Influence of Omeprazole and Famotidine on the Antiplatelet Effects of Clopidogrel in Addition to Aspirin in Patients With Acute Coronary Syndromes

– A Prospective, Randomized, Multicenter Study –

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Background: It remains unclear whether concomitant use of omeprazole attenuates platelet function as compared with that of famotidine in patients with acute coronary syndromes (ACS) who receive clopidogrel.

Methods and Results: In this prospective study, 130 ACS patients treated with aspirin and clopidogrel who underwent stent implantation were randomly assigned to receive a Japanese standard dose of omeprazole 10 mg daily or famotidine 20 mg daily for at least 4 weeks. Between 14 and 28 days after enrollment, there was no significant difference in the platelet reactivity index (PRI) measured with vasodilator-stimulated phosphoprotein phosphorylation assay between the omeprazole group (n=65) and famotidine group (n=65) ($55 \pm 17\%$ vs. $51 \pm 19\%$; $P=0.26$). The cumulative rate of adverse cardiovascular events at 12 months was similar in the groups (13% vs. 17%; $P=0.81$). The PRI was similar ($54.9 \pm 17.9\%$ vs. $54.0 \pm 17.8\%$; $P=0.83$) in the omeprazole group (n=33) and the famotidine group (n=39) among patients with ST-elevation myocardial infarction (STEMI). However, there was a trend toward a higher PRI ($55.2 \pm 15.9\%$ vs. $46.4 \pm 19.4\%$; $P=0.06$) in the omeprazole group (n=32) as compared with the famotidine group (n=26) among patients without persistent ST-segment elevation ACS.

Conclusions: As compared with famotidine, concomitant use of low-dose omeprazole does not significantly attenuate the antiplatelet effects of clopidogrel in patients with ACS, especially in those with STEMI. (*Circ J* 2012; **76**: 2673–2680)

Key Words: Acute coronary syndrome; Antiplatelet therapy; Clopidogrel; Platelets; Stents

The benefits of dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel have been established in patients with acute coronary syndromes (ACS), including those who undergo percutaneous coronary intervention (PCI).^{1–3} However, large clinical trials have recently demonstrated that DAPT is the most powerful predictor of gastrointestinal (GI) bleeding, which is independently associated with higher mortality in patients with ACS.^{4,5} Proton pump inhibitors (PPI) in combination with DAPT have thus been recommended in patients with multiple risk factors for GI bleeding.⁶

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Clopidogrel is a prodrug that must be metabolized by a 2-step, cytochrome P (CYP) 450-dependent process (with CYP3A4/5 and CYP2C19 playing the most important roles) to generate its active metabolite and acquire antiplatelet properties.⁷ Several studies have shown a broad variability in biologic response to clopidogrel, and patients with high on-treatment platelet reactivity (HTPR) who undergo PCI are at increased risk for death, myocardial infarction, and stent throm-

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basis.^{8–10} Previous pharmacodynamic studies have revealed that PPI attenuate the antiplatelet effect of clopidogrel in patients with stable coronary artery disease or healthy subjects and diminish the clinical efficacy of clopidogrel in patients with coronary artery disease, including ACS.^{11,12} However, recent studies have shown no increase in the risk of cardiovascular events in patients treated with clopidogrel plus PPI.^{13–16} To our knowledge, no study has prospectively examined whether concomitant use of omeprazole attenuates the antiplatelet effects of clopidogrel in patients with ACS including ST-segment elevation myocardial infarction (STEMI).

Strategies using H2 receptor antagonists (H2RA) such as famotidine might be a reasonable alternative to PPI, because the effect of famotidine is independent of CYP2C19 genotype.¹⁷ To date, the impact of gastric acid-suppressing strategies (PPI vs. H2RA) on HTPR rates remains unclear. The aim of this randomized study is to assess the impacts of omeprazole and famotidine on the antiplatelet effects of clopidogrel plus aspirin in Japanese patients with ACS who undergo PCI.

