—Regular Article—

Efficacy and Safety of Concomitant Use of Rabeprazole during Dual-antiplatelet Therapy with Clopidogrel and Aspirin after Drug-eluting Stent Implantation: A Retrospective Cohort Study

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After coronary stent implantation, dual-antiplatelet therapy (DAT), such as aspirin and clopidogrel, is essential to prevent stent thrombosis. Proton-pump inhibitors (PPIs) may be used to prevent gastrointestinal (GI) bleeding during DAT, but there is no evidence for the efficacy of PPIs in this setting. Because both clopidogrel and PPIs are metabolized by cytochrome P450 (CYP) 2C19, there is a possibility that, through drug interaction, PPIs diminish the antiplatelet effect of clopidogrel. In this retrospective cohort study, we evaluated the efficacy and safety of rabeprazole in patients receiving DAT of clopidogrel and aspirin after drug-eluting stent implantation. In 199 patients treated with DAT alone (control group) and 103 patients treated with rabeprazole plus DAT (rabeprazole group), we examined the incidences of GI bleeding and major adverse cardiac events (MACE) including stent thrombosis. The incidence of GI bleeding was not significantly different between the groups (hazard ratio 0.47 [95% confidence interval 0.15–1.42], $P=0.18$; $P=0.17$ in log-rank test), although no patient with severe bleeding was observed in the rabeprazole group. The use of rabeprazole did not increase the incidence of MACE (hazard ratio 1.28 [95% confidence interval 0.54–3.00], $P=0.56$; $P=0.56$ in log-rank test). One patient who developed subacute stent thrombosis under DAT was genetically proven to be a CYP2C19 poor metabolizer. The effect of rabeprazole to prevent GI bleeding is limited in patients receiving DAT. It remains to be confirmed whether these results may depend on CYP2C19 polymorphisms or a class of PPIs.

Key words——clopidogrel; rabeprazole; GI bleeding; stent thrombosis; drug interaction; CYP2C19

INTRODUCTION

The standard dual-antiplatelet therapy (DAT) consisting of clopidogrel and aspirin is quite important to prevent stent thrombosis after coronary stent implantation. After drug-eluting stent (DES) implantation, DAT is recommended to be continued for at least one year.[1] However, aspirin leads to the risk of upper gastrointestinal (GI) bleeding, and its combination with clopidogrel further increases the risk of bleeding.[2] Therefore, prophylactic use of proton-pump inhibitors (PPIs) with DAT is recommended by consensus guidelines.[3]

Clopidogrel, which irreversibly binds to the platelet P2Y12 receptors and blocks their activation and aggregation, is a safer drug with a lower incidence of hematologic and liver complications than ticlopidine. Clopidogrel is a pro-drug, which needs to be activated through the action of cytochrome P450 (CYP) 1A2, 2B6, 2C9, 2C19, and 3A. CYP2C19 polymorphism has been suggested as the cause of clopidogrel resistance[4] and affects clinical outcomes.[5,6] CYP2C19 is also involved in the metabolism of PPIs such as omeprazole, lansoprazole, and rabeprazole.[7] Therefore, PPIs may interact with clopidogrel. In fact, several studies have shown the possibility that PPIs, especially omeprazole, might diminish the antiplatelet effects of clopidogrel through inhibition of CYP2C19.[8] On the other hand, there are also conflicting data that the interaction between clopidogrel and PPI had no effect on clinical outcome.[9] Thus, the clinical significance of concomitant administration of PPI and clopidogrel remains to be determined.

The frequency of CYP2C19 poor metabolizer in Japan is about 20%,[10] which is higher than that in Western countries. Therefore, we hypothesized that Japanese patients receiving DAT and PPI might be at increased risk of major adverse cardiac events (MACE) including stent thrombosis. To our knowledge, this issue has not been determined in Japanese patients to date. The objectives of this study are to in-

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vestigate whether rabeprazole reduces the risk of GI bleeding, and increases the incidence of MACE during DAT after DES implantation in Japanese patients.

