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Clopidogrel에 Proton Pump Inhibitors 병용 시 급성 관동맥 증후군 환자의 심장관련 부작용에 미치는 영향

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Influence of the Concomitant Use of Clopidogrel and Proton Pump Inhibitors on Adverse Cardiovascular Events in Korean Patients with Acute Coronary Syndrome

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Purpose: Recent investigations suggest that the antiplatelet effect of clopidogrel may be decreased when this medication is taken together with certain proton pump inhibitors (PPIs). However, there has been no study conducted in Korea regarding the clinical effect of clopidogrel-PPI interaction. This study targeted patients who received stents to investigate the effect of the concomitant use of clopidogrel and PPIs on the occurrence of adverse cardiovascular events in Korean patients. Methods: The patients who received a stent insertion at the Yeouido St. Mary's Hospital between January 2010 and April 2011 were included. The patients were divided into two groups, clopidogrel and clopidogrel + PPI, and followed for 12 months after the date of stent insertion using prescription history and medical records. The recurrence rates of the cardiovascular events among the two patient groups were statistically analyzed. Results: There was no difference between the two groups in the basic characteristics of the 157 patients in the clopidogrel group and the 62 patients in the clopidogrel + PPI group. Simple logistic regression showed a significantly higher rate of re-hospitalization in the clopidogrel + PPI group (OR=1.893, 95% CI 1.040-3.445, p=0.037). However, the results of the multivariate logistic regression of the variables found to have statistical significance by crosstabulation showed no significant difference in the rate of adverse cardiovascular events or re-hospitalization between the two groups. Conclusions: There was no significant difference between the clopidogrel and clopidogrel+PPI group among new patients with cardiovascular stents with respect to the occurrence of revascularization procedures, stent thrombosis, or chest pain, or with respect to the re-hospitalization rate for all cardiovascular events.

□ Key words - clopidogrel, proton pump inhibitors, interaction, adverse cardiovascular events, acute coronary syndrome

Acute coronary syndrome is an ischemic heart disease that is accompanied by severe chest pain due to the stenosis or occlusion of the coronary arteries, leading to decreased myocardial perfusion. This condition includes unstable angina and myocardial infarctions (MIs) with or without ST elevation on echocardiogram (STEMI or NSTEMI, respectively), and severe cases can lead to death. In the United States, approximately 780,000 people suffer from acute coronary syndrome, with 470,000 recurrences. Furthermore, patients with coronary artery diseases now represent over half of the cardiovascular disease patients under the age of 75.[1)]

As a treatment for acute coronary syndrome, medical revascularization can be implemented via antiplatelet agents, anticoagulants, anti-ischemic drugs, percutaneous coronary intervention (PCI), or coronary artery bypass graft

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(CABG). Of the interventional procedures used in coronary arteries, stenting has a high success rate and a low rate of restenosis and is thus performed frequently.[2-4)]

American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend a concomitant treatment of the antiplatelet agents aspirin and clopidogrel for a minimum of 12 months after PCI.[5, 6)] A concomitant treatment with these two drugs reduces the risk of major adverse cardiac events (MACEs) among patients with PCI.[7)] Proton pump inhibitors (PPIs) have been frequently prescribed to reduce the risk of GI bleeding in patients receiving aspirin and clopidogrel. However, studies conducted in the past several years suggest that PPIs can reduce the antiplatelet effect of clopidogrel.[8)] The US Food and Drug Administration (FDA) published an early communication on the safety review of the potential interaction between clopidogrel and PPIs.

Clopidogrel is a pro-drug that is metabolised by the cytochrome P450 (CYP) 2C19 enzyme, and it exerts its antiplatelet effect by irreversibly interfering with the binding of adenosine-5-diphosphate (ADP) to the P2Y12-receptor on platelets.[9,10)] PPI medications, including esomeprazole, lansoprazole, omeprazole, and rabeprazole, are also metabolised by CYP 2C19, and it has been suggested that these drugs may interfere with the metabolism of clopidogrel.[11,12)] Many patients undergo PCI annually, and this number is on the rise; thus, understanding the potential interactions between clopidogrel and PPI is important for patients who need long-term clopidogrel treatment.