Methods

We conducted a prospective, open-label, randomized, multi-center study and enrolled patients with ACS who were scheduled for coronary stent implantation and received aspirin and clopidogrel. Patients with STEMI undergoing primary PCI had to have ischemic symptoms lasting 20 min or more, and ST-segment elevation of ≥ 1 mm in ≥ 2 continuous precordial leads or in ≥ 2 limb leads within 12 h after symptom onset. The inclusion criteria for ACS patients without persistent ST-segment elevation were ischemic symptoms that occurred within 72 h before study entry and lasted for ≥ 10 min, and either ST-segment depression of ≥ 1 mm or elevated levels of a cardiac biomarker of necrosis.

Exclusion criteria included major bleeding events within 7

days before enrollment, a recent history of gastric or duodenal ulcer, a serum hemoglobin level of <10 g/dl or >18 g/dl, a platelet count of $<100,000/\text{mm}^3$ or $>500,000/\text{mm}^3$, hematologic or malignant disease, a serum creatinine level of >2.0 mg/dl, severe liver dysfunction, or the use of any PPI, H2RA, warfarin, thienopyridine derivative, cilostazole, glycoprotein IIb/IIIa inhibitor, or fibrinolytic agent within 7 days before enrollment. Patients with ACS caused by stent thrombosis or in-stent restenosis were also excluded. In addition, patients were excluded from analysis if they did not receive stent implantation within 14 days after symptom onset, underwent coronary artery bypass grafting (CABG), or received oral anticoagulant agents before final platelet function tests, performed between 14 and 28 days after clopidogrel loading. The study protocol was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all patients.

According to a computer-generated randomization sequence at the central registration center, patients were assigned to receive a Japanese standard dose of omeprazole 10 mg once daily or famotidine 20 mg once daily for at least 4 weeks. Randomization was to occur before PCI was performed, and the study drug was to be administered as soon as possible after randomization. All patients also received aspirin 100 mg/day and a 300-mg loading dose of clopidogrel followed by a maintenance dose of 75 mg/day for at least 4 weeks. The study drug and DAPT were given at the same time. Baseline platelet function tests were performed before clopidogrel loading by means of vasodilator-stimulated phosphoprotein (VASP) phosphorylation analysis. Between 14 and 28 days after clopidogrel loading, the final platelet function test was performed. CYP2C19 *2 and CYP2C19 *3 variant alleles were also determined. The attending physician was blinded to the results of VASP phosphorylation analysis and CYP2C19 genotype.

Whole blood samples were processed within 48 h after col-

Table 1. Patient Characteristics and Angiographic Findings

	Omeprazole group (n=65)	Famotidine group (n=65)	P-value
Age (years)	67±11	66±11	0.58
Male gender	77%	81%	0.51
Height (cm)	164±9	164±7	0.75
Body weight (kg)	65±14	64±10	0.63
History of hypertension	68%	68%	1.00
History of diabetes mellitus	29%	15%	0.05
History of dyslipidemia	60%	62%	0.85
Habitual smoker	62%	57%	0.51
Previous myocardial infarction	6%	0%	–
Prior PCI	8%	2%	0.09
Prior CABG	0%	2%	–
Previous gastroduodenal ulcer	2%	3%	0.56
3-vessel disease	15%	11%	0.68
Vessel treated			0.28
Left main	3%	0%	
Left anterior descending	53%	43%	
Left circumflex	14%	20%	
Right coronary artery	30%	37%	
Primary PCI for STEMI patients	51%	60%	0.29
Planned PCI for the culprit artery	49%	40%	0.29
Drug-eluting stent use	37%	20%	0.05
Ejection fraction at discharge (%)	57±10	56±10	0.54

Values are percentages or means±SD.