METHODS

Patients We performed a retrospective cohort study in 423 patients who underwent DES implantation in the Department of Cardiology and Catheterization Laboratory of our hospital between June 2006 and March 2009. Exclusion criteria were as follows: the discontinuation of DAT or losts from the follow-up within one year, concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, corticosteroids, histamine H2-receptor antagonist, or other PPIs such as omeprazole and lansoprazole for more than one week. The use of gastric mucosal protective agents (other than histamine H2-receptor antagonist, omeprazole, or lansoprazole), warfarin, antiplatelet drugs, or over-the-counter drugs was not restricted.

Finally, 302 patients were included in this study (Fig. 1). Of these patients, 103 were treated with DAT and rabeprazole at 10 mg/day for one year after DES implantation (rabeprazole group). On the other hand, 199 patients were treated only with DAT (control group). In both groups, the maintenance regimen of DAT was clopidogrel (50–75 mg/day) and aspirin (100–200 mg/day) for at least one year. Enteric-coated tablets of aspirin were used in all patients. All patients underwent coronary angiography one year after DES implantation.

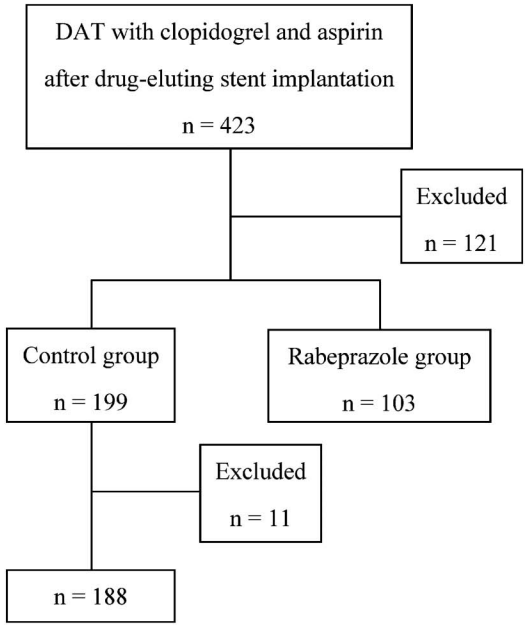

Fig. 1. Design of Study.

Clinical Assessment In these patients, we assessed whether rabeprazole reduces the risk of GI bleeding during DAT. Upper GI bleeding was defined as hematemesis or melena with bleeding erosions confirmed by endoscopy. The severity of upper GI bleeding was determined based on Thrombolysis In Myocardial Infarction (TIMI) trial bleeding criteria[11] with modification: mild bleeding was defined as a decrease in hemoglobin ≤ 3 g/dl, moderate bleeding as a decrease in hemoglobin >3 g/dl but ≤ 5 g/dl, and severe bleeding as a decrease in hemoglobin >5 g/dl. Lower GI bleeding was defined as melena, rectal bleeding, or a positive fecal occult blood test with negative results on upper endoscopy. The severity of lower GI bleeding was defined as the same as that of upper GI bleeding. The relationship of triple antithrombotic therapy (TAT), DAT plus warfarin or cilostazol, with GI bleeding was also examined.

In addition, we assessed whether rabeprazole increases the risk of MACE. During the follow-up period, rabeprazole was temporarily used for upper GI bleeding or gastroesophageal reflux disease in 11 of the 199 patients in the control group. Therefore, the relationship between rabeprazole and MACE was investigated in the remaining 188 patients (Fig. 1). MACE was defined as cardiac death, acute coronary syndrome, stent thrombosis, and target lesion revascularization. Stent thrombosis was defined according to the Academic Research Consortium definition, and classified as acute (within 24 hours after DES implantation), subacute (24 hours to 30 days), or late (30 days to one year).[12]

During the follow-up period of 395.1 ± 27.7 days, the information on complete blood count, blood chemistry, drug adherence, other medication, and clinical outcomes was collected from medical records.

This study was conducted according to the Ethical Guidelines for Epidemiological Research. The ethical committee of our hospital approved this study. One patient who underwent genotyping gave informed consent for genotyping.

