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**EXPERT
OPINION**

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Esomeprazole and rabeprazole did not reduce antiplatelet effects of aspirin/clopidogrel dual therapy in patients undergoing percutaneous coronary intervention: a prospective, randomized, case–control study

Li-Peng Liu, Yan Wang, Rui Si, Ming Yuan, Kang Cheng[†] & Wen-Yi Guo[‡]

[†]Department of Cardiovascular Medicine, Xijing Hospital, Fourth Military Medical University, Xi'an, China

Objectives: Controversy has been prompted based on drug interaction between proton pump inhibitors (PPIs) and aspirin/clopidogrel leading to weakened effects. However, whether such interaction was drug-specific or class effect remains controversial. This study predicted the impact of esomeprazole and rabeprazole on efficacy of dual antiplatelet therapy (DAPT).

Methods: This study, involving 150 patients, evaluated the efficacy of DAPT upon concomitant use of esomeprazole (40 mg/d) or rabeprazole (20 mg/d). Platelet reactivity was assessed by value of ADP-induced light transmittance aggregometry (LTA) and vasodilator-stimulated phosphoprotein phosphorylation-platelet reactivity index (VASP-PRI) at day 1, day 3 and day 30 end points after initiation of DAPT.

Results: No significance were observed by post-hoc analysis of treatment-by-period interaction in LTA value and VASP-PRI value when compared with non-PPI users, which suggests no carryover effect in both PPIs over the 30-day treatment period. Moreover, no statistical differences was in LTA or VASP-PRI value in esomeprazole group while rabeprazole group showed decreased in antiplatelet function of DAPT at the day 3 and day 30 end points.

Conclusion: Although antiplatelet effect of DAPT were not affected upon concomitant use of both PPIs over the 30-day treatment period, esomeprazole exerts much more stable impact on antiplatelet effect than rabeprazole among respective end points.

Keywords: dual antiplatelet therapy, drug interaction, esomeprazole, platelet reactivity, rabeprazole

Expert Opin. Pharmacother. [Early Online]

1. Introduction

Percutaneous coronary artery stenting is increasingly used for the treatment of coronary heart disease (CHD), particularly in patients with risks of myocardium infarction. In addition, it is also being investigated as an alternative to surgery intervention such as coronary artery bypass grafting. Accumulating evidence from multiple centers supports the utility of antiplatelet and anticoagulant therapies as standard care before percutaneous coronary intervention (PCI) procedure and life-long following revascularization. Dual antiplatelet therapy (DAPT) consisting of aspirin and adenosine diphosphate (ADP) receptor antagonist clopidogrel prompts

greater prevention of thrombotic complications in most clinical settings.[1–3] However, numerous studies have shown that patients with high on-treatment platelet reactivity remain at increased risk of recurrent ischemic events.[4] Allowing for aspirin/clopidogrel dual antiplatelet therapy usually increased the risks of gastrointestinal mucosal injury and major bleeding, so consensus of professional societies recommended proton pump inhibitors (PPIs) for the prevention of bleeding complications.[5] Although concomitant prescription of PPIs and aspirin/clopidogrel has become increasingly common, it is a remarkable turn during the past 5 years that PPIs might antagonize antiplatelet and anticoagulant actions of dual antiplatelet therapy, and the myocardial infarction risks are more than three times higher when PPIs are concomitantly used.[6] As a frequently prescribed PPIs during the initiation and sometimes maintenance of dual antiplatelet therapy, omeprazole had been reported to competitively inhibit clopidogrel transformation, resulting in decreased clopidogrel antiplatelet activity. In the OCLA (Omeprazole Clopidogrel Aspirin) study, 20 mg/d omeprazole is reported to diminish clopidogrel's inhibition on platelet ADP receptor P2Y₁₂. The acute myocardial infarction rates in 1-year follow-up of patients receiving clopidogrel with and without omeprazole showed a significant increased rate for infarction in the PPIs high-exposure group (5.03%) compared to nonusers (1.38%).[7] In another retrospective cohort study of 8205 participants, concomitant use of clopidogrel and various kinds of PPIs conferred with an increased risk of acute coronary syndrome and reinfarction.[8] However, conflicting data from the COGENT trial demonstrated no apparent difference in adverse cardiovascular events in prophylactic PPIs (20 mg/d omeprazole) users and the nonusers.[9] New generations of PPIs, such as esomeprazole and rabeprazole, are commercially available; however, whether the clopidogrel–PPIs interaction is a class effect or a drug-specific effect was still controversial. In fact, other PPIs that may be less influential on CYP2C19 activity have not been well explored and is still a matter of debate. [10,11] Therefore, the aim of this study was to evaluate the effect of esomeprazole and rabeprazole, PPIs with low potential to inhibit CYP2C19 enzyme, on the antiplatelet efficiency of DAPT in a Chinese cohort with CHD following PCI.

