

## Effect of Low-dose, Enteric Coated Aspirin on Gastrointestinal Bleeding in Patients with Coronary Artery Disease

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**Background/Aims:** This study was performed to determine whether low-dose aspirin and/or clopidogrel can induce gastrointestinal bleeding and gastroduodenal mucosal injury. **Methods:** A total of 387 patients who underwent coronary angiography at Seoul National University Bundang Hospital were assigned to one of three antiplatelet treatment groups: (1) control, (2) 100-mg enteric coated aspirin, and (3) 100-mg enteric coated aspirin plus clopidogrel. The incidences of gastroduodenal mucosal injury and gastrointestinal bleeding were prospectively evaluated, and risk factors for gastrointestinal bleeding were analyzed. **Results:** The rate of gastroduodenal mucosal injury was higher in the aspirin-plus-clopidogrel group than in the aspirin group ( $p=0.012$ ), and higher in the aspirin group than in the control group ( $p=0.049$ ). The rate of gastrointestinal bleeding was significantly higher in the aspirin-plus-clopidogrel group (9.4%) than in the control group (2.4%,  $p=0.048$ ). The risk factors for gastrointestinal bleeding were older age ( $\geq 60$  years) and the presence of at least two comorbid disorders. **Conclusions:** Low-dose enteric coated aspirin was found to be safe in patients with coronary artery disease, but the addition of clopidogrel increased the rate of gastrointestinal bleeding. Combined clopidogrel and aspirin should be used with caution in older patients having at least two comorbid conditions. (*Gut and Liver* 2008;2:99-104)

**Key Words:** Aspirin; Clopidogrel; Gastroduodenal; Injury; Bleeding

## INTRODUCTION

In Western countries, cardiovascular disease accounts for more than 40% of total deaths. Low-dose aspirin is widely used for the prevention and treatment of cardiovascular disease because the antiplatelet therapy with low-dose aspirin (75-325 mg/day) has been reported to be effective in lowering the risk of developing cardiovascular deaths, nonfatal myocardial infarction and stroke in patients with a history of myocardial infarction, unstable angina, nonhemorrhagic stroke or transient ischemic attack.<sup>1-3</sup> Furthermore, low-dose aspirin has also been effective in preventing cardiovascular events in a much wider range of patients than previously assumed. These patients include those with peripheral vascular disease, those who underwent coronary angioplasty or coronary bypass grafting<sup>4</sup> or high-risk patients for the primary prevention of cardiovascular events. Clopidogrel also further reduces the risk of ischemic events in a broad spectrum of patients when they first present and when they have acute coronary syndrome over the long term.

Many studies have reported that antiplatelet agents, such as aspirin, cause mucosal ulceration that can lead to gastrointestinal bleeding.<sup>5-9</sup> In addition, combined antiplatelet treatment conferred particular risk and was associated with a high incidence of gastrointestinal bleeding.<sup>10</sup> However, controversial opinions exist regarding whether low dose aspirin and/or clopidogrel cause gastrointestinal adverse events. Recently, the population over 60 year-old has rapidly increased along with the prevalence of car-

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diovascular disease in Korea. Thus, the population of patients that take aspirin and/or clopidogrel, has also quite increased. The prevalence of atrophic gastritis in the Japanese has been reported to be higher than in Western population,<sup>11</sup> suggesting that the effect of aspirin or antiplatelet agents in Asians including Koreans could be different from that reported in the West. However, there is limited data on Asians and little information is available on Koreans regarding this issue.

Therefore, in this prospective study, we evaluated the safety of low-dose (100 mg) enteric coated aspirin or the combination therapy of aspirin and clopidogrel in patients who underwent coronary angiography.