Statistical Analysis Data are expressed as mean $\pm$S.D. Characteristics were compared between the two groups using the Mann-Whitney U test or χ^2 test, as appropriate. For each end-point category, Kaplan-Meier time-to-event curves were used to estimate the

absolute risk of each event at 1 year for each group, with log-rank test. To determine whether rabeprazole affect the risk of each end-point, univariate Cox proportional hazards regression analysis was performed. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 11.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline characteristics of the patients are shown in Table 1. Age, gender, body mass index, the prevalence of diabetes mellitus, hypertension, dyslipidemia, and smoking were similar between control and rabeprazole groups. However, previous myocardial infarction and family history of ischemic heart disease were more frequently found in rabeprazole group, with statistically significant differences. The number of implanted DES was significantly larger in rabeprazole group. The rabeprazole group was more frequently treated with calcium-channel blocker and β-blocker. The gastromucosal protective agents used were rebamipide ($n=9$), sucralfate ($n=3$), and tepurenone ($n=14$) in control group, and rebamipide ($n=5$), sucralfate ($n=1$), tepurenone ($n=1$), and ecabet ($n=1$) in rabeprazole group. The DAT regimens in control group were: aspirin 100 mg+clopidogrel 75 mg in 63 patients (31.7%), aspirin 200 mg+clopidogrel 50 mg in 82 (41.2%), and aspirin 200 mg+clopidogrel 75 mg in 54 (27.1%). The DAT regimen in rabeprazole group were: aspirin 100 mg+clopidogrel 75 mg in 50 patients (48.5%), aspirin 200 mg+clopidogrel 50 mg in 26 (25.2%), and aspirin 200 mg+clopidogrel 75 mg in 27 (26.2%).

Table 2 shows GI bleeding in the follow-up. Upper GI bleeding occurred in 7 patients of control group and 1 of rabeprazole group. The incidences of upper GI bleeding were not different between the groups, as shown in Fig. 2 ($P=0.19$ in log-rank test). In addition, the incidences of lower GI bleeding were not different between the groups (Fig. 3, $P=0.50$ in log-rank test). The causes of lower GI bleeding were as follows: diverticular bleeding in 6 patients, ischemic enteritis in 2, colon cancer in 1, colon polyp in 1, hemorrhoid in 1, and small colon ulcer in 1. Diverticular bleeding was the leading cause, but asymptomatic in all patients. Total incidence of upper and lower GI bleeding was not different between the groups (Fig. 4, $P=0.17$ in log-rank test). In univariate Cox proportional hazards regression analysis, hazard ratio of rabeprazole administration was 0.27 [95% confidence interval (CI) 0.03–2.22, $P=0.22$] for upper GI bleeding, 0.64 (95% CI 0.17–2.38, $P=0.51$) for lower GI bleeding, and 0.47 (95% CI 0.15–1.42, $P=0.18$) for GI bleeding.

As shown in Table 3, 3 patients of control group experienced severe upper GI bleeding, but none of