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; STEMI, ST-segment elevation myocardial infarction.

lection for VASP phosphorylation analysis. We used a standardized flow-cytometric analysis (PLT VASP/P2Y12; BioCytex, Marseille, France), which is an adaptation of the method previously described by Schwarz et al.¹⁸ The platelet reactivity index (PRI) was calculated from the median fluorescence intensity (MFI) of samples incubated with prostaglandin E1 alone (PGE1) or PGE1 and adenosine diphosphate simultaneously (PGE1+ADP) according to the following calculation:

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

The rates of clopidogrel resistance as defined by a PRI of ≥50% on VASP analysis were determined in each treatment group as proposed previously.¹⁹ CYP2C19 genotypes were determined by Invader assay. Genotyping was done for CYP2C19*2 (rs4244285, c.681G>A) and CYP2C19*3 (rs4986893, c.636G>A) variants, because previous studies have reported that the CYP2C19*2 and CYP2C19*3 alleles are frequent, whereas the CYP2C19*17 allele is rare in Asians.^{20,21} Genomic DNA was extracted from whole blood using a commercially available QIAamp DNA Blood Mini kit (Qiagen, Venlo, Netherlands). Patients were classified into categories of metabolizer phenotypes with the use of established common-consensus star allele nomenclature. Thus, patients without a *2 or *3 allele were classified as “extensive metabolizers,” those with one *2 or *3 allele were classified as “intermediate metabolizers,” and those with two *2 or *3 alleles were classified as “poor metabolizers.” Carriers of at least 1 loss-of-function allele were classified as “loss-of-function allele carriers”.

PCI was performed in a standard manner. Primary PCI was performed immediately after administration of a loading dose of clopidogrel (300 mg, the Japanese standard dose). Planned PCI was performed 6 to 24 h after the loading dose of clopi-

grel. The choice of vessels treated, devices used (including stent type), and adjunctive medication administered to support PCI was left to the discretion of the treating physician. At the time of the study, glycoprotein IIb/IIIa inhibitors and intravenous anticoagulants other than unfractionated heparin were not approved for use in patients with ACS or stent implants (or both) in Japan. All patients were required to receive aspirin indefinitely and clopidogrel for at least 12 months after stent implantation. Clinical, procedural, and outcome data were prospectively collected by independent research personnel unaware of the study aims and entered into a central database. Follow-up visits were conducted at our hospitals for at least 12 months. Patients who became unable or who were unwilling to come to our hospitals were contacted by telephone.

The primary endpoint was the incidence of clopidogrel resistance as defined by a PRI of ≥50% at 14 to 28 days of treatment in the 2 groups. The secondary endpoint was the incidence of adverse cardiovascular events at 12 months (including death from cardiovascular causes, spontaneous myocardial infarction, unstable angina, stent thrombosis, target vessel revascularization, non-target vessel revascularization, and ischemic stroke). Myocardial infarction was diagnosed according to the universal definition proposed in 2007.²² Stent thrombosis was classified as definite or probable according to the Academic Research Consortium definitions.²³ Similar to REPLACE-2 trial,²⁴ non-CABG related major bleeding was defined as: symptomatic intracranial, intraocular, or retroperitoneal hemorrhage, clinically overt blood loss including GI bleeding resulting in a decrease in hemoglobin by >3 g/dl, or bleeding requiring transfusion of ≥2 units of red blood cells. To assess the impact of gastric acid-suppressing strategies on protective effect of upper GI damage, we also analyzed the incidence of

Table 2. Blood Examinations and Medications

	Omeprazole group (n=65)	Famotidine group (n=65)	P-value
CYP2C19 phenotype			0.26
EM	29%	17%	
IM	60%	66%	
PM	11%	17%	
Blood examination at 14–28 days			
Leukocytes	6,275±1,348	6,194±1,574	0.76
Hemoglobin	13.4±1.5	13.0±1.5	0.12
Platelet count (×10 ⁴)	25.7±5.2	22.9±6.9	0.01
Renal insufficiency*	23%	38%	0.05
Aspirin use on admission	11%	14%	0.59
Medications at 14–28 days			
Aspirin	100%	100%	1.00
Clopidogrel	100%	100%	1.00
Calcium channel blockers	25%	17%	0.28
β-blockers	55%	52%	0.72
ACE inhibitors	45%	51%	0.48
Angiotensin II receptor blockers	28%	22%	0.41
Statins	89%	83%	0.30
CYP3A4 metabolized statins	35%	28%	0.34

Values are percentages or means±SD.

CYP, cytochrome; EM, extensive metabolizers; IM, intermediate metabolizers; PM, poor metabolizers.

*Renal insufficiency was defined as estimated glomerular filtration rate <60 (ml·min⁻¹·1.73 m⁻²).

