (%)	–13.83	13.80	0.31
Previous MI, n (%)	33.87	14.92	0.02
Previous CABG, n (%)	26.86	19.64	0.17
Multivessel disease, n (%)	16.48	18.33	0.36
Platelet count, x10^3/µl	1.11	0.12	<0.001
Serum creatinine, mg/dl	70.05	30.80	0.02

Clopidogrel low-response and PPI treatment

The cut-off value for MEA measurements under clopidogrel treatment defining the upper quintile (20%) of patients for the entire study population was 456 AU*min. According to this cut-off value, 200 patients were defined as clopidogrel low-responders. The remaining patients (n=800) were defined as normal-responders.

The proportion of patients with a low-response to clopidogrel was significantly higher in patients with concomitant omeprazole treatment (n=64) compared to patients without omeprazole treatment (n=936) (32.8% vs. 19.1%, p=0.008). No significant differences were observed for the proportion of patients with a low-response to clopidogrel between patients under pantoprazole treatment (n=162) vs. patients without (n=838) pantoprazole treatment (19.1% vs. 20.2%; p=0.76) or patients with esomeprazole treatment (n=42) vs. patients without (n=958) esomeprazole treatment (19.0 % vs. 20.0 %; p=0.87).

Discussion

To the best of our knowledge this is the first study comparing the impact of concomitant treatment with three different PPIs including pantoprazole, omeprazole and esomeprazole on platelet response to clopidogrel treatment in a large cohort of CAD patients with previous PCI. In addition, this trial is the first with an assessment of low-response status to clopidogrel in the context of different PPIs by using a whole blood based point-of-care assay (MEA) and established (13) cut-off values for defining low-responsiveness to clopidogrel. The major result of the study is that no influence on platelet response to clopidogrel was observed for the PPI pantoprazole and for the PPI esomeprazole as well. A significant influence of PPI co-administration on platelet response to clopidogrel was observed solely for omeprazole. Patients under concomitant PPI treatment with omeprazole exhibited approximately 30% higher values of ADP-induced platelet aggregation and about one third of patients under omeprazole treatment were found to be clopidogrel low-responders. By showing diverging effects on clopidogrel response for different PPIs in one and the same study population, we were able to demonstrate that attenuating effects of PPI treatment on clopidogrel response are not a phenomenon observed for all PPIs in general. Major results of our study are corroborated by the fact that – besides omeprazole treatment – other known predictors of platelet response to clopidogrel, such as diabetes mellitus (25–27), body mass index (6), renal insufficiency (26) and smoking (28) were also found to be independent predictors of platelet response to clopidogrel maintenance treatment.

Findings of our trial are in line with the results of another study showing no influence of the two PPIs pantoprazole and esomeprazole on platelet inhibition by clopidogrel (29). In a further study investigating the PPI lansoprazole it was shown in a subgroup of subjects with high inhibition of platelet aggre-

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gation (IPA) that lansoprazole decreased IPA (30). However, both studies (29, 30) could not compare the impact of omeprazole with other PPIs on platelet response to clopidogrel; such data is provided by the present study. Concerning the PPI omeprazole, results of the present study confirm – for the first time – the results reported in the OCLA trial (17). In the OCLA trial and in our study, an approximately 30% relative increase in platelet function parameters (P2Y12 reactivity index using vasodilator-stimulated phosphoprotein (VASP) phosphorylation in the OCLA study and AU*min using MEA in the present trial) was observed in the group of patients with concomitant omeprazole treatment. The assays used for platelet function testing were different for both trials: For the OCLA study (17), a whole blood and flow-cytometry based assay, that measures the phosphorylation of VASP, was used. For the present study we used the MEA technique on the Multiplate analyser, which is a newly developed point-of-care assay based on the principles of impedance aggregometry (22). Despite the different platelet function assays used in both studies, we were able to confirm the results obtained in the OCLA study with the MEA technique in a large population of clopidogrel treated patients. Both assays provided similar results regarding the impact of omeprazole on clopidogrel response, which is a strong clue for the effect observed.

The relevance and usefulness of the MEA technique for easy and standardised assessment of platelet function in different clinical settings is increasingly recognised (13, 20, 21, 31–33). Besides a good correlation of MEA with light transmission aggregometry (LTA) (20), MEA is capable of detecting the amount of platelet inhibition achieved using different P2Y12 antagonists including clopidogrel, cangrelor and the active metabolites of clopidogrel and prasugrel in varying doses (32, 34). Recently, we were able to demonstrate that low-response to clopidogrel treatment assessed with MEA is significantly associated with an increased risk of stent thrombosis and other ischaemic events following PCI (13).