According to a prior study by Ho *et al*., which included the observation of patients admitted and treated between 2003 and 2006 at one of the 127 Veterans Health Administration (VHA) medical centers due to acute coronary syndrome[13)], the 5244 patients treated with clopidogrel and a PPI (omeprazole or rabeprazole) had 1.86 times the rate of recurrent acute coronary syndrome (adjusted odds ratio, AOR=1.86; 95% confidence interval, CI=1.57-2.20) and 1.49 times the revascularization procedures (AOR=1.49; 95% CI=1.30-2.71) compared with the 2961 patients who received only clopidogrel. Furthermore, death or re-hospitalization due to side effects was 1.25 times higher in the group receiving both PPI and clopidogrel (AOR=1.86; 95% CI=1.57-2.20).

According to a randomized double-blinded study by Gilard *et al*.[14)] that investigated 124 patients, the platelet reactivity index (PRI) was 83.2% (SD 5.6) in the clopidogrel-only group and 83.9% (SD 4.6) in the clopidogrel+omeprazole group on day 1 of treatment; on day 7, the numbers were 39.8% (SD 15.4) and 51.4% (SD 16.4), respectively, with an elevated PRI in the clopidogrel + omeprazole group ($p < 0.0001$).

Clopidogrel and PPIs are commonly used in Korea. However, there has been no study conducted in Korea regarding the clinical effect of clopidogrel-PPI interaction. Therefore, the present study targeted Korean patients who were admitted with acute coronary syndrome and treated with stent insertion. The patients were divided into two groups, one receiving only clopidogrel and the other receiving a PPI in addition to clopidogrel, to compare and evaluate the occurrence rates of MACEs between the two groups through retrospective analysis of prescriptions and medical records.

METHODS

Study subjects

This study targeted patients who were admitted with acute coronary syndrome and treated with a stent insertion at the Department of Cardiology of Yeouido St. Mary's Hospital. The hospital is located in Seoul, South Korea, and is a tertiary health care facility with a 770-bed capacity.

1) Eligibility criteria

(1) Patients who were admitted with acute coronary syndrome and treated by PCI (stent insertion) at the Department of Cardiology of Yeouido St. Mary's Hospital during the study period (January 2010 to April 2011)

(2) Patients who had received a stent procedure at Yeouido St. Mary's Hospital and had been prescribed clopidogrel or clopidogrel + PPI at discharge or at the outpatient clinic and who were able to be followed up for 12 months for observation

2) Exclusion criteria

(1) Patients taking an H_2-antagonist or with a gastrointestinal ulcer

(2) Patients with thrombocytopenia or bleeding disorders

(3) Patients with renal failure or liver failure

(4) Patients who were lost to follow-up in the electronic medical record during the 12 months following the stenting procedure

(5) Patients who were discontinued from clopidogrel therapy during the 12 months following the stenting procedure

Data Collection and Method

The list of the patients who were admitted to the cardiology department with acute coronary syndrome and treated with a stent insertion during the 16-month period from January 2010 to April 2011 was analyzed. Approval was obtained from the Institutional Review Board of the Yeouido St. Mary's Hospital after submitting a clinical research plan, ethical considerations, and case report forms. Discharge prescriptions and prescriptions at outpatient visits after the discharge of eligible patients were reviewed, and the patients were assigned to either a group receiving clopidogrel or a group receiving clopidogrel and a PPI at least once concomitantly (clopidogrel + PPI). The electronic medical records of all of the eligible patients were reviewed to collect the following information.

First, basic patient information was analyzed to reflect the variables between the two groups. Patient gender, age, and weight and the effectiveness of stent were examined. In addition, the risk factors for coronary artery disease, including chronic diseases, such as hypertension, diabetes, and stroke; current smoking status; and a previous history of percutaneous coronary intervention, were examined.

Second, any other medications used with clopidogrel were categorized as a β-blocker, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), calcium channel blocker (CCB), nitrate, warfarin, or non-steroidal anti-inflammatory drug (NSAID) and then investigated.