Table 3. Platelet Function Measurements and Clinical Outcomes

	Omeprazole group (n=65)	Famotidine group (n=65)	P-value
Vasodilator-stimulated phosphoprotein assay			
PRI at baseline (%)	82.3±7.0	80.9±9.3	0.38
PRI at 14–28 days (%)	55.1±16.9	51.0±18.7	0.26
PRI ≥50% (%)	61.50%	53.80%	0.38
Mean PRI variation (%)	−32.1±20.2	−35.3±33.3	0.52
Duration of clopidogrel therapy before final platelet function test (days)	19.3±4.3	19.7±4.5	0.68
Adverse cardiovascular events (%)	13%	17%	0.85
Non-CABG-related bleeding (%)	5%	2%	0.30
Symptoms of upper gastrointestinal damage (%)	0%	3%	0.24

PRI, platelet reactivity index; CABG, coronary artery bypass graft.

symptoms of upper GI events, such as epigastric pain, heartburn, nausea, vomiting, hematemesis, or tarry stool, confirmed by endoscopic examination with obvious findings of gastroduodenal ulcer or erosion as well as bleeding. The study was designed and conducted by the authors. The sponsor had no role in the design or conduct of the study, in the analysis of the results, or in the decision to publish the results.

Categorical variables were compared by the chi-square test and were reported as percentages. Continuous variables were compared by Student's t-test and are reported as means±SD. Potential predictors with P-values of <0.10 on univariate analysis were included in multivariate logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Event-free rates from the time of randomization were estimated by the Kaplan-Meier method and compared with the use of the log-rank test. P-values of <0.05 were considered to indicate statistical significance. Data were analyzed with SAS version 9.2 (SAS Institute Inc, Cary, NC, USA).

The required number of treated patients was estimated on the basis of a previous pharmacodynamic study.²⁵ We estimated that a study sample size of 130 would enable an 8 percentage-point difference in PRI to be detected, with a standard deviation of 16, an 80% statistical power, and a 5% 2-tailed significance level. To ensure that this sample size would be available for analysis, 50 extra patients were randomized and included.

Results

Between December 2009 and March 2011, a total of 292 consecutive patients with ACS who were scheduled to undergo coronary stent implantation were assessed for eligibility. After excluding 112 patients who met the exclusion criteria, 180 were randomly assigned to treatment. Ninety patients were assigned to the omeprazole group and 90 to the famotidine group. Data on 50 patients were not analyzed: 6 underwent CABG, 5 started to receive oral anticoagulant therapy, 21 did

Figure 2. Mean PRI at baseline and at 14 to 28 days in the 2 groups. PRI, platelet reactivity index.

Figure 3. Kaplan-Meier curve of freedom from adverse cardiovascular events including death from cardiovascular causes, spontaneous myocardial infarction, unstable angina, stent thrombosis, any revascularization, and ischemic stroke according to group.

not undergo stent implantation within 14 days, final blood samples were not obtained from 8 patients, and 10 patients were excluded because of serum hemoglobin levels or platelet counts meeting the exclusion criteria at final platelet function testing. The final analysis thus included data on 130 patients: 65 patients in the omeprazole group and 65 in the famotidine group. Among these patients, 72 had STEMI and 58 had ACS without persistent ST-segment elevation. A flowchart of the patients is shown in [Figure 1](#). There was no significant difference in the baseline characteristics between 130 patients and 50 patients who were not excluded (data not shown).

Although platelet count at 14 to 28 days was higher (25.7 ± 5.2 vs. 22.9 ± 6.9 ; $P=0.01$), and the incidence of diabetes mellitus (29% vs. 15%; $P=0.05$) and drug-eluting stent use (37% vs. 20%; $P=0.05$) tended to be higher in the omeprazole group than in the famotidine group, there were no clinically significant differences in age, sex, or the incidence of other coronary risk factors between the 2 treatment groups. More than half of