Table 1. Patient Baseline Characteristics

	Control group	Rabeprazole group	p
n	199	103	
Age (year)	67.4±10.1	69.0±9.6	0.113
Male patients (n, %)	144 (72.4)	69 (67.0)	0.332
Body mass index (kg/m^2)	23.2±3.2	23.6±3.9	0.514
Hypertension (n, %)	129 (64.8)	66 (64.1)	0.898
Diabetes mellitus (n, %)	79 (39.7)	36 (35.0)	0.421
Dyslipidemia (n, %)	115 (57.8)	70 (68.0)	0.085
Current smoking (n, %)	54 (27.1)	25 (24.3)	0.591
Chronic kidney disease[1] (n, %)	75 (37.7)	40 (38.8)	0.846
Hemodialysis/peritoneal dialysis (n, %)	9 (4.5)	1 (1.0)	0.102
Previous myocardial infarction (n, %)	35 (17.6)	33 (32.0)	0.004
Family history of ischemic heart disease (n, %)	30 (15.1)	29 (28.2)	0.007
Stroke (n, %)	23 (11.6)	11 (10.7)	0.189
Peripheral arterial disease (n, %)	18 (9.0)	11 (10.7)	0.648
Peptic ulcer (n, %)	9 (4.5)	7 (6.8)	0.403
Gastroesophageal reflux disease (n, %)	8 (4.0)	5 (4.9)	0.735
Stable angina pectoris (n, %)	114 (57.3)	57 (55.3)	0.746
Acute coronary syndrome (n, %)	54 (27.1)	28 (27.2)	0.993
Number of implanted stents	2.5±1.6	3.1±1.9	0.004
Sirolimus-eluting stent (n, %)	124 (62.3)	62 (60.2)	0.720
Paclitaxel-eluting stent (n, %)	101 (50.8)	55 (53.4)	0.663
DES+bare metal stent (n, %)	49 (24.6)	31 (30.1)	0.307
Angiotensin converting enzyme-inhibitor (n, %)	38 (19.1)	21 (20.4)	0.788
Angiotensin II receptor blocker (n, %)	67 (33.7)	34 (33.0)	0.908
Calcium-channel blocker (n, %)	70 (35.2)	49 (47.7)	0.037
β-blocker (n, %)	60 (30.2)	44 (42.7)	0.029
HMG-CoA reductase inhibitor (n, %)	137 (68.8)	80 (77.7)	0.106
Gastric mucosal protective agent (n, %)	26 (13.1)	8 (7.8)	0.167
Warfarin (n, %)	7 (3.5)	9 (8.7)	0.055
Cilostazol (n, %)	7 (3.5)	5 (4.9)	0.573

[1] Chronic kidney disease was defined as estimated glomerular filtration <60 ml/min/1.73 m^2. DES, drug-eluting stent.

Table 2. GI Bleeding in Follow-up

	Control group	Rabeprazole group
n	199	103
GI bleeding (*n*, %)	16 (8.0)	4 (3.9)
Upper GI bleeding (*n*, %)	7 (3.5)	1 (1.0)
Mild bleeding	3	0
Moderate bleeding	1	1
Severe bleeding	3	0
Lower GI bleeding (*n*, %)	9 (4.5)	3 (2.9)
Mild bleeding	5	2
Moderate bleeding (*n*, %)	3	0
Severe bleeding (*n*, %)	1	1
Hospitalization for GI bleeding (*n*, %)	8 (4.0)	2 (1.9)

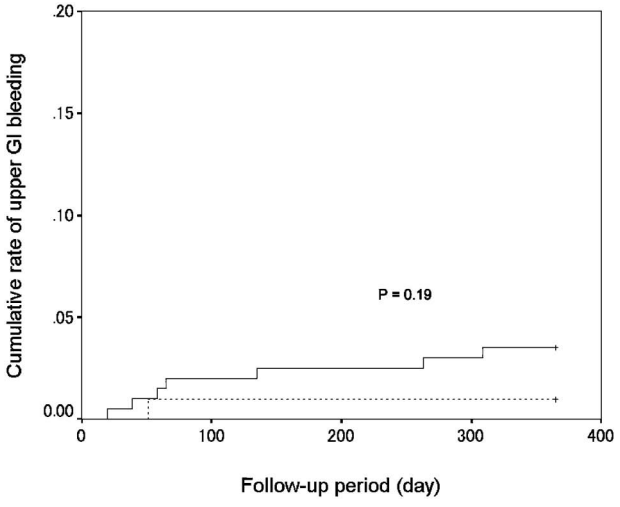

Fig. 2. Cumulative Rate of Upper Gastrointestinal Bleeding
The solid line indicates control group and the broken line indicates rabeprazole group. There was no difference in the incidence of upper GI bleeding in the follow-up (P=0.19, log-rank test).