2. Methods and materials

2.1 Patients and selection criteria

We conducted this prospective, randomized trial to evaluate the effects of esomeprazole and rabeprazole on platelet inhibition by DAPT. We prospectively recruited clopidogrel-naïve hospitalized patients who were admitted to the Department of Cardiology of the Xijing Hospital. The inclusion criteria included the following: (I) age \geq 18 years; (II) under the condition of acute coronary syndromes; (III)

undergone PCI; (IV) received a 600 mg clopidogrel and 300 mg aspirin loading dose between 12 and 24 h before PCI. We excluded all subjects that could be classified as follows: (I) heart failure at class IV (New York Heart Association); (II) thrombocytopenia (platelet count $< 100 \times 10^9/l$) or anemia (hemoglobin < 10 g/dl); (III) any chronic illness, such as cancer, liver cirrhosis or end-stage renal failure; (IV) history of hemorrhagic disorder, stroke or gastrointestinal ulcer; (V) patients who refused to participate in the study.

All patients were prescribed with aspirin (300 mg/d loading dose and 100 mg/d maintenance dose) (Bayer HealthCare AG, Germany) in combination with clopidogrel (600 mg/d loading dose followed by 75 mg/d maintenance dose) (Sanofi Aventis, Bridgewater, NJ). The patients in esomeprazole group were receiving esomeprazole 40 mg/d (AstraZeneca LP, Wilmington, DE), while rabeprazole group were receiving rabeprazole 20 mg/d (Eisai Pharmaceuticals Co, Tokyo); administration of PPIs was at the same time of clopidogrel/aspirin. Regimen of nonusers of PPIs group was without taking esomeprazole, rabeprazole or any other gastric acid-suppressing agents.

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee and Institutional Review Board of Xijing Hospital, Fourth Military Medical University. Writing consent was sent to each patient before the initiation of the study. An independent data safety monitoring committee was instituted for adjudication of adverse clinical events.

2.2 Follow-ups and study end point

The primary outcome measure was residual platelet reactivity which was assessed by the value of ADP-induced light transmittance aggregometry (LTA) and vasodilator-stimulated phosphoprotein phosphorylation-platelet reactivity index (VASP-PRI) at three time points. Blood sampling for platelet function evaluation were conducted at the following time points: (1) day 1 end point (baseline platelet function tests which were performed 24 h after administration of a loading dose of aspirin/clopidogrel), [12] (2) 3 days after maintenance dose of aspirin/clopidogrel (concomitant intake of study medication) and (3) 30 days after maintenance dose of aspirin/clopidogrel (concomitant intake of study medication). All platelet function tests were performed on the same day and within 2 h of sampling. Baseline assessment included recording of demographic data, cardiovascular risk factors and concomitant medications. EDTA and citrate (3.2 and 3.8%) blood collection tubes were used for blood sampling. Drug therapy compliance was assessed by telephone calls once per week after discharge and at the outpatient clinic visit 30 day end point. The treating physician and the investigators who evaluated the clinical end points were blinded to the results of the platelet function activity.

2.3 ADP-induced platelet aggregation test

Platelet aggregation was performed using LTA. The whole blood specimens were drawn into Vacutainer tubes with 3.8% trisodium citrate and centrifuged at 800 revolutions/min for 10 min to obtain platelet-rich plasma (PRP). The platelet-poor plasma (PPP) was further obtained by a second centrifugation of the blood fraction at 2500 revolutions/min for 10 min. The platelet count in PRP was adjusted to the range of 250,000/ μ l by dilution with autologous plasma when platelet count was out of range. Light transmission was adjusted to 100% line with PPP and a 0% baseline with PRP before addition of the agonist; the agonist used was ADP 20 μ mol/l due to light transmittance aggregometry induced by 20 μ mol/l ADP recommended for use by a current Chinese Society of Cardiology proposed guideline on platelet function testing in response of patients undergoing antiplatelet drugs.[13] A 0.45 ml portion of PRP were incubated at 37°C for 3 min, then agonist was added into the PRP. Maximal platelet aggregation (MPA) and late platelet aggregation (LPA) values (5 min after the addition of ADP) of on-treatment platelet aggregation were measured. Results were given as MPA and LPA values according to the following formula:

$$[\text{Disaggregation (\%)} = 100 \times (1 - \text{LPA/MPA})].$$

2.4 Vasodilator-stimulated phosphoprotein phosphorylation assay

VASP-phosphorylation was performed by a diagnostic kit from Biocytex (Marseille, France).[14] Briefly, the citrated blood sample was incubated with prostaglandin E1 (PGE1) alone or PGE1+ADP; both were fixed with paraformaldehyde. After a cellular permeabilization, VASP under its phosphorylated state was labeled with a primary monoclonal antibody against serine 239-phosphorylated VASP (clone 16C2) is followed by a secondary fluorescein isothiocyanate-conjugated polyclonal goat anti-mouse antibody. Final analyses were performed on a quantitative flow cytometry (Biocytex Inc., Marseille, France). A PRI was calculated using mean fluorescence intensity (MFI) in the presence of PGE1 alone or PGE1+ADP according to the following formula:

$$\text{PRI (\%)} = [\text{MFI}_{(\text{PGE1})} - \text{MFI}_{(\text{PGE1+ADP})}] / \text{MFI}_{\text{PGE1}} \times 100$$

2.5 Statistical analysis

The number to treat was estimated on the basis of previous experience.[7] We estimated that a study sample size of 120 would enable a one-half standard deviation (SD) difference (i.e., a 10% difference in PRI between groups) to be detected, which with a statistical power of 0.8 and an α of 0.05. To ensure that this sample size would be available for analysis, 30 extra patients were randomized and included. Platelet function measures were obtained in blood samples taken at day 1, day 3 and day 30 of the double-blind treatment period. General Linear Model Repeated Measures

ANOVA was used to evaluate values of ADP-induced LTA and VASP-PRI at three end points of administration of aspirin/clopidogrel, results were analyzed by a mixed-model and the model included the effects of treatment, therapeutic time and treatment-by-period interaction.[15] For the assessment of treatment-by-period interaction among three groups, Scheffe multiple comparison of *post hoc* analysis was used. Comparisons of respective regimen on each end point and same regimen on different end points were obtained from the model and compared by a one-way ANOVA and *post hoc* analysis. Statistical analysis of present study was performed using SPSS v22.0 software (SPSS Inc., Chicago, IL, USA). A *p* value <0.05 was considered statistically significant throughout the analyses. All laboratory data were normally distributed and were described as mean \pm SD or *n* (%).

3. Results

3.1 Patient disposition and baseline characteristics

Between March 2014 and October 2014, 162 clopidogrel-naive hospitalized patients were assessed for eligibility according to the inclusion and exclusion criteria. Ten patients refused to participate in the study and two patients developed gastrointestinal complications prior to the initial test. A total of 150 patients between the ages of 34 and 75 years were enrolled and well balanced; baseline characteristics and procedural features were presented in TABLES 1 and 2. All eligible patients were randomly divided into non-PPI user group (without any placebo or other gastric acid-suppressing agents) (*n* = 30), esomeprazole group (*n* = 60) and rabeprazole group

Table 1. Baseline characteristics of enrolled patients.

Variables	Esomeprazole <i>n</i> = 60	Rabeprazole <i>n</i> = 60	Control <i>n</i> = 30	<i>p</i> value
Gender, males	43/17	38/22	22/8	0.51
Age, years	63 \pm 10	61 \pm 12	59 \pm 10	0.24
Risk Factor				
Diabetes	14(23.3)	13(21.7)	5(16.7)	0.76
Hypertension	32(53.3)	34(56.7)	15(50)	0.83
Hyperlipidemia	9(15)	13(21.7)	8(26.7)	0.39
Current smoker	26(43.3)	28(46.7)	18(60)	0.32
Acute MI	9(15)	12(20)	8(26.7)	0.41
Previous MI	9(15)	7(11.7)	8(26.7)	0.18
Family history	2(3.3)	4(6.7)	2(6.7)	0.67
Previous Medication				
β -blocker	53(88.3)	47(78.3)	28(93.3)	0.12
ACEI/ARB	52(86.7)	50(83.3)	23(76.7)	0.49
Statin	60(100)	60(100)	30(100)	N/A
Heparin	60(100)	60(100)	30(100)	N/A

The values are expressed as the mean \pm SD or *n* (%).

ACE: Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; MI: Myocardial infarction; N/A: Not Applicable.

Table 2. Procedural characteristics according to the randomized treatment.

	Esomeprazole <i>n</i> = 60	Rabeprazole <i>n</i> = 60	Control <i>n</i> = 30	<i>p</i> value
Treated vessel				
Left main	2(3.3)	3(5)	1(3.3)	0.88
Left anterior descending	40(66.7)	37(61.7)	18(60)	0.78
Left circumflex	12(20)	15(25)	7(23.3)	0.80
Right coronary artery	6(10)	5(8.3)	4(13.3)	0.75
Multivessel intervention	50(83.3)	47(78.3)	21(70)	0.34
Any PCI				
Balloon angioplasty only	3(5)	1(1.7)	2(6.7)	0.46
Stent implantation	57(95)	59(98.3)	28(93.3)	0.46
Drug-eluting stents	55(91.7)	53(88.3)	26(86.7)	0.73
Arterial access, no. (%)				
Transfemoral	15(25)	10(16.7)	4(13.3)	0.33
Transradial	45(75)	50(83.3)	26(86.7)	0.33

The values are expressed as the *n* (%).

