

# The effect of esomeprazole vs famotidine on aspirin/clopidogrel dual therapy after percutaneous coronary intervention

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## Abstract

**Background.** Regarding drug interactions between proton pump inhibitors (PPIs) and dual antiplatelet therapy (DAPT), controversies have arisen over the possibility that PPIs may interfere with the antiplatelet effect of DAPT. However, whether this interaction is drug-specific or a class effect needs to be determined. It is not clear whether famotidine, an H<sub>2</sub>-receptor antagonist (H<sub>2</sub>RA), interacts with DAPT.

**Objectives.** The aim of this study was to assess the impact of esomeprazole and famotidine on the efficacy of DAPT.

**Material and methods.** The study involved 160 patients undergoing elective percutaneous coronary interventions and treated with DAPT and concomitant use of esomeprazole (40 mg/d) or famotidine (40 mg/d). Platelet reactivity was measured with adenosine diphosphate (ADP)-induced light transmittance aggregometry (LTA) and vasodilator-stimulated phosphoprotein phosphorylation-platelet reactivity index (VASP-PRI) at baseline, 14 and 30 days after applying randomized acid-suppressing agents.

**Results.** No significance differences were observed in treatment-by-period interactions with LTA values ( $p = 0.298$ ) and VASP-PRI values ( $p = 0.867$ ), which suggested no carryover effect in either regimen over the 30-day treatment period. Intergroup comparisons were done between the 2 groups at 3 times, and similar findings were observed at each time (all  $p > 0.05$ ). As for intragroup measurements among the separate times, significantly lower LTA and VASP-PRI values existed on day 14 for both agents (both  $p < 0.05$ ).

**Conclusions.** The antiplatelet effect of DAPT was not affected by concomitant use of esomeprazole or famotidine. These 2 agents were much less likely than CYP2C19 polymorphisms to influence aspirin/clopidogrel therapy, supporting the assertion that the pharmacodynamic interaction between aspirin/clopidogrel and acid-suppressing agents is a drug-specific rather than a class effect.

**Key words:** platelet reactivity, drug–drug interaction, dual antiplatelet therapy, esomeprazole, famotidine

## Cite as

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Coronary heart disease (CHD) is the leading cause of death worldwide.<sup>1</sup> Percutaneous coronary intervention (PCI) with stent implantation is increasingly used for the treatment of ischemic heart disease. In China, more than 600,000 CHD patients underwent PCI in 2016, as published in the surveillance report from the Chinese Heart Association.<sup>2</sup> Accumulating evidence supports the utility of antiplatelet therapy as lifelong standard care following revascularization. Dual antiplatelet therapy (DAPT) consisting of aspirin and an adenosine diphosphate (ADP) receptor blocker such as clopidogrel is used to protect against thrombotic complications<sup>3</sup>; however, patients with high on-treatment platelet reactivity remain at high risk of recurrent ischemic events.<sup>4</sup> Aspirin/clopidogrel dual antiplatelet therapy usually increases the risks of major gastrointestinal bleeding, with events increased from 0.7% in patients on aspirin alone to 1.3% in those with aspirin and clopidogrel co-therapy during 12 months of treatment.<sup>5,6</sup> Several societies have therefore recommended acid-suppressing agents for the prevention of bleeding complications.<sup>7</sup> Clopidogrel requires metabolism by liver cytochrome p450 enzymes (CYPs) to become an active metabolite. Among the CYPs, CYP2C19 is now regarded to play the most important role.<sup>8</sup> Although proton pump inhibitors (PPIs) used in clinical settings are inactivated by CYP2C19, the extent of inactivation by CYP2C19 is dependent on the type of PPI; therefore, the association between PPIs and increased risk of serious cardiovascular events in patients receiving clopidogrel has led to a warning label by the FDA.<sup>9</sup>

As a frequently prescribed PPI during the maintenance of dual antiplatelet therapy, omeprazole had been reported to competitively inhibit clopidogrel transformation, resulting in decreased clopidogrel antiplatelet activity.<sup>9–11</sup> Nevertheless, whether the clopidogrel-PPI interaction is a class effect or a drug-specific effect is still a matter of debate. H<sub>2</sub>-receptor antagonist (H2RA) has been used as an alternative to PPIs. In a previous study, H2RA was reported to be effective in the prevention of ulcers with aspirin.<sup>12</sup> However, another study comparing PPI and H2RA regimens indicated that famotidine was inferior to pantoprazole in preventing digestive bleeding.<sup>13</sup> Whether famotidine causes any interference with the platelet inhibitory effect of aspirin/clopidogrel is unknown. The aim of this study was to investigate the antiplatelet efficacy of DAPT with concomitant use of esomeprazole and famotidine.