patients had CYP2C19 loss-of-function alleles (71% vs. 83%) and STEMI (51% vs. 60%), with no significant differences between the groups ([Tables 1,2](#)). The median duration of clopidogrel therapy before final platelet function test was similar in the omeprazole and famotidine groups (19.3 ± 4.3 days vs. 19.7 ± 4.5 days; $P=0.68$) ([Table 3](#)). The mean PRI at baseline ($82.3 \pm 7.0\%$ vs. $80.9 \pm 9.3\%$; $P=0.38$) was similar in the groups, and the PRI at 14 to 28 days significantly decreased from baseline in both groups and did not differ significantly between the groups ($55.1 \pm 16.9\%$ vs. $51.0 \pm 18.7\%$; $P=0.26$) ([Figure 2](#)). The proportion of patients with clopidogrel resistance as defined by a PRI of $\geq 50\%$ also did not differ (61.5% vs. 53.8%; $P=0.38$). The mean PRI variation was -32.1% in the omeprazole group and -35.3% in the famotidine group ($P=0.52$) ([Table 3](#)). The individual data was shown in [Figures S1A](#) and [S1B](#).

No patient was lost to follow-up. The cumulative frequency of adverse cardiovascular events at 12 months was similar in the groups (13% vs. 17%; $P=0.81$) ([Figure 3](#)). The most com-

Table 4. Patient Characteristics and Platelet Function Measurements According to Types of ACS

	Patients with STEMI			Patients without persistent ST elevation		
	Omeprazole group (n=33)	Famotidine group (n=39)	P-value	Omeprazole group (n=32)	Famotidine group (n=26)	P-value
Age (years)	67±10	64±12	0.33	67±12	69±10	0.52
Male gender	76%	85%	0.19	78%	77%	0.91
Height (cm)	164±8	165±8	0.37	164±9	163±8	0.65
Body weight (kg)	62±12	66±10	0.52	68±16	62±10	0.07
History of hypertension	82%	67%	0.14	53%	69%	0.21
History of diabetes mellitus	27%	15%	0.21	31%	15%	0.16
History of dyslipidemia	49%	69%	0.07	72%	50%	0.08
Habitual smoker	70%	54%	0.16	53%	62%	0.52
Previous myocardial infarction	0%	0%	—	13%	0%	—
Prior PCI	0%	3%	—	16%	0%	—
Prior CABG	0%	0%	—	0%	0%	—
Previous gastroduodenal ulcer	0%	3%	—	3%	4%	0.88
Renal insufficiency*	18%	44%	0.02	28%	31%	0.82
3-vessel disease	9%	15%	0.72	22%	4%	0.11
Drug-eluting stent use	9%	0%	0.17	66%	50%	0.17
Ejection fraction at discharge (%)	57±11	53±11	0.19	58±9	60±8	0.27
CYP2C19 phenotype			0.28			0.79
EM	32%	17%		25%	17%	
IM	57%	64%		64%	70%	
PM	11%	19%		11%	13%	
Vasodilator-stimulated phosphoprotein assay						
PRI at baseline (%)	81.9±8.7	80.3±11.5	0.53	82.8±4.7	81.8±4.4	0.42
PRI at 14–28 days (%)	54.9±17.9	54.0±17.8	0.83	55.2±15.9	46.4±19.4	0.06
PRI ≥50% (%)	58%	59%	0.90	66%	46%	0.13
Mean PRI variation (%)	−32.1±21.8	−29.2±37.8	0.70	−32.1±18.9	−44.6±22.7	0.03

Values are percentages or means±SD.

ACS, acute coronary syndromes. Other abbreviations as in Tables 1–3.

Renal insufficiency was defined as estimated glomerular filtration rate <60 (ml·min^{−1}·1.73 m^{−2}).

Table 5. Predictors of PRI ≥50% at 14 to 28 Days

	OR (95%CI)	P-value
IM or PM	3.59 (1.21–10.60)	0.02
Calcium channel blockers use	2.87 (0.84–9.79)	0.09
Obesity*	2.12 (0.76–5.92)	0.15

OR, odds ratio; CI, confidence interval. Other abbreviations as in Tables 2,3.

Potential predictors, which were demographic, clinical, and angiographic variables with P-values of <0.10 on univariate analysis, were included in a multivariate logistic regression analysis.