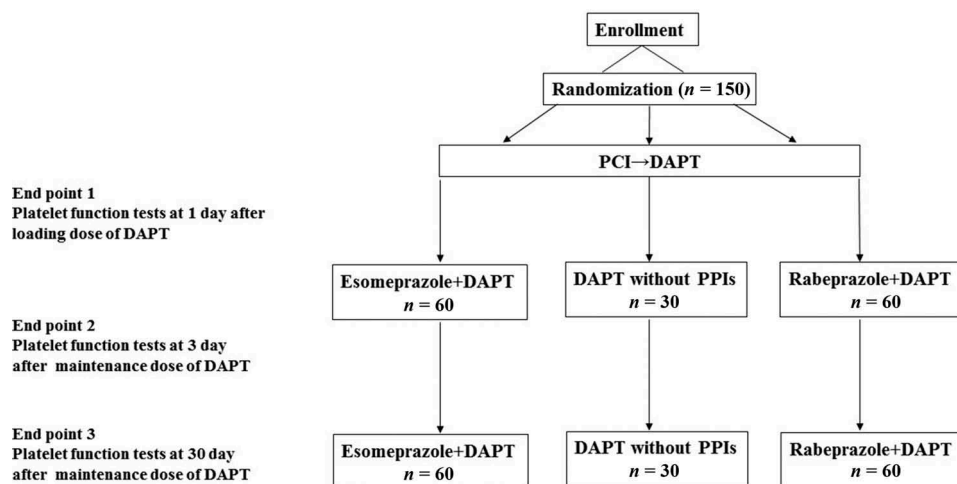


Figure 1. Flow diagram of the study design. DAPT: Dual antiplatelet therapy; PCI: percutaneous coronary intervention.

(*n* = 60) on a background of DAPT. The study design of the present investigation is illustrated in [FIGURE 1](#). The demographic and clinical characteristics, cardiovascular risk factors and concomitant medications did not differ significantly between the groups. None of the patients experienced bleeding or cardiac death.

3.2 Impact of PPIs on efficacy of DAPT over the 30-day treatment period

Measurements are displayed for ADP-induced LTA and VASP-PRI on day 1, 3 and 30 end points. [FIGURE 2](#) presented distribution of LTA and VASP-PRI values over the treatment periods, and result was showing a linear unconditionally stable in the duration of treatment among regimens. *Post hoc* analysis (Scheffe multiple comparisons) indicated

that no statistically significant differences were observed by treatment-by-period interaction, with LTA value of esomeprazole ($p = 0.88$) and rabeprazole ($p = 0.94$), as well as VASP-PRI value of esomeprazole ($p = 0.79$) and rabeprazole ($p = 0.76$) when compared with non-PPI users, which suggested no carryover effect in both regimens upon concomitant use of esomeprazole or rabeprazole.

3.3 Impact of PPIs on efficacy of DAPT between day 1 and day 3 end points

According to [TABLE 3](#), as for same regimen at different end points, when compared LTA and VASP-PRI values at day 1 and day 3 endpoints, there were no statistical significance in esomeprazole and non-PPI regimens. [FIGURE 3](#) showed similar LTA value (39.9 ± 9.1 versus 38.9 ± 7.3 , $p = 0.46$) and PRI value