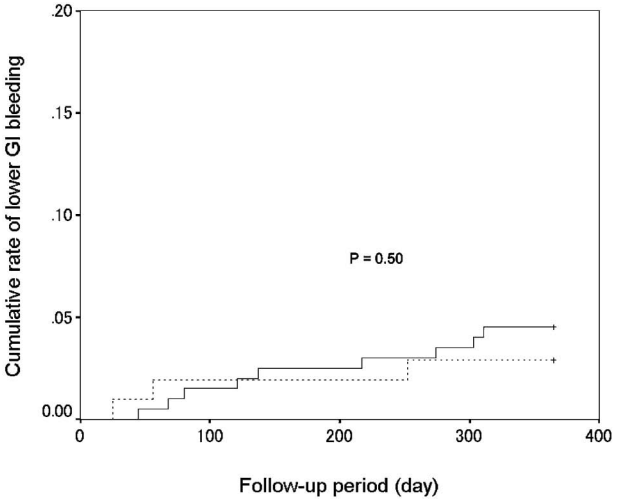

Fig. 3. Cumulative Rate of Lower Gastrointestinal Bleeding
The solid line indicates control group and the broken line indicates rabeprazole group. There was no difference in the incidence of lower GI bleeding in the follow-up (P=0.50, log-rank test).

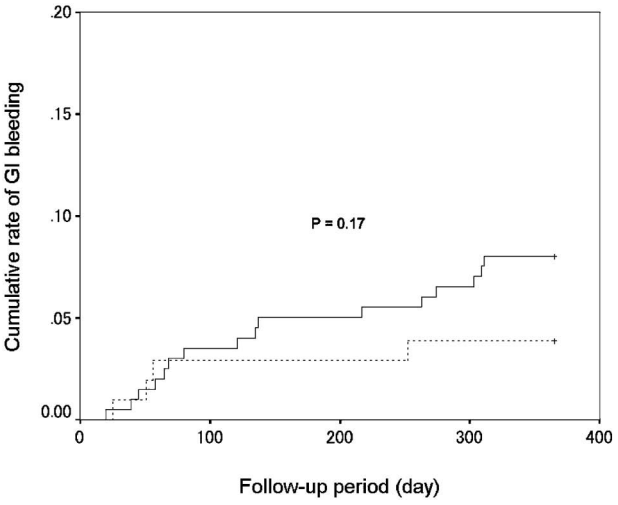

Fig. 4. Cumulative Rate of Gastrointestinal Bleeding
The solid line indicates control group and the broken line indicates rabeprazole group. There was no difference in the incidence of upper and lower GI bleeding in the follow-up (P=0.17, log-rank test).

those in rabeprazole group experienced. The control group included 9 patients with a history of peptic ulcer, and upper GI bleeding occurred in 3 of them during DAT. In rabeprazole group, however, none of the 7 patients with a history of peptic ulcer had upper GI bleeding.

Of the 302 patients, 28 received TAT for atrial fibrillation or peripheral arterial disease. Upper GI bleeding occurred in 1 (3.6%) of the patients receiving TAT and in 7 (2.6%) of those not receiving TAT, which was not significantly different (P=0.87 in log-rank test). Lower GI bleeding occurred in 3 (10.7%) of those receiving TAT and in 9 (3.3%) of those not receiving TAT. This difference was marginally significant (P=0.27 in log-rank test).

As shown in Table 4, MACE occurred in 9 patients (8.7%) of rabeprazole group and 13 (6.9%) in control group in the follow-up. Subacute stent thrombosis occurred in one patient of rabeprazole group. There was no significant difference in the incidence of MACE, as shown in Fig. 5 (P=0.56 in log-rank test). Hazard ratio of rabeprazole for MACE was 1.28 (95% CI 0.54–3.00, P=0.56).