*Obesity was defined as body mass index >25 (kg/m²).

mon adverse events were target vessel revascularization and non-target vessel revascularization. Only 1 patient had ischemic stroke; however, there was no death from cardiovascular causes, myocardial infarction, or stent thrombosis during follow-up. Three patients had non-CABG-related, major colonic bleeding in the omeprazole group, and 1 patient had major bleeding from a gastric ulcer in the famotidine group. Only 2 patients in the famotidine group had symptoms of upper GI damage (including upper GI bleeding in 1 patient) (Table 3).

As a post-hoc analysis, we compared the impact of gastric acid-suppressing agents on the antiplatelet effects of clopidogrel in patients with STEMI (n=72) and those without persistent ST-segment elevation ACS (n=58). Among patients with

STEMI, there were no significant differences between the omeprazole group (n=33) and the famotidine group (n=39) in baseline characteristics other than the rate of renal insufficiency (18% vs. 44%; P=0.02). The mean PRI at baseline (81.9±8.7% vs. 80.3±11.5%; P=0.53) and at 14 to 28 days (54.9±17.9% vs. 54.0±17.8%; P=0.83) were similar in the treatment groups (Table 4). Among patients without persistent ST-segment elevation ACS, there were no significant differences in patient characteristics other than platelet count at 14 to 28 days (20.6±6.1 (×10⁴) vs. 24.2±4.9 (×10⁴); P=0.02) between the omeprazole group (n=32) and the famotidine group (n=26). Although the baseline PRI was similar in the treatment groups (82.8±4.7% vs. 81.8±4.4%; P=0.42), there were trends toward a higher PRI at 14 to 28 days (55.2±15.9% vs. 46.4±19.4%; P=0.06) and a higher rate of clopidogrel resistance as defined by a PRI of ≥50% (65.6% vs. 46.2%; P=0.13) in the omeprazole group as compared with the famotidine group. The mean PRI variation was −32.1% in the omeprazole group as compared with −44.6% in the famotidine group after 14 to 28 days of treatment (P=0.03) (Table 4). On multivariate logistic regression analysis, CYP2C19 loss-of-function allele carriage (intermediate metabolizers or poor metabolizers) was the only independent predictor of PRI ≥50% at 14 to 28 days (OR: 3.59, 95% CI: 1.21–10.60, P=0.02), whereas concomitant PPI use, previous PCI, diabetes mellitus, renal insufficiency, primary PCI for STEMI, and drug-eluting stent use were not (Table 5).

Discussion

In the present randomized study, as compared with famotidine, omeprazole did not significantly decrease the antiplatelet effect of clopidogrel as evaluated by VASP phosphorylation at 14 to 28 days in patients with ACS who underwent stent implantation (primary endpoint). The cumulative rate of adverse outcomes at 12 months did not differ between the omeprazole group and famotidine group. There was no significant difference in the incidence of non-CABG related major bleeding between the groups. Only 2 patients in the famotidine group had symptoms of upper GI damage. In the comparison of the PRI at 14 to 28 days between types of ACS, there were trends toward a higher PRI and the smaller PRI variation in the omeprazole group as compared with the famotidine group among those without persistent ST-segment elevation ACS; however, they were similar in the treatment groups among patients with STEMI. Multivariate logistic regression analysis showed that at least 1 CYP2C19 loss-of-function allele carriage was the only independent predictor of clopidogrel resistance.

In contrast to the results of previous pharmacodynamic studies in patients with stable coronary disease,^{25–27} our findings showed that the concomitant use of omeprazole did not significantly attenuate the antiplatelet effects of clopidogrel as compared with famotidine in the setting of ACS. Several reasons might account for the negative impact of clopidogrel responsiveness in patients who received omeprazole, compared with famotidine. First, a low dose of omeprazole (10 mg/day) was used in the study. This dose level is usually prescribed to prevent the development of aspirin-induced gastric ulcers in Japanese patients. Second, more than half of our patients had STEMI and received primary PCI. Among patients treated with famotidine, there was a trend toward a higher PRI at 14 to 28 days in patients with STEMI than in those without persistent ST-segment elevation (54.0±17.8% vs. 46.4±19.4%; $P=0.12$). This result suggests that increased platelet activation might persist beyond 14 days after primary PCI,²⁸ potentially limiting the effectiveness of a standard dose of antiplatelet agents in patients with STEMI. Third, the incidence of CYP2C19 loss-of-function alleles was extremely high among our participants. A pharmacodynamic study has demonstrated that omeprazole decreases the antiplatelet effect of clopidogrel in noncarriers, but not in carriers of CYP2C19 loss-of-function alleles.²⁹ In the present study, there was no significant difference in the PRI at 14 to 28 days between patients treated with omeprazole and those with famotidine among each CYP2C19 phenotype, respectively (Table S1). A larger sample size might be needed to find a significant difference in the PRI between the groups among non-carriers.