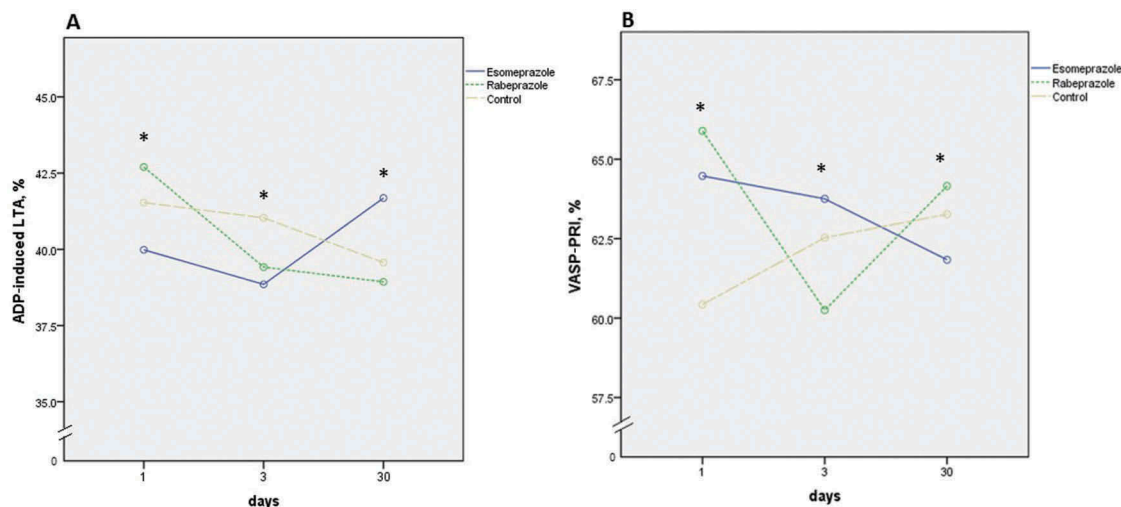


Figure 2. Serial changes in the level of antiplatelet effect of DAPT. A. 20 $\mu\text{mol/l}$ ADP-induced LTA values across day 1, 3 and 30 in DAPT of three groups; **B.** VASP-PRI values across day 1, 3 and 30 after DAPT of three groups. *Nonsignificant probability value for all comparisons at this time point. DAPT: Dual antiplatelet therapy; LTA: Light transmittance aggregometry; PRI: Platelet reactivity index; VASP: Vasodilator-stimulated phosphoprotein.

Table 3. Platelet function tests in users of esomeprazole, rabeprazole versus nonusers of proton-pump inhibitors on day 1, day 3 and day 30 end points.

Platelet function test	Esomeprazole (n = 60)	Rabeprazole (n = 60)	Control (n = 30)	Esomeprazole vs. rabeprazole (p value)	Esomeprazole vs. control (p value)	Rabeprazole vs. control (p value)
ADP-induced LTA, %						
Day 1	39.9 \pm 9.1	42.7 \pm 8.0	41.5 \pm 6.9	0.07	0.40	0.53
Day 3	38.9 \pm 7.3	39.4 \pm 8.2	41.0 \pm 9.2	0.70	0.23	0.37
Day 30	41.7 \pm 8.3	38.8 \pm 9.3	40.0 \pm 7.7	0.08	0.40	0.53
VASP-PRI, %						
Day 1	64.5 \pm 14.3	65.9 \pm 12.2	60.4 \pm 12.8	0.56	0.17	0.07
Day 3	63.8 \pm 12.0	59.6 \pm 12.9	62.5 \pm 13.4	0.07	0.67	0.30
Day 30	61.8 \pm 14.1	64.2 \pm 10.4	63.3 \pm 10.2	0.29	0.60	0.74

The values are expressed as the mean \pm SD, unless otherwise indicated.

ADP: Adenosine diphosphate; Control: Nonusers of PPI; DAPT: Dual antiplatelet therapy; LTA: Light transmittance aggregometry; PRI: Platelet reactivity index; VASP: Vasodilator-stimulated phosphoprotein.

(64.5 \pm 14.3% versus 63.8 \pm 12.0%, $p = 0.77$) for esomeprazole group while **FIGURE 5** showed LTA values (41.5 \pm 6.9% versus 41.0 \pm 9.2, $p = 0.81$) and PRI values (60.4 \pm 12.8% versus 62.5 \pm 13.4%, $p = 0.51$) for control group. However, a significantly higher value was obtained with rabeprazole group in 1 day in comparison to 3 day end point in both LTA value (42.7 \pm 8.0% versus 39.4 \pm 8.2%, $p = 0.04$) and PRI (65.9 \pm 12.2% versus 59.6 \pm 12.9%, $p < 0.01$) (**FIGURE 4**).

3.4 Impact of PPIs on efficacy of DAPT between day 1 and day 30 end points

The lack of significance was also observed at day 1 in comparison to day 30 end point because no statistical

difference existed in esomeprazole and control group, distribution of LTA value (39.9 \pm 9.1% versus 41.7 \pm 8.3%, $p = 0.26$) and VASP-PRI value (64.5 \pm 14.3% versus 61.8 \pm 14.1%, $p = 0.29$) for esomeprazole, as well as LTA value (41.5 \pm 6.9% versus 40.0 \pm 7.7, $p = 0.48$) and VASP-PRI value (60.4 \pm 12.8% versus 63.3 \pm 10.2%, $p = 0.37$) for control group in respective end points were illustrated in **FIGURES 3** and **5**. **FIGURE 4** showed parallel findings which observed with rabeprazole regimens—VASP-PRI values did not significantly separate at these two time points (65.9 \pm 12.2% versus 64.2 \pm 10.4%, $p = 0.42$); however, significant values were found in LTA value (42.7 \pm 8.0% versus 38.8 \pm 9.3%, $p = 0.02$).