## Material and methods

### Patients and selection criteria

We conducted this prospective, randomized trial to assess the effects of esomeprazole and famotidine on platelet inhibition by DAPT. We recruited clopidogrel-naïve

hospitalized patients who had been admitted to the Department of Cardiology of the Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China. The inclusion criteria included: (A) age  $\geq 18$  years, (B) diagnosis of acute coronary syndromes, (C) performed PCI, and (D) received 600 mg clopidogrel and 300 mg aspirin loading dose between 12 h and 24 h prior to the PCI. We excluded all subjects that could be classified as having (A) class IV heart failure according to New York Heart Association (NHA) criteria, (B) thrombocytopenia (platelet count  $< 100 \times 10^9/L$ ) or anemia (hemoglobin  $< 10$  g/dL), (C) any chronic illness, such as cancer, liver cirrhosis or end-stage renal failure, (D) a history of hemorrhagic disorder, stroke or gastrointestinal ulcer, (E) known allergies to esomeprazole or famotidine, or who (F) refused to participate in the study.

In patients without prior antiplatelet therapy, the loading was 300 mg of aspirin (Bayer HealthCare AG, Leverkusen, Germany) and 600 mg of clopidogrel (Sanofi Aventis, Bridgewater, USA). Subsequently, the patients were maintained with 100 mg of aspirin and 75 mg daily of clopidogrel. The patients in the esomeprazole group received 40 mg/day of esomeprazole (AstraZeneca LP, Wilmington, USA), while the famotidine group received 40 mg/day of famotidine (Eisai Pharmaceuticals Co., Tokyo, Japan). The administration of these drugs was at the same time as the clopidogrel/aspirin. The patients were followed up daily during their hospital stay. After discharge, drug therapy compliance was assessed through a telephone call every 3 days and outpatient clinic visits on the 14<sup>th</sup> and 30<sup>th</sup> day. All the patients were instructed to bring their drug bags for examination.

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee and Institutional Review Board of the Second Affiliated Hospital of Zhejiang Chinese Medical University. All the participants provided their written informed consent. An independent data safety monitoring committee was instituted for the adjudication of adverse clinical events.

### Study endpoint

The study endpoint was residual platelet reactivity, which was assessed with the value of ADP-induced light transmittance aggregometry (LTA) and vasodilator-stimulated phosphoprotein phosphorylation-platelet reactivity index (VASP-PRI). Blood sampling for evaluating platelet function was conducted at 3 timepoints: (1) baseline (prior to randomization), (2) on the 14<sup>th</sup> day of treatment with randomized acid-suppressing agents and (3) on the 30<sup>th</sup> day of treatment with randomized acid-suppressing agents.

The baseline characteristics recorded included demographic data, cardiovascular risk factors and concomitant medications. All the investigators who evaluated the clinical endpoints were blinded to the results of platelet function activity.

## Platelet function tests

All platelet function tests were performed on the same day and within 2 h of sampling. Platelet aggregation was performed using LTA, as described in a previous study.<sup>14</sup> In short, whole blood was centrifuged at 800 rpm for 10 min to obtain platelet-rich plasma (PRP); platelet-poor plasma (PPP) was obtained by a 2<sup>nd</sup> centrifugation of the blood fraction at 2,500 rpm for 10 min. Light transmission was adjusted to the 100% line with PPP and a 0% baseline with PRP before the addition of the agonist. The agonist used was 20 µmol/L of ADP. Then, 0.45 mL PRP was incubated at 37°C for 3 min, after which the agonist was added to 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. The results were given as MPA and LPA values according to the formula:

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

VASP-PRI was also performed as described in a previous study.<sup>15</sup> Briefly, citrated blood samples were incubated with prostaglandin E1 (PGE1) alone or with PGE1+ADP, and both were fixed with paraformaldehyde. After a cellular permeabilization, VASP in its phosphorylated state was labeled with a primary monoclonal antibody against serine 239-phosphorylated VASP (clone 16C2), followed by a secondary fluorescein isothiocyanate-conjugated polyclonal goat anti-mouse antibody. Final analyses were performed using quantitative flow cytometry (Biocytex Inc., Marseille, France). A platelet reactivity index (PRI) was calculated using mean fluorescence intensity (MFI) in the presence of PGE1 alone or PGE1+ADP according to the formula:

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

## Statistical analysis

Calculation of the sample size for the present study was based on previous experience.<sup>10,14</sup> We estimated that a study sample size of 120 would enable detection of a one-half standard deviation (SD) difference (i.e., a 10% difference in platelet reactivity between groups) with an 80% statistical power and a 5% alpha risk. To ensure that this sample size would be available for analysis, 60 extra patients were randomized and included. All the laboratory data was normally distributed and was described as mean ±SD or n (%). The baseline variables of the 2 groups were compared using Pearson's  $\chi^2$  test when appropriate for categorical baseline variables and the two-sample t-test for continuous baseline variables. Repeated measures analysis of variance (ANOVA) was used to evaluate the values of ADP-induced LTA and VASP-PRI at 3 points in time.<sup>16</sup> Intergroup comparison of the respective regimens at each time point and intragroup comparison of the same regimen among the different timepoints were compared with the two-sample t-test. A p-value <0.05 was

considered statistically significant throughout the analyses. The statistical analysis was performed using SPSS v. 22.0 software (IBM Corp., Armonk, USA).

## Results

Between March and October 2017, 188 clopidogrel-naïve hospitalized patients were qualified for the study according to the inclusion and exclusion criteria. Among these, 18 patients refused to participate in the study and 10 developed gastrointestinal complications prior to the initial test; therefore, a total of 160 participants were enrolled. The baseline characteristics are presented in Table 1. All the participants were randomly divided into

Table 1. Baseline characteristics of the subjects

Variables	Esomeprazole (n = 80)	Famotidine (n = 80)	p-value
Men, n (%)	50 (62.5)	48 (60.0)	0.746
Age [years]	62.3 ±8.3	61.8 ±9.1	0.717
BMI	29.0 ±5.3	28.2 ±5.7	0.359
Medical history, n (%)			
Hypertension	32 (40.0)	27 (33.8)	0.413
Hyperlipidemia	39 (48.8)	43 (53.8)	0.527
Current smoker	31 (38.8)	28 (35.0)	0.623
Diabetes	21 (26.3)	18 (22.5)	0.581
PCI data, n (%)			
Chronic CAD	23 (28.8)	19 (23.8)	0.472
STEMI	17 (21.2)	21 (26.2)	0.457
NSTEMI	8 (10.0)	11 (13.8)	0.463
UA	32 (40.0)	29 (36.2)	0.625
Biochemistry detection			
FBG [mmol/L]	6.17 ±1.97	5.86 ±2.12	0.340
TG [mmol/L]	1.56 ±0.76	1.71 ±0.83	0.235
TC [mmol/L]	3.70 ±0.91	3.84 ±1.06	0.371
HDL-C [mmol/L]	1.16 ±0.39	1.05 ±0.32	0.385
LDL-C [mmol/L]	2.11 ±0.93	2.31 ±0.84	0.155
HbA1C [%]	8.27 ±1.88	8.02 ±1.95	0.410
Creatinine [mmol/L]	90 ±18	93 ±21	0.334
Current treatment, n (%)			
β-blocker	52 (65.0)	46 (57.5)	0.330
Heparin	60 (100)	60 (100)	N/A
CCB	9 (11.2)	12 (15.0)	0.482
ACEI/ARB	51 (63.8)	48 (60.0)	0.625
Insulin	4 (5.0)	7 (8.8)	0.349
Statin	60 (100)	60 (100)	N/A

TG – triglyceride; TC – total cholesterol; FBG – fasting blood glucose; CR – creatinine; UA – uric acid; STEMI – ST-elevation myocardial infarction; NSTEMI – non-ST-elevation myocardial infarction; UA – unstable angina; BMI – body mass index; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; CCB – calcium channel blocker; N/A – not applicable.