In one patient of rabeprazole group who experienced subacute stent thrombosis, CYP2C19 genotype was examined by using a genotyping service

Table 3. Patients with Upper GI Bleeding

Age	Group	Previous peptic ulcer	Gastric mucosal protective agents	Bleeding severity	DAT	Time after DES implantation
87	Control	Yes	No	Severe GU, DU	Aspirin 100 mg Clopidogrel 75 mg	58 days
56	Control	Yes	No	Severe GU	Aspirin 100 mg Clopidogrel 75 mg	263 days
50	Control	No	Sucralfate	Severe GU	Aspirin 200 mg Clopidogrel 50 mg	20 days
70	Control	No	No	Moderate GU	Aspirin 200 mg Clopidogrel 50 mg	309 days
72	Control	No	No	Mild GU	Aspirin 100 mg Clopidogrel 75 mg Warfarin 2 mg	39 days
64	Control	Yes	No	Mild GU	Aspirin 200 mg Clopidogrel 50 mg	65 days
75	Control	No	No	Mild DU	Aspirin 100 mg Clopidogrel 75 mg	135 days
69	Rabeprazole	No	No	Moderate GU	Aspirin 200 mg Clopidogrel 75 mg	51 days

DAT, dual-antiplatelet therapy; DES, drug-eluting stent; DU, duodenal ulcer; GU, gastric ulcer.

Table 4. Major Adverse Cardiac Events in Follow-up

	Control group	Rabeprazole group
n	188	103
Major adverse cardiac events (*n*, %)	13 (6.9)	9 (8.7)
Cardiac death (*n*, %)	2 (1.1)	0 (0)
Acute coronary syndrome (*n*, %)	0 (0)	1 (1.0)
Stent thrombosis (*n*, %)	1 (0.5)	1 (1.0)
Acute	0	0
Subacute	0	1
Late	1	0
Target lesion revascularization (*n*, %)	10 (5.3)	7 (6.8)

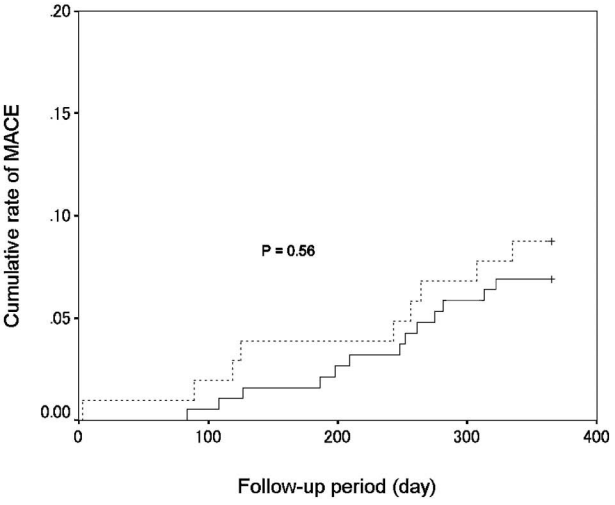

Fig. 5. Cumulative Rate of Major Adverse Cardiac Events
The solid line indicates control group and the broken line indicates rabeprazole group. There was no difference in the incidence of MACE in the follow-up (P=0.56, log-rank test).

(BML, Inc., Japan). The result was a CYP2C19 *3 homozygote (*3/*3), which indicated a poor metabolizer.

DISCUSSION

The incidence of DAT-induced GI bleeding was reported to be 2.52% in MATCH trial[13] and 1.0% in BAT study.[14] In a previous case-control study, the hazard ratio of severe bleeding was 1.1 in clopidogrel monotherapy, 1.8 in aspirin monotherapy, and 7.4 in DAT compared with that in no antiplatelet therapy.[15] In patients receiving DAT, prophylactic use of PPI is recommended, but the effects of PPI remain to be elucidated. Two case-control studies with limited sample size showed that PPIs prevented clopidogrel-induced gastroduodenal bleeding.[16,17] In our study, the incidence of GI bleeding during DAT was comparable between control group and rabeprazole group. Although it seems somewhat notable that there was no severe bleeding in the rabeprazole group, the efficacy of rabeprazole in reducing the risk of DAT-induced upper GI bleeding was not found. As shown in Table 3, administered doses of aspirin and

clopidogrel did not seem to be related to bleeding. The exact reasons why we could not identify the effects of PPI in this study are unknown, but generally the incidence of upper GI bleeding is not high in patients receiving DAT. In fact, Ray *et al*. recently reported that, in a retrospective cohort study including 20,596 patients with coronary artery disease, concurrent use of PPI with clopidogrel was associated with reduced incidence of hospitalization for gastroduodenal bleeding.[18] In addition, *Helicobacter pylori* infection might affect the result, as in the previous study,[3] but we did not examine *H. pylori* infection in our patients.