In the present study, only a few patients had symptoms of upper GI damage in the famotidine group, and no patient who received low-dose omeprazole reported such symptoms. Recent studies demonstrated that concomitant use of a PPI and clopidogrel was not associated with an increased risk of adverse outcomes with a higher frequency of GI events in Japanese patients treated with stents,^{30,31} although both larger studies were non-randomized and use of PPI other than omeprazole was permitted. Our results might explain the mechanism of the results of above 2 larger studies, which could provide a rationale for the concomitant use of PPI in Japanese patients who receive DAPT, particularly those at greatest risk for upper GI bleeding. The rate of major bleeding was not low (3.1%) in the present study. The incidence of major bleeding ranged from 0.2% to 9.1% in the recent large randomized clinical trials evaluating antithrombotic drugs in ACS and PCI, because of

the variation in bleeding definitions used.³² Our result seems comparable to the incidence of major bleeding (3.2%) in the REPLACE-2 trial.

Another important issue related to HTPR is CYP2C19 polymorphisms. It is not evident why the prevalence of CYP2C19 LOF allele carriers is high in our study patients with ACS. There was no significant difference in the percentage of patients with CYP2C19 loss-of-function allele carriage between analyzed patients and 62 patients with ACS who were excluded from the study and determined CYP2C19 phenotype (77% vs. 68%, $P=0.15$) (data not shown). Recent studies have reported the role of CYP epoxygenase system regulating inflammation and vascular tone, which is connected with the cardiovascular protective effects.³³ Genomic substudy of the CHARISMA trial revealed that there was an increased risk for cardiovascular events among carriers of CYP2C19 polymorphisms in the placebo arm in comparison with non-carriers. These findings suggest that CYP2C19 polymorphisms itself might be conferring excess risk even in patients who do not receive clopidogrel.

Our study had several important limitations. First, clinical outcomes were evaluated in a small group of patients. Second, platelet function might not have reached a stable state 14 to 28 days after PCI in some of the participants, because all patients underwent coronary stent implantation during the acute phase of ACS. We did not perform additional platelet function tests >28 days after clopidogrel loading. However, the risk of stent thrombosis has been reported to be highest within 30 days after stent implantation, especially in patients with ACS who undergo emergency PCI.^{34–36} Third, platelet function testing was performed only by a single method with the use of VASP phosphorylation analysis. However, VASP phosphorylation analysis is the only test that specifically assesses P2Y₁₂ receptor activity.¹⁹ Fourth, the present study was not placebo-controlled. The gastric acid-suppressing effect of H2RA might reduce intestinal absorption of clopidogrel; however, there is no inhibitory potential of famotidine on the metabolic activation of clopidogrel.³⁷ We therefore used famotidine as a control agent. Finally, the definition of HTPR has not been established in Japanese patients. Although the proportion of patients showing HTPR was high, the incidence of thrombotic events was very low in our study. Cardiovascular events such as stent thrombosis have been reported to be less common in Asians than in Westerners.^{34,36,38}

Conclusions

As compared with famotidine, concomitant use of low-dose omeprazole does not significantly attenuate the antiplatelet effects of clopidogrel in patients with ACS, especially in those with STEMI.

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Supplementary Files

Supplementary File 1

Figure S1. (A) Individual data of the platelet reactivity index (PRI) in the omeprazole group.

Table S1. Platelet Function Measurements Among Each CYP2C19 Phenotype

Please find supplementary file(s);
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