## MATERIALS AND METHODS

### 1. Patients

In this single-center, prospective, three-arm study pool of 3,620 patients who underwent coronary angiography for evaluation of ischemic heart disease at Seoul National University Bundang Hospital between May 2003 and December 2005, 520 patients were recruited. Exclusion criteria included history of malignancy such as stomach cancer, peptic ulcer, inflammatory bowel disease, antiplatelet medication, gastrointestinal bleeding, liver cirrhosis and esophageal varices. After coronary angiography the patients were allocated to one of three groups; control, acetyl-salicylic acid (ASA) group and ASA+clopidogrel group. The subjects without significant coronary artery stenosis were the control group, and they did not take aspirin or clopidogrel. In the ASA group who had significant coronary artery disease not requiring stent insertion, low-dose enteric coated aspirin was administered at a dose of 100 mg/day. In the ASA+clopidogrel group who had significant coronary artery disease requiring stent insertion, low-dose enteric coated aspirin 100 mg plus clopidogrel 75 mg was administered. They were followed up at one or two months interval and monitored for the development of symptoms such as melena, hematochezia or hematemesis suggestive of gastrointestinal bleeding for 24 months. If those symptoms developed, esophagogastroduodenoscopy and colonofiberscopy were performed and hemoglobin was checked to rule out bleeding, and medications were stopped. When there was no bleeding episode during follow-up period, esophagogastroduodenoscopy was recommended one year after enrollment, with the same medications until the end of the study period. Initially, the patient and control groups were matched regarding sex (male : female) and age (age  $\geq 60$  year-old :  $< 60$  year-old), and total 387 patients finished this protocol. There were 156 patients in the ASA

group, 149 in the ASA+clopidogrel group 149, and 82 in the control group. In the control group, follow-up loss was frequent, especially when they did not have any gastrointestinal symptoms. In each group, the incidence of gastrointestinal adverse events including gastroduodenal mucosal injury and gastrointestinal bleeding was analyzed.

### 2. Clinical assessment

Clinical characteristics including age, gender, smoking history, a history of other medications (non-steroidal anti-inflammatory drugs (NSAIDs), COX inhibitors, warfarin or oral steroids), comorbidities such as diabetes mellitus, hypertension, chronic renal failure, hyperlipidemia, or previous cerebrovascular diseases, and gastrointestinal bleeding were analyzed. Gastroduodenal mucosal injury was diagnosed when endoscopic findings showed gastroduodenal ulcer, hemorrhagic gastritis or erosive gastritis. Hemorrhagic gastritis was defined as presence of blood clots associated with acute inflammation; acute erosive gastritis was defined as multiple areas of mucous membrane damage less than 5 mm. Gastrointestinal bleeding was defined when there was definite melena, hematemesis or hematochezia associated with a decrease of the hemoglobin  $\geq 2$  g/dL compared with a previous result. Upper gastrointestinal bleeding was divided by the Forrest classification into active bleeding of the spurting type (type Ia), oozing (type Ib), non-bleeding visible vessels (type IIa), and adherent blood clots (type IIb). The risk factors for gastrointestinal bleeding such as NSAID and warfarin medication were analyzed. The presence of *H. pylori* infection was judged by carrying out any one of histology using modified Giemsa staining from two biopsy specimens taken from the greater curvature of both the antrum and the mid body of the stomach, or the CLO test (Delta West, Bentley, Australia) from the lesser curvature of the antrum and the mid body. Cancer was excluded by biopsy when a gastric ulcer or mass was identified.

### 3. Statistical analysis

All statistical analyses were performed using SPSS software (version 12.0, SPSS Inc., Chicago, IL, USA). The student's *t*-test was used to compare two groups and analysis of variance (ANOVA) to compare multiple groups. Analysis of the risk factors for gastrointestinal bleeding was performed using  $\chi^2$ -test. *p* values of  $< 0.05$  were regarded as statistically significant.

## RESULTS

### 1. Baseline characteristics

The patient baseline characteristics are shown in Table

1. Overall, the mean age was  $60.2 \pm 10.6$  years and the male-to-female ratio was 226 : 161. Among the three groups, there was a significant difference in the cardiology diagnosis, number of comorbidities, and the prevalence of smokers. However, there was no difference regarding gender and age, and prevalence of alcohol use.