Third, when clopidogrel and a PPI were prescribed together, the PPI medications were categorized as esomeprazole, lansoprazole, or rabeprazole (all with a hospital prescription code), and all cases of concomitant usage of more than one day were investigated.

Fourth, based on the information from medical records, including coronary angiography records and PCI records, the number of stented vessels and the location of the treated vessel, which was classified as left main coronary (LM), left anterior descending (LAD), left circumflex (LCX), or right coronary artery (RCA), were investigated.

Fifth, re-hospitalization records within 12 months of the PCI procedure date were reviewed; in the cases of MACE occurrence, the effectiveness of the stent was investigated by categorizing the adverse outcomes as follows: revascularization procedure performed, occurrence of stent thrombosis, and chest pain or dyspnea. For those patients whose records did not persist for the 12-month follow-up period, it was difficult to determine whether the loss of record was due to the transfer of care to another institution or mortality. As such, the number of expired patients could not be confirmed.

Statistical Analysis

Of the variables between the PPI group and the non-PPI group, two nominal variables, age and weight, were analyzed for the mean and standard deviation (SD) of each group, and an independent t-test was performed on the two groups.

Other ordinal variables underwent crosstabulation to determine the p-value. In the cases in which there were only two categories of response, such as for the variables of the presence of diabetes and the presence of hypertension, only the frequency and percentage of responses affirming the presence of the conditions were recorded. For those variables with three or more response categories, such as diagnosis and intervention location, the frequency and percentage of all of the categories were recorded. A chi-square test or Fisher's exact test was performed for the crosstabulation analysis. Furthermore, each of the factors for re-hospitalization due to a cardiac event (i.e., revascularization, thrombosis, or chest pain) were crosstabulated to obtain the odds ratio (OR) and the p-value.

Multiple logistic regression analysis was performed on the variables found to have statistical significance on crosstabulation ($p < 0.1$), and Fisher's exact test was performed to determine whether each of the PPI medications (esomeprazole, lansoprazole, and rabeprazole) had a different effect on the occurrence rate of major cardiovascular events. SPSS 12.0 version (SPSS Inc, Chicago, IL, USA)

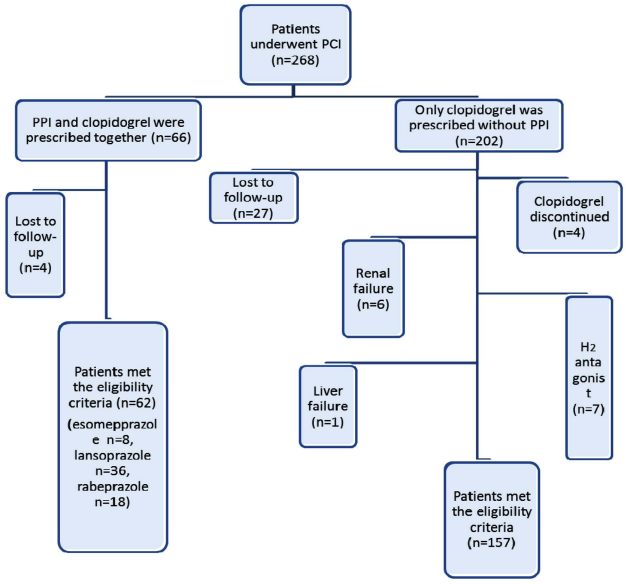

Fig. 1. Study design.

was used, and statistical significance was defined as a p value less than 0.05.

RESULTS

Characteristics of the Subjects

A total of 268 patients were admitted to the Cardiology Department of Yeouido St. Mary's Hospital and underwent PCI. Sixty-six of these patients were prescribed clopidogrel and a PPI together, whereas 202 were only prescribed clopidogrel. Out of the 66 patients in the clopidogrel + PPI group, 62 met the eligibility criteria, with eight receiving esomeprazole, 36 receiving lansoprazole, and 18 receiving rabeprazole. Omeprazole, which has a relatively established interaction with clopidogrel, was never prescribed during the follow-up period. Of the 202 patients who were prescribed only clopidogrel without a PPI, 157 met the eligibility criteria (Fig. 1).