Results of our study provide further evidence for a relevant drug-drug interaction of clopidogrel and the PPI omeprazole at the level of their hepatic CYP metabolisation. For the CYP-dependent metabolisation of clopidogrel, a relevant part of the isoenzyme CYP2C19 has been demonstrated in different pharmacokinetic and pharmacodynamic studies (4, 9, 10).

Similar to clopidogrel, hepatic metabolisation of PPIs is also CYP-dependent. However, the different PPIs are metabolised by the two isoenzymes CYP2C19 and CYP3A4 to varying and PPI specific degrees (35). Whereas omeprazole is the PPI with the highest affinity to CYP2C19 and is therefore predominantly metabolized by this isoenzyme, pantoprazole and esomeprazole exhibit a high affinity to both CYP2C19 and CYP3A4 (18, 36). In a comparison of inhibitory effects of different PPIs on different human cytochrome P450 enzymes, esomeprazole showed less inhibitory potency on CYP2C19 compared with omeprazole (37). Moreover, the PPI pantoprazole is unique for its metabolisation since it is also metabolised by a cytosolic sulfotransferase, which is non-saturable and not a part of the CYP system (35). Currently available PPI agents differ in their propensities to interact with other drugs, a finding which is mainly attributed to their CYP or non-CYP dependent metabolisation (18). Due to its specific dependence on CYP2C19 compared to other PPIs, a number of studies have shown that omeprazole carries a considerable potential for drug interactions, whereas pantoprazole or esomeprazole – due to their more flexible metabolisation properties – appear to have lower potential for interactions with other medications (18, 38). This circumstance is in line with the results of our study as a significant impact on platelet response to clopidogrel was restricted to the use of omeprazole.

As current guidelines recommend prescription of a PPI in all patients under dual antiplatelet treatment (16), findings of the present study may have important clinical implications in terms of PPI selection in patients under dual antiplatelet treatment. Recently, different retrospective cohort studies have provided more evidence for a relevant clinical impact of concomitant PPI use in clopidogrel treated patients (39–41). However, the definite impact of concomitant PPI treatment on adverse events in the time period after PCI has to be determined in specifically designed and sufficiently powered randomised clinical trials. Results of the present study may provide the basis for such studies.

What is known about this topic ?

- Pantoprazole and esomeprazole do not attenuate the antiplatelet action of clopidogrel.
- Omeprazole attenuates the antiplatelet action of clopidogrel as assessed with VASP analysis.

What does this paper add?

- A comparative analysis for the proton pump inhibitors (PPIs) omeprazole, pantoprazole and esomeprazole: By showing diverging effects on clopidogrel response for different PPIs in one and the same study population, we were able to demonstrate that attenuating effects of PPI treatment on clopidogrel response are not a phenomenon observed for all PPIs in general.
- Using the multiple electrode platelet aggregometry (MEA) technique, results of the present study confirm – for the first time – the attenuating effects on clopidogrel response reported in the OCLA trial for the PPI omeprazole.
- Assessment of low-response status to clopidogrel in the context of different PPIs using MEA and established cut-off values for defining low-response to clopidogrel demonstrated that about one third of patients under omeprazole treatment were found to be clopidogrel low-responders.

Limitations

The present study has limitations that merit mention. Although providing similar results for the PPIs pantoprazole and esomeprazole, the study was only powered to assess the impact of pantoprazole treatment on platelet response to clopidogrel. An influence of esomeprazole cannot be excluded and the post-hoc power to detect a 30% relative increase in ADP-induced platelet aggregation for esomeprazole treatment was 57%. In addition, the number of patients with omeprazole treatment was small as well and the post-hoc power to detect the observed significant increase in ADP-induced platelet aggregation for the PPI omeprazole was 80%. Furthermore, we only provide pharmacodynamic

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(platelet aggregation) data for clopidogrel treatment with a single technique (MEA). Pharmacokinetic data on the metabolisation of clopidogrel in the presence of the different PPI agents is not provided. Finally, we assessed platelet function parameters for all patients at only one single time point and we did not assess intraindividual differences for each single patient with and without concomitant PPI treatment.

Conclusion

Attenuating effects of concomitant PPI treatment on platelet response to clopidogrel were restricted to the use of omeprazole. No attenuating effects on platelet response to clopidogrel were observed for pantoprazole or esomeprazole.

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