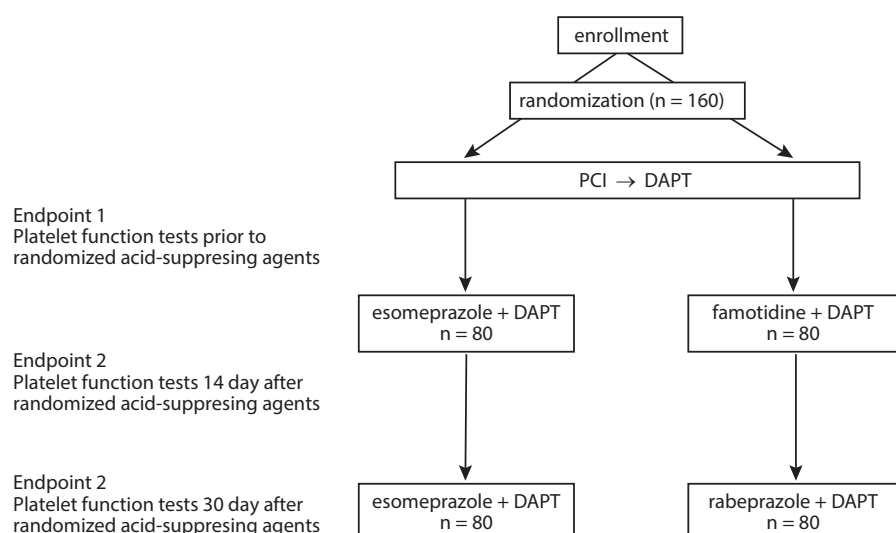


Fig. 1. Progress of the patients during the study

DAPT – dual antiplatelet therapy;  
PCI – percutaneous coronary intervention.

an esomeprazole group ( $n = 80$ ) and a famotidine group ( $n = 80$ ) with the concomitant use of DAPT. The study design of the present investigation is illustrated in Fig. 1. The rate of compliance with the study drug was 100%, and no patients were lost to follow-up. The baseline characteristics of both groups were comparable. None of the patients experienced bleeding or cardiac death.

Measurements were performed for ADP-induced LTA and VASP-PRI at baseline, day 14 and day 30 (Fig. 2,3). At days 14 and 30, a reduction was documented in both LTA and PRI values when compared to the baseline (both  $p < 0.001$ ). No statistically significant differences were observed in treatment-by-period interactions with LTA values ( $p = 0.298$ ) and VASP-PRI values ( $p = 0.867$ ) between the 2 regimens, which suggested no carryover effect in either regimen over the 30-day treatment period.

Intergroup comparisons between the esomeprazole and famotidine groups were done at 3 separate times (Table 2). The baseline LTA value was  $41.4 \pm 7.9$  in the esomeprazole group and  $40.3 \pm 6.4$  in the famotidine group ( $p = 0.316$ ), while the baseline VASP-PRI value was  $68.4 \pm 11.4$

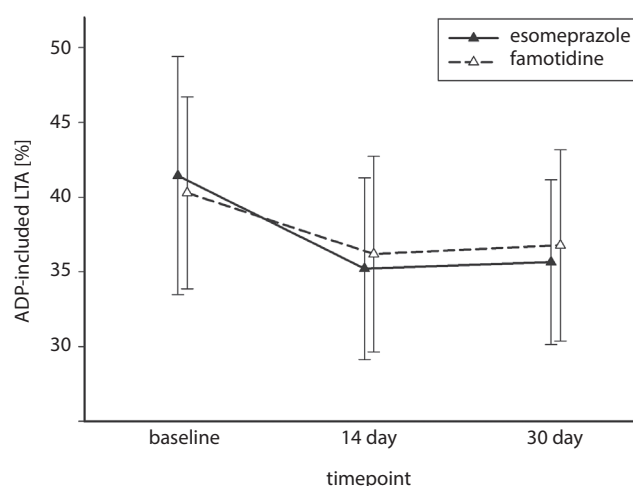


Fig. 2. 20 μmol/L ADP-induced LTA values across the baseline, day 14 and day 30 of randomized acid-suppressing agents

ADP – adenosine diphosphate; LTA – light transmittance aggregometry.