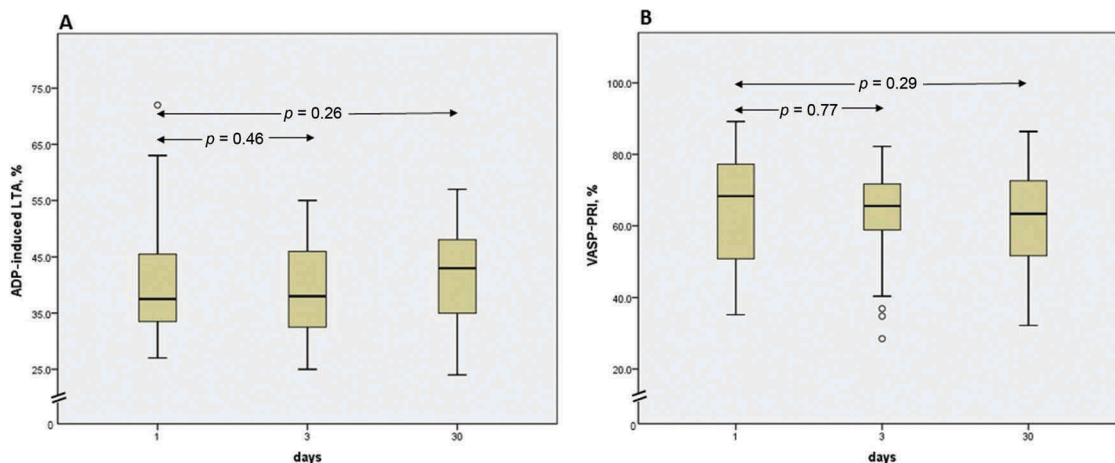


Figure 3. Impact of the esomeprazole on DAPT-induced antiplatelet effects characterized by LTA and PRI values in three time points. LTA and PRI values are expressed as least-squares means. Error bars indicate standard deviations of the mean. DAPT: Dual antiplatelet therapy; LTA: Light transmittance aggregometry; PRI: Platelet reactivity index; VASP: Vasodilator-stimulated phosphoprotein.

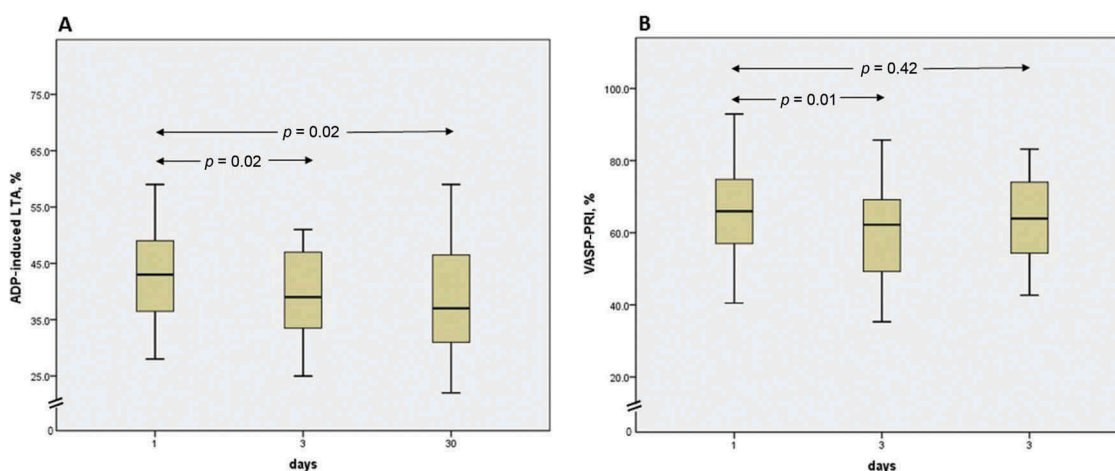


Figure 4. Impact of the rabeprazole on DAPT-induced antiplatelet effects characterized by LTA and PRI values in three time points. LTA and PRI values are expressed as least-squares means. Error bars indicate standard deviations of the mean. DAPT: Dual antiplatelet therapy; LTA: Light transmittance aggregometry; PRI: Platelet reactivity index; VASP: Vasodilator-stimulated phosphoprotein.

3.5 Clinical outcome and safety assessment

No cardiovascular events such as cardiovascular death, nonfatal myocardial infarction, gastrointestinal bleeding or ischemic stroke had been recorded in either group in 30-day treatment period. Esomeprazole and rabeprazole are generally safe and excellent for short-term utilization. However, concerns have been raised about paresthesia, diarrhea, nausea, constipation, abdominal pain and severe allergic reactions. More severe side effects may be associated with a greater risk of pneumonia, *Clostridium difficile* infection and hip fractures. During the treatment, there were no subjective symptoms or signs in any patients that met the adverse effect above.