The clopidogrel-only group and the clopidogrel + PPI group showed a significant difference in the percentage of patients with hypertension (55.4% vs. 71.0%; p=0.046), with more patients with hypertension in the group with concomitant PPI therapy. With this exception, the other basic characteristics were not significantly different between the two groups (Table 1).

Table 1. Basic information on the clopidogrel-only group and the clopidogrel + PPI group.

	Clopidogrel without PPI (n=157)	Clopidogrel with PPI (n=62)	p-value**
Age, mean (SD), y	63.0 (10.5)	66.2 (11.3)	0.055
Sex			
Male	103 (65.6)	35 (56.5)	0.217
Female	54 (34.4)	27 (43.5)	
Weight, mean (SD), kg	66.9 (11.8)	64.0 (11.4)	0.098
Smoking	38 (24.2)	12 (19.4)	0.480
Diabetes	69 (43.9)	22 (35.5)	0.288
Hypertension	87 (55.4)	44 (71.0)	**0.046***
Stroke history	5 (3.2)	1 (1.6)	1.000
PCI history	14 (8.9)	11 (17.7)	0.096
Diagnosis			
Angina	125 (79.6)	43 (69.4)	0.113
MI	32 (20.4)	19 (30.4)	
Medications			
β-blocker	81 (51.6)	40 (640.5)	0.098
ACE inhibitor	12 (7.6)	4 (6.5)	1.000
ARB	110 (70.1)	40 (64.5)	0.519
CCB	54 (34.4)	24 (38.7)	0.639
Nitrate	21 (13.4)	6 (9.7)	0.504
Aspirin	154 (98.1)	60 (96.8)	0.623
Warfarin	1 (0.6)	1 (1.6)	0.487
NSAIDs	14 (8.9)	10 (16.1)	0.150
Procedure location			
LAD	64 (40.8)	28 (45.2)	0.195
LCX	22 (14.0)	8 (12.9)	
RCA	20 (12.7)	14 (22.6)	
LM	2 (1.3)	0 (0.0)	
≥ 2 sites	49 (31.2)	12 (19.4)	

Values are expressed as number (percentage) unless otherwise indicated
*p < 0.05.
**The p-values of continuous variables (i.e., age and weight) are derived from independent t-tests.
The p values of categorical variables are derived from a chi-square test or Fisher's exact test.
ACE inhibitor (Angiotensin-converting enzyme inhibitor); ARB (Angiotensin receptor blocker); CCB (Calcium channel blocker); MI (Myocardial infarction); NSAIDs (Non-steroidal anti-inflammatory drugs); PPI (Proton pump inhibitor); LAD (Left anterior descending); LCX (Left circumflex); LM (Left main coronary); RCA (Right coronary artery)

Analysis of Factors Affecting the Occurrence of Each Cardiovascular Event

The results of an analysis of the factors affecting revascularization found that diabetes (p=0.060), diagnosis (p=0.088), concomitant PPI therapy (p=0.066), and beta-blocker therapy (p=0.004) were significantly correlated with the occurrence of revascularization at a significance

Table 2. Result of crosstabulation of variables affecting revascularization.

	Occurrence of Revascularization		p-value**
	No (n=192)	Yes (n=27)	
Age, mean (SD), y	63.7 (11.0)	65.5 (9.5)	0.427
Sex			
Male	121 (63.0)	17 (63.0)	1.000
Female	71 (37.0)	10 (37.0)	
Weight, mean (SD), kg	66.4 (11.9)	63.7 (10.5)	0.257
Smoking	45 (23.4)	5 (18.5)	0.635
Diabetes	75 (39.1)	16 (59.3)	**0.060**
Hypertension	113 (58.9)	18 (66.7)	0.532
Stroke history	5 (2.6)	1 (3.7)	0.550
PCI history	20 (10.4)	5 (18.5)	0.206
Diagnosis			**0.088**
Angina	151 (78.6)	17 (63.0)	
MI	41 (21.4)	10 (37.0)	
Medications			
PPI	50 (26.0)	12 (44.4)	**0.066**
β-blocker	99 (51.6)	22 (81.5)	**0.004***
ACE inhibitor	15 (7.8)	1 (3.7)	0.700
ARB	132 (68.8)	18 (66.7)	1.000
CCB	72 (37.5)	6 (22.2)	0.138
Nitrate	23 (12.0)	4 (14.8)	0.753
Aspirin	187 (97.4)	27 (100.0)	1.000
Warfarin	1 (0.5)	1 (3.7)	0.232
NSAIDs	21 (10.9)	3 (11.1)	1.000
Procedure location			
LAD	84 (43.8)	8 (29.6)	0.597
LCX	25 (13.0)	5 (18.5)	
RCA	29 (15.1)	5 (18.5)	
LM	2 (1.0)	0 (0.0)	
≥ 2 sites	52 (27.1)	9 (33.3)	