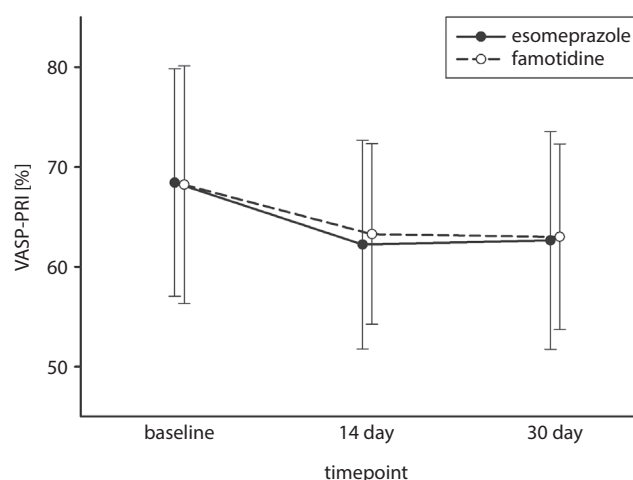


Fig. 3. VASP-PRI values across baseline, day 14 and day 30 of randomized acid-suppressing agents.

VASP – vasodilator-stimulated phosphoprotein; PRI – platelet reactivity index.

Table 2. Platelet function tests in users of esomeprazole vs famotidine at baseline and after 14 and 30 days of randomized acid-suppressing agents

Platelet function test	Esomeprazole (n = 80)	Famotidine (n = 80)	p-value
ADP-induced LTA [%]			
Baseline	41.4 ± 7.9	40.3 ± 6.4	0.316
Day 14	35.2 ± 6.1	36.2 ± 6.5	0.330
Day 30	35.6 ± 5.5	36.8 ± 6.4	0.235
VASP-PRI [%]			
Baseline	68.4 ± 11.4	68.3 ± 11.9	0.912
Day 14	62.2 ± 10.5	63.3 ± 9.1	0.497
Day 30	62.6 ± 10.9	63.0 ± 9.3	0.820

The values are expressed as the mean ± SD, unless otherwise indicated. ADP – adenosine diphosphate; LTA – light transmittance aggregometry; VASP – vasodilator-stimulated phosphoprotein; SD – standard deviation.



in the esomeprazole group and  $68.3 \pm 11.9$  in the famotidine group ( $p = 0.912$ ). Similar findings were also observed on day 14 ( $p = 0.330$  for LTA and  $p = 0.497$  for VASP-PRI) and day 30 ( $p = 0.235$  for LTA and  $p = 0.820$  for VASP-PRI).

As for intragroup measurements among the different points in each group, statistically significant differences existed between the baseline and day 14 in both LTA (both  $p < 0.001$  for esomeprazole and famotidine) and VASP-PRI values ( $p < 0.001$  for esomeprazole and  $p = 0.004$  for famotidine). Moreover, comparing day 14 and day 30 of randomized acid-suppressing agents, similar LTA values ( $p = 0.634$  for esomeprazole and  $p = 0.567$  for famotidine) and VASP-PRI values ( $p = 0.805$  for esomeprazole and  $p = 0.852$  for famotidine) were shown in the 2 groups. No cardiovascular events such as cardiovascular death, nonfatal myocardial infarction, gastrointestinal bleeding, or ischemic stroke were recorded in either group in the 30-day treatment period.