4. Discussion

In the present prospective, randomized, case-control study, we administered esomeprazole (40 mg/d) and rabeprazole (20 mg/d), a common used dose for prophylaxis of side effects of gastrointestinal disorders in DAPT. This study demonstrated that over the treatment periods, result was showing a linear unconditionally stable in the duration of treatment among regimens, and no carryover effects in esomeprazole and rabeprazole group were shown when compared with non-PPI users in the setting of CHD over the 30-day treatment period.

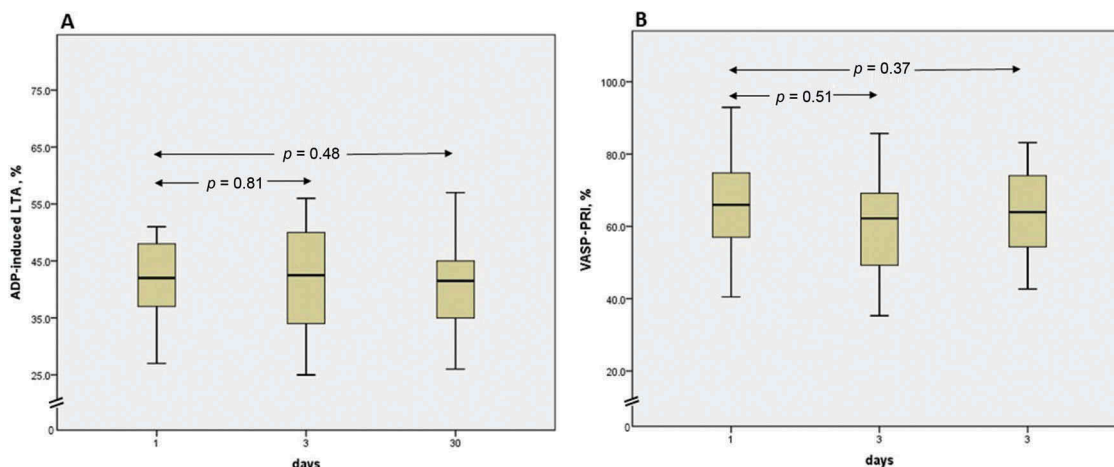


Figure 5. DAPT-induced antiplatelet effects of control group characterized by LTA and PRI values in three time points. LTA and PRI values are expressed as least-squares means. Error bars indicate standard deviations of the mean. DAPT: Dual antiplatelet therapy; LTA: Light transmittance aggregometry; PRI: Platelet reactivity index; VASP: Vasodilator-stimulated phosphoprotein.

Other than treatment-by-period interaction, platelet function evaluations were also conducted at three time points separately. Lack of significant difference in LTA value and VASP-PRI value was observed at day 1 when compared with the day 3 and day 30 end points existed in esomeprazole and control group. However, a significantly higher value was obtained with rabeprazole group at day 1 in comparison to day 3 end point in both LTA and VASP-PRI value. Moreover, higher LTA value was also found in rabeprazole group at day 1 than the day 3 end point during treatment. In comparison to esomeprazole group, rabeprazole group exerted a decreased antiplatelet function of DAPT day 3 and day 30 end points when compared with the 1 day end point. In view of this, we concluded that although use of rabeprazole did not have any carryover effect during 30-day period, esomeprazole might exert much more stable residual platelet reactivity among separate time points than rabeprazole.

Concomitant use of PPIs is usually prescribed to reduce hemorrhagic complications; however, a major concern is PPIs might abrogate antiplatelet efficiency. Therefore, even a small increase in cardiovascular risk caused by this drug interaction may have significant consequences. Although the implications correlated with the reduced pharmacodynamics effects in patient undergone DAPT as a cause of PPIs drug interaction remain controversial, this has prompted expert consensus to provide warning for the concomitant administration of these drugs.[16,17] According to a previous review by Fernando *et al.*, different PPIs inhibit CYP2C19 to various degrees.[18] Most of the available effect on the PPI–clopidogrel interaction is with omeprazole, a moderate CYP2C19 inhibitor. Gilard *et al.* reported antiplatelet response to DAPT regimen was significantly diminished upon

synchronous omeprazole administration following PCI. In this study, 7-day concomitant use of 20 mg/d omeprazole increased platelet activity for more than twofold in comparison with the non-omeprazole users group.[7] In another research in healthy volunteers, 40 mg/d omeprazole also antagonized clopidogrel-induced pharmacodynamic effects.[19]