Values are expressed as number (percentage) unless otherwise indicated
*p<0.05.
**The p values of continuous variables (i.e., age and weight) are derived from independent t-tests.
The p-values of categorical variables are derived from a chi-square test or Fisher's exact test.
ACE inhibitor (Angiotensin-converting enzyme inhibitor); ARB (Angiotensin receptor blocker); CCB (Calcium channel blocker); MI (Myocardial infarction); NSAIDs (Non-steroidal anti-inflammatory drugs); PPI (Proton pump inhibitor); LAD (Left anterior descending); LCX (Left circumflex); LM (Left main coronary); RCA (Right coronary artery)

Table 3. The results of the crosstabulation of variables affecting thrombosis.

	Occurrence of Thrombosis		p-value**
	No (n=216)	Yes (n=3)	
Age, median (range), y	65.0 (35.0-88.0)	64.0 (53.0-68.0)	0.637
Sex			
Male	136 (63.0)	2 (66.7)	1.000
Female	80 (37.0)	1 (33.3)	
Weight, median (range), kg	65.0 (37.0-110.0)	75.0 (65.0-80.0)	0.208
Smoking	50 (23.1)	0 (0.0)	1.000
Diabetes	90 (41.7)	1 (33.3)	1.000
Hypertension	128 (59.3)	3 (100.0)	0.276
Stroke history	6 (2.8)	0 (0.0)	1.000
PCI history	24 (11.1)	1 (33.3)	0.306
Diagnosis			
Angina	166 (76.9)	2 (66.7)	0.550
MI	50 (23.1)	1 (33.3)	
Medications			
PPI	60 (27.8)	2 (66.7)	0.194
β-blocker	118 (54.6)	3 (100.0)	0.255
ACE inhibitor	15 (6.9)	1 (33.3)	0.204
ARB	148 (68.5)	2 (66.7)	1.000
CCB	78 (36.1)	0 (0.0)	0.554
Nitrate	27 (12.5)	0 (0.0)	1.000
Aspirin	211 (97.7)	3 (100.0)	1.000
Warfarin	1 (0.5)	1 (33.3)	**0.027***
NSAIDs	24 (11.1)	0 (0.0)	1.000
Procedure location			1.000
LAD	90 (41.7)	2 (66.7)	
LCX	30 (13.9)	0 (0.0)	
RCA	34 (15.7)	0 (0.0)	
LM	2 (0.9)	0 (0.0)	
≥ 2 sites	60 (27.8)	1 (33.3)	

Values are expressed as number (percentage) unless otherwise indicated
*p<0.05.
**The p values of continuous variables (i.e., age and weight) are derived from independent t-tests.
The p values of categorical variables are derived from a chi-square test or Fisher's exact test.
ACE inhibitor (Angiotensin-converting enzyme inhibitor); ARB (Angiotensin receptor blocker); CCB (Calcium channel blocker); MI (Myocardial infarction); NSAIDs (Non-steroidal anti-inflammatory drugs); PPI (Proton pump inhibitor); LAD (Left anterior descending); LCX (Left circumflex); LM (Left main coronary); RCA (Right coronary artery)

level of 0.1 (Table 2). Only warfarin therapy (p=0.027) was found to be significantly correlated with the occurrence of thrombosis (Table 3). The occurrence of chest pain or dyspnea was significantly influenced by age (p=0.058), past history of PCI (p=0.012), and CCB therapy (p=0.014) (Table 4). Thus, occurrences of thrombosis and chest pain were not affected by concomitant PPI therapy at a significance level of 0.1.