## Discussion

In the present prospective, randomized, case-control study, we administered esomeprazole (40 mg/day) and famotidine (40 mg/day), commonly used doses for preventing upper gastrointestinal disorders in patients receiving a combination of aspirin and clopidogrel. This study demonstrated that over the 30-day treatment period, there was no significant difference in antiplatelet effects between the 2 treatment groups. There are linear unconditionally stable results in the duration of treatment between the regimens, and no carryover effect was found in the esomeprazole or famotidine group in the setting of CHD patients receiving DAPT. Neither esomeprazole nor famotidine reduced the platelet inhibitory effect of DAPT in CHD patients who had undergone PCI. This study complements previous research, and also leads to further interest in PPIs or H2RA for upper gastrointestinal protection in DAPT users.

Concomitant use of acid-suppressing agents is usually prescribed to reduce upper gastrointestinal bleeding, but a major concern is that certain PPI drugs might abrogate antiplatelet efficiency. Because the implications correlated with the reduced pharmacodynamic effects in patients undergoing DAPT as a result of PPI drug interaction remain controversial, several studies have provided warnings against the concomitant administration of certain PPIs.<sup>17,18</sup> Most of the available results on PPI-clopidogrel interaction is with omeprazole, a moderate CYP2C19 inhibitor,<sup>19,20</sup> but limited data is available on the pharmacodynamic effects of other PPIs, such as esomeprazole. Because famotidine is excreted by the kidneys, hepatic enzymes (such as CYP2C19) do not metabolize such agents, and no interactions with clopidogrel and H2RAs have been reported.<sup>21</sup> Therefore, to avoid drug-drug interaction, famotidine may be an alternative for patients treated with DAPT. Uotani

et al. reported that anti-platelet drug-induced gastric injury was alleviated by famotidine without attenuation of anti-platelet functions.<sup>22</sup> However, the sample size in their study was only 20, and the subjects were all young, healthy volunteers, not CHD patients after undergoing PCI and taking DAPT.

There have been several reports on the relationship between DAPT and the concomitant use of esomeprazole and famotidine therapy, but a definite conclusion has not yet been determined.<sup>23–25</sup> Chan et al. showed that both treatments were comparable in preventing upper gastrointestinal bleeding in patients undergoing DAPT,<sup>23</sup> while another study by Ng et al. reported that PPIs were superior to H2RAs in the prevention of upper gastrointestinal bleeding.<sup>24</sup> Our findings were similar to the only existing study comparing the influence of the 2 agents on the platelet inhibitory effect of DAPT in which famotidine was found to have similar effects to esomeprazole during DAPT.<sup>25</sup> However, in that report, only 88 patients completed the study protocol and they were mostly male (84%); moreover, geographical locations and racial differences could be considered another important factor. In view of this, limited data is available on the pharmacodynamic interaction between esomeprazole and famotidine and DAPT.

This study has certain limitations. Firstly, we did not distinguish the genetic polymorphism of CYP2C19. It may be argued that CYP2C19 polymorphisms could have affected the pharmacodynamic response to clopidogrel. However, the influence of CYP2C19 loss-of-function allelic variations on clopidogrel-mediated effects is considered relatively small (5–12%).<sup>8,26</sup> Notably, prior studies have failed to identify any influence of CYP2C19 polymorphisms on adverse outcomes in PPI-treated patients.<sup>27,28</sup> Secondly, this study was limited by a relatively short follow-up period, and by the cohort of average-risk DAPT users without a prior history of gastrointestinal bleeding. It has been shown that a history of upper gastrointestinal bleeding is the most important risk factor with DAPT use. Whether there are any unintended effects of concomitant use of acid-suppressing agents in longer follow-up and high-risk DAPT users should be studied further.

## Conclusions

The objective of this study was to demonstrate that the concomitant use of esomeprazole or famotidine did not antagonize DAPT in Chinese patients who had undergone PCI. Our research indicates a lack of any statistically significant differences between esomeprazole and famotidine users in LTA and VASP values in treatment-by-period interaction, which suggests that neither agent had a carryover effect on DAPT during the 30-day treatment. All these results showed that esomeprazole and famotidine were much less likely than CYP2C19 to influence the patients'

response to clopidogrel, indicating that the pharmacodynamic interaction between clopidogrel and acid-suppressing agents is a drug-specific effect rather than a class effect.

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