Stent thrombosis is a rare complication after stent implantation, but is associated with high morbidity and mortality. According to a study from Japan, the incidence of stent thrombosis was 0.68% within one year after stent implantation.[19] In our study, the incidences of stent thrombosis were 1.0% in rabeprazole group and 0.5% in control group. Rabeprazole was not associated with increased risk of stent thrombosis during DAT. Considering the fact that the patients of rabeprazole group had severe coronary artery lesions requiring more DES in PCI, it seems that PPIs do not diminish the antiplatelet effects of clopidogrel. Similarly, the results obtained using vasodilator-stimulated phosphoprotein phosphorylation assay and aggregometry showed that pantoprazole and esomeprazol had little effect on the platelet inhibition by clopidogrel.[20] Ray *et al*. recently reported that concurrent use of pantoprazole with clopidogrel was not associated with increased risk for serious cardiovascular disease.[18] However, there remains a possibility that the effects of PPI on inhibiting clopidogrel action may depend on the class of PPI used. For example, omeprazole is a potent inhibitor of CYP2C19[21] and reported to inhibit the antiplatelet effect of clopidogrel.[8] On the other hand, pantoprazole is reported not to inhibit CYP2C19[7,21] and not to influence the effect of clopidogrel.[20]

Another problem is CYP2C19 genotype. The frequency of CYP2C19 poor metabolizer in Japan is higher than that in Western countries.[10] Recent studies suggest that CYP2C19 polymorphism may be a risk factor for stent thrombosis and cardiac events.[22–24] In the patients treated with DAT plus PPI, however, it was reported that CYP2C19 genotype was not associated with cardiovascular events.[9] We identified the genotype in one patient of rabeprazole group, who experienced subacute stent thrombosis in the follow-up. CYP2C19 enzyme activity is divided into 3 categories based on genotype: extensive, intermediate, and poor. CYP2C19 *2/*2, *2/*3, and *3/*3 indicate a poor metabolizer in Japanese populations.[25] As a result, the genotype of the patient was homozygous (*3/*3) for the mutant CYP2C19 *3 allele. Homozygous mutation should lead to a pronounced decrease in activation of clopidogrel activation, although CYP3A4, 1A2, or 2B6 might partly compensate for clopidogrel metabolism. In fact, Sibbing *et al*. reported that the incidence of stent thrombosis within 30 days following PCI was highest in patients with homozygous mutation (CYP2C19 *2/*2 genotype).[26] Subacute stent thrombosis observed in the patients of rabeprazole group may be attributable to CYP2C19 genotype, rather than the possible interaction between clopidogrel and rabeprazole.

TAT was used in 28 of our patients. Gao *et al*. reported that, in the patients with atrial fibrillation, warfarin plus DAT was associated with decreased incidence of MACE compared with DAT alone.[27] However, the data on bleeding complications related to TAT seem conflicting.[27–29] In our study, there was a trend that TAT increased lower GI bleeding. Further studies are required to examine the efficacy and safety of TAT.

Our study has some limitations. The first limitation was a single-center, retrospective cohort study design. Secondly, the differences between control group and rabeprazole group, such as previous myocardial infarction and family history of ischemic heart disease, could affect the occurrence of MACE in the follow-up. Finally, because of low incidence of GI bleeding and MACE, the obtained results were not definitely conclusive with low statistical power. The required sample size of each group calculated using a two-sided log-rank test with a significance level of 0.05 and a statistical power of 80% on the basis of our study were 270 patients in GI bleeding and 2073 patients in MACE.

In conclusion, in patients receiving DAT after DES implantation, the clinical effect of rabeprazole to prevent GI bleeding is limited. The additional administration of rabeprazole in these patients does not increase the incidence of MACE including stent thrombosis. These results should be confirmed in genetically-proven CYP2C19 poor metabolizer, or in use

of other class of PPIs.

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