Re-hospitalization occurrence, defined as all combined cases of revascularization, thrombosis, and chest pain, was found to be significantly associated with hypertension (p=0.064), diagnosis (p=0.013), and concomitant PPI ther-

Table 4. The results of the crosstabulation of variables affecting chest pain or dyspnea.

	Occurrence of Chest Pain or Dyspnea		p-value**
	No (n=165)	Yes (n=54)	
Age, mean (SD), y	64.7 (10.6)	66.1 (12.2)	**0.058**
Sex			0.520
Male	106 (64.2)	32 (59.3)	
Female	59 (35.8)	22 (40.7)	
Weight, mean (SD), kg	66.1 (12.2)	65.9 (10.4)	0.884
Smoking	35 (21.2)	15 (27.8)	0.352
Diabetes	72 (43.6)	19 (35.2)	0.340
Hypertension	94 (57.0)	37 (68.5)	0.152
Stroke history	4 (2.4)	2 (3.7)	0.638
PCI history	24 (14.5)	1 (1.9)	**0.012***
Diagnosis			0.137
Angina	131 (79.4)	37 (68.5)	
MI	34 (20.6)	17 (31.5)	
Medications			
PPI	45 (27.3)	17 (31.5)	0.603
β-blocker	94 (57.0)	27 (50.0)	0.431
ACE inhibitor	12 (7.3)	4 (7.4)	1.000
ARB	112 (67.9)	38 (70.4)	0.741
CCB	51 (30.9)	27 (50.0)	**0.014***
Nitrate	22 (13.3)	5 (9.3)	0.486
Aspirin	160 (97.0)	54 (100.0)	0.337
Warfarin	2 (1.2)	0 (0.0)	1.000
NSAIDs	17 (10.3)	7 (13.0)	0.618
Procedure location			0.908
LAD	69 (41.8)	23 (42.6)	
LCX	23 (13.9)	7 (13.0)	
RCA	26 (15.8)	8 (14.8)	
LM	1 (0.6)	1 (1.9)	
≥2 sites	46 (27.9)	15 (27.8)	

Values are expressed as number (percentage) unless otherwise indicated
*p<0.05.
**The p values of continuous variables (i.e., age and weight) are derived from independent t-tests.
The p values of categorical variables are derived from a chi-square test or Fisher's exact test.
ACE inhibitor (Angiotensin-converting enzyme inhibitor); ARB (Angiotensin receptor blocker); CCB (Calcium channel blocker); MI (Myocardial infarction); NSAIDs (Non-steroidal anti-inflammatory drugs); PPI (Proton pump inhibitor); LAD (Left anterior descending); LCX (Left circumflex); LM (Left main coronary); RCA (Right coronary artery)

Table 5. The results of the crosstabulation of variables affecting overall re-hospitalization.

	Occurrence of All Events**		p-value*
	No (n=137)	Yes (n=82)	
Age, mean (SD), y	64.7 (10.8)	62.7 (10.7)	0.198
Sex			0.666
Male	88 (64.2)	50 (61.0)	
Female	49 (35.8)	32 (39.0)	
Weight, mean (SD), kg	66.5 (12.5)	65.3 (10.5)	0.463
Smoking	30 (21.9)	20 (24.4)	0.740
Diabetes	56 (40.9)	35 (42.7)	0.887
Hypertension	75 (54.7)	56 (68.3)	**0.064**
Stroke history	3 (2.2)	3 (3.7)	0.674
PCI history	19 (13.9)	6 (7.3)	0.188
Diagnosis			
Angina	113 (82.5)	55 (67.1)	0.013*
MI	24 (17.5)	27 (32.9)	
Medications			
PPI	32 (23.4)	30 (36.6)	**0.044***
β-blocker	71 (51.8)	50 (61.0)	0.208
ACE inhibitor	10 (7.3)	6 (7.3)	1.000
ARB	93 (67.9)	57 (69.5)	0.881
CCB	45 (32.8)	33 (40.2)	0.308
Nitrate	18 (13.1)	9 (11.0)	0.678
Aspirin	132 (96.4)	82 (100)	0.160
Warfarin	1 (0.7)	1 (1.2)	1.000
NSAIDs	14 (10.2)	10 (12.2)	0.660
Procedure location			
LAD	60 (43.8)	32 (39.0)	0.968
LCX	18 (13.1)	12 (14.6)	
RCA	21 (15.3)	13 (15.9)	
LM	1 (0.7)	1 (1.2)	
≥ 2 sites	37 (27.0)	24 (29.3)	