Limited data are available on the pharmacodynamic effects of other PPIs, such as esomeprazole or rabeprazole. A research conducted by Fernando *et al.* suggested that patients should avoid taking esomeprazole for gastro-protection while on clopidogrel due to the biochemical interaction, which may increase a patient's risk of adverse clinical events. However, in comparison to ours, there may exist many differences in this study which have accounted for different results. One of them was that only 29 patients completed the study protocol and they were mostly male (93%); moreover, geographical location and racial difference should be considered as another important factor.[20] Previous pharmacokinetic studies have shown that rabeprazole is with lower potential influenced by CYP2C9 and CYP3A4,[21] while esomeprazole (S-isomer of omeprazole) tends to follow a similar pathway to the racemic mixture, but slightly less of this drug is metabolized by CYP2C19.[22] A cross-section study showing that ADP-induced platelet aggregation was not significantly different in patients taking esomeprazole when compared with those not prescribed a PPI.[23] Tunggal *et al.* reported esomeprazole did not reduced the platelet inhibitory effect of DAPT in patients elective for PCI, and platelet reactivity units (PRUs) in the esomeprazole group (20 mg/d, $n = 44$) on day 28 end point were not different from the baseline.[24] Yamane *et al.* showed that platelet aggregability during rabeprazole intake was

comparable to those who were undergoing DAPT without taking PPI.[25] A recent published study on effects of esomeprazole on platelet reactivity in CHD patients during DAPT indicated that concomitant use of esomeprazole with DAPT is not associated with reduced antiplatelet efficacy or increased risk of cardiovascular events, irrespective of CYP2C19 genotype [26] However, the number of patient administered esomeprazole was only 50 in this study. Moreover, they do not measure the baseline value before and after the initiation of DAPT, so it is not determined whether a higher platelet reactivity can be explained in terms of underlying platelet hyper-reactivity *per se*.

In accordance with prior researches, our study demonstrated that the concomitant use of esomeprazole or rabeprazole did not antagonized aspirin/clopidogrel dual antiplatelet therapy in Chinese patients who underwent PCI over the 30-day treatment period. Although our findings were not identical with the recommendation of American FDA, the current difference possibly due to the recommendation of FDA usually depends on the final results from clinical trial in US population. Comparing with people in Western countries, there is a great difference in interaction between PPI and (DAPT in Chinese patients. In view of this, results of this research were not necessarily in contradiction to present recommendation.

There are some limitations of our study. First, we did not distinguish the genetic polymorphism of CYP2C19. It may be argued that the CYP2C19 polymorphisms could have associated the pharmacodynamics response to clopidogrel. However, the influence of CYP2C19 loss-of-function allelic variations on clopidogrel-mediated effects is considered to be relatively small (5 – 12%).[27,28] Of note, prior studies failed to identify any influence of CYP2C19 polymorphisms on adverse outcomes of PPI-treated patients.[29,30] Second, although all of the 150 patients enrolled in our research were under the condition of acute coronary syndromes, we have not classified the specific subtype of acute coronary syndrome of enrolled patients; thus, subgroup analysis cannot be performed to evaluate the separate effect of each subtype in our research. Third, the longest follow-up in our study was 30 days. Whether there are any unintended results of concomitant use of esomeprazole or rabeprazole in longer follow-up end points might to be studied further.

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5. Conclusion

The objective of this study was to elucidate the pharmacodynamic interaction between esomeprazole, rabeprazole and DAPT in 30-day period. Our research indicated the lack of any statistically significant differences of LTA and VASP values in treatment-by-period interaction between esomeprazole, rabeprazole and non-PPI users during 30-day treatment. However, when compared with stability of antiplatelet effect in esomeprazole group, there was decrease in antiplatelet function at day 3 and day 30 end points in rabeprazole group on the background of DAPT.

All these results showed that esomeprazole and rabeprazole were much less likely to influence CYP2C19, supporting that the pharmacodynamic interaction between clopidogrel and PPIs is a drug-specific rather than a class effect. Most importantly, if a PPI medication is necessitated in patients at high risk of a gastrointestinal bleed while administrating antiplatelet therapy, esomeprazole might exert much more stable impact on antiplatelet effect of DAPT than rabeprazole and to be regarded as a more reasonable option.

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Declaration of interest

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Affiliation

Li-Peng Liu*, Yan Wang*, Rui Si, Ming Yuan, Kang Cheng[†] & Wen-Yi Guo[†]

[†]Author for correspondence

Department of Cardiovascular Medicine, Xijing Hospital, Fourth Military Medical University, 127 Changle West Road, Xi'an, 710032, China.

Tel: 86 29 84773465

Fax: 86 29 84773465

E-mail: wenyi_guo@126.com and chengkang2009@foxmail.com

*These authors contributed equally to this work as first author.