Values are expressed as number (percentage) unless otherwise indicated
*p<0.05
**One of revascularization, thrombosis or chest pain episodes occurred.
*** The p values of continuous variables (i.e., age and weight) are derived from independent t-tests.
The p-values of categorical variables are derived from a chi-square test or Fisher's exact test.
ACE inhibitor (Angiotensin-converting enzyme inhibitor); ARB (Angiotensin receptor blocker); CCB (Calcium channel blocker); MI (Myocardial infarction); NSAIDs (Non-steroidal anti-inflammatory drugs); PPI (Proton pump inhibitor); LAD (Left anterior descending); LCX (Left circumflex); LM (Left main coronary); RCA (Right coronary artery)

apy (p=0.044) (Table 5).

Univariate Logistic Regression Analysis between the Clopidogrel-only Group and the Clopidogrel + PPI group

Univariate logistic regression analysis was performed on each of the revascularization, thrombosis, chest pain or dyspnea, and re-hospitalization groups, with PPI use as the only variable in comparing the clopidogrel-only group and the clopidogrel + PPI group.

The result of the analysis found that the re-hospitalization rate was 1.893 times higher in the clopidogrel + PPI

therapy group (p=0.037) compared with the clopidogrel group when cases of re-hospitalization due to all adverse cardiac events were considered. However, there were no significant differences in revascularization, thrombosis, or chest pain or dyspnea between the two groups.

Multivariate Logistic Regression Analysis between the Clopidogrel-only Group and the Clopidogrel + PPI Group

Multivariate logistic regression analysis was performed using the variables found to have statistically significant effects on the occurrence of cardiac events, i.e., revascularization, thrombosis, chest pain or dyspnea, and re-hospitalization, as explanatory variables, but there were no significant differences between the two groups.

Adverse Cardiac Event Occurrence of Each PPI Medication in the Clopidogrel + PPI Group

The crosstabulation of the re-hospitalization rate and cardiovascular event occurrence due to esomeprazole, lansoprazole, and rabeprazole in the clopidogrel + PPI group did not reveal any meaningful differences.

DISCUSSION

Along with the global trend of an increasing incidence of diseases such as diabetes, dyslipidemia, and hypertension due to the increasing aging population and dietary and lifestyle changes, the incidence of coronary artery disease is also rising. Increasing cardiovascular disease means that PCI is gaining importance as a treatment method. Of the PCI procedures, stent insertion has a lower rate of restenosis than balloon angioplasty and can be performed in multi-vessel disease and in a small, long lesion.[2-4] However, thrombosis or restenosis can occur after stent insertion, which can lead to acute myocardial infarction or sudden cardiac death.[15] The use of antiplatelet agents after PCI procedures to prevent these complications is extremely important. Recent clinical studies reported that the early discontinuation of antiplatelet agents, renal failure, bifurcation lesion, and low right atrial ejection are predictive factors for major cardiovascular events after stenting, with the early discontinuation of antiplatelet agents playing the largest role.[16] The US FDA recommends the use of antiplatelet agents, such as aspirin or clopidogrel, for a minimum of one year, and ACC/AHA guidelines recommend a dual therapy of aspirin and clopidogrel for more than one year after a stenting procedure.[5,17,18]

PPIs have been frequently prescribed to reduce the risk of gastrointestinal bleeding during treatment with both aspirin and clopidogrel. The active metabolite of clopidogrel irreversibly inhibits the ADP receptor P2Y12 to achieve an antiplatelet effect and is metabolised by the CYP 2C19 enzyme, which is also known to be responsible for metabolising PPIs.[19, 20] Recent studies reported an increase in the recurrence of MACEs due to the interaction between the two drugs and the subsequent reduction in the antiplatelet effect of clopidogrel.[21-25] P. Michael Ho and colleagues used omeprazole and rabeprazole to identify a significantly higher cardiac readmission rate and mortality rate in the group using clopidogrel and PPI together compared with the group taking only clopidogrel.[13]

The results of our study found no significant difference in basic patient characteristics, such as age, gender, and weight, between the clopidogrel-only group and the clopidogrel+PPI group. Furthermore, no differences were found in the diagnosis (angina and myocardial infarction) or currently used medications between the two groups. Although no differences were found for the risk factors for acute MI, including smoking, diabetes, stroke, and history of PCI, 71.0% of the PPI group had hypertension, which was significantly higher than the 55.4% in the clopidogrel-only group (p=0.046).

The results of this study differ from those of a previous large-scale study by Ho *et al*., which reported an increased risk of MACEs and resulting hospitalizations when PPI and clopidogrel were prescribed together in patients with acute coronary syndrome,[13] as well as from those of a study by Schmidt *et al*.[26] A study by Ho *et al*.[13] targeted 8205 patients who were admitted with acute coronary syndrome and treated with the PPIs omeprazole and rabeprazole prescribed together with clopidogrel. The results showed that the recurrence of ACS was 1.86 times higher

in the clopidogrel+PPI group compared with the clopidogrel-only group (AOR=1.86; 95% CI= 1.57-2.20), and the rate of revascularization procedures was 1.49 times higher (AOR=1.49; 95% CI=1.30-2.71). Death or readmission due to side effects was also found to be 1.25 times more likely in the clopidogrel + PPI group (AOR=1.86; 95% CI=1.57-2.20). The PPIs investigated in the study by Schmidt *et al*.[26] were esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. The group prescribed a PPI and clopidogrel were 0.57 times (95% CI 0.44-0.74) more likely to suffer a cardiovascular event compared with those who did not also take clopidogrel; however, in the non-PPI group, the clopidogrel group had 0.47 times (95% CI 0.42-0.53) the likelihood of those without clopidogrel, showing a lower recurrence of cardiovascular event in the clopidogrel group without concomitant PPI therapy.

A major difference between this study and the other studies is that omeprazole, which has a relatively well-established interaction with clopidogrel, was not included in this study. Another previous study by Yasu *et al*.[27] only included rabeprazole and investigated 199 patients who were prescribed only clopidogrel and 103 patients who were prescribed both rabeprazole and clopidogrel. The results of this study found no relationship between concomitant therapy using rabeprazole and clopidogrel and the risk of coronary vascular event occurrence (HR=1.28; 95% CI=0.54-3.00; p=0.56). In contrast to many studies published on the interaction between omeprazole and clopidogrel.[28-30] there are few studies conducted on other PPIs, such as esomeprazole, lansoprazole, rabeprazole, and pantoprazole. Thus, no definite evidence has been established.[31] The results of the current study also found no statistically significant increase in the risk of cardiovascular events, highlighting the potential for combination therapy using clopidogrel and a PPI.

However, this study is limited by targeting only patients in a single tertiary hospital at a certain geographic location. Furthermore, it could not be determined if the reason for the discontinuation of treatment within the 12-month follow-up period was transfer to another hospital or death; as such, mortality rates could not be included for the MACEs investigated in this study, which is another limitation. Furthermore, no consideration was given to the degree of risk increase with PPI therapy without clopidogrel. Accordingly, more detailed, multi-perspective research investigating the risk of a recurrent cardiovascular event associated with a PPI therapy and the interaction between clopidogrel and each different PPI medication will be necessary to reduce the recurrence of cardiovascular events through the benign effect of clopidogrel in patients with acute coronary syndrome.

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