## 2. Endoscopic findings

The incidence of gastroduodenal mucosal injuries such as ulcer, hemorrhagic gastritis or acute erosive gastritis was 29.3% in the control group, 42.9% in the ASA group and 57.7% in the ASA+clopidogrel group; these differ-

**Table 1.** Baseline Characteristics

	Control (n=82)	ASA (n=156)	ASA+ clopidogrel (n=149)	p
Sex				0.130
Male	40 (48.8%)	89 (57.1%)	97 (65.1%)	
Female	42 (51.2%)	67 (42.9%)	52 (34.9%)	
Mean age (y)	57.5	60.2	61.8	0.094
Cardiologic diagnosis				0.001
Normal or not significant	56 (68.3%)	45 (28.8%)	9 (6.0%)	
Variant angina	12 (14.6%)	11 (7.1%)	3 (2.0%)	
Stable angina	11 (13.4%)	66 (42.3%)	64 (43.0%)	
Unstable angina	2 (2.4%)	28 (17.9%)	40 (26.8%)	
NSTEMI	0 (0%)	4 (2.6%)	4 (2.7%)	
STEMI	1 (1.2%)	2 (1.3%)	29 (19.5%)	
Number of comorbidities				0.001
0	35 (42.7%)	28 (17.9%)	24 (16.1%)	
1	34 (41.5%)	83 (53.2%)	66 (44.3%)	
2	11 (13.4%)	33 (21.2%)	52 (34.9%)	
$\geq 3$	2 (2.4%)	12 (7.7%)	7 (4.7%)	
Smoking	21 (28.4%)	54 (39.1%)	66 (46.8%)	0.031
Alcohol	24 (32.4%)	58 (42.0%)	63 (44.7%)	0.213

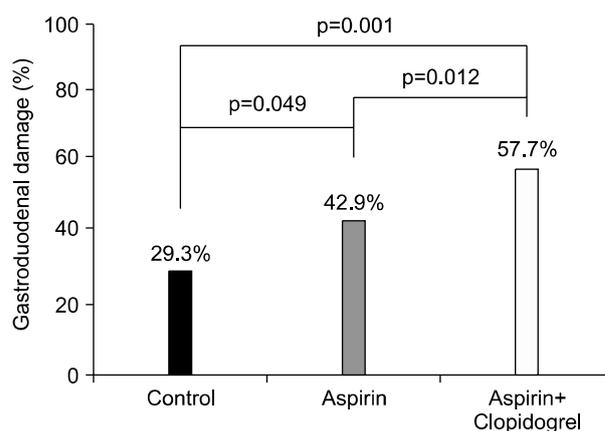
NSTEMI, non ST segment elevated myocardial infarct; STEMI, ST segment elevated myocardial infarct; ASA, acetyl salicylic acid.

**Table 2.** Endoscopic Findings

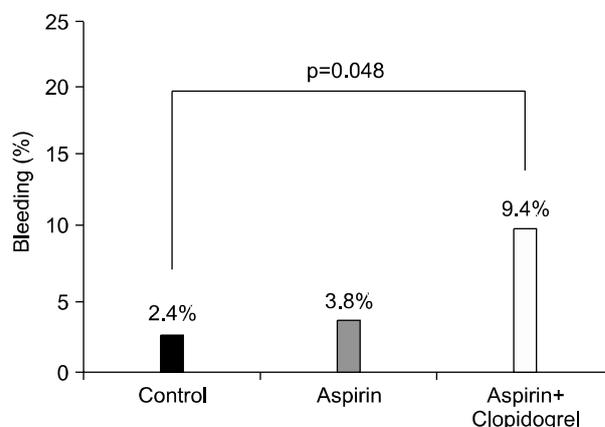
	Control (n=82)	ASA (n=156)	ASA+ clopidogrel (n=149)	p
Gastroscopic diagnosis				
Acute erosive, hemorrhagic gastritis, or ulcer	24 (29.3%)	67 (42.9%)	86 (57.7%)	0.001
Bleeding				0.160
Upper GI	2 (2.4%)	6 (3.8%)	14 (9.4%)	
Lower GI	1 (1.2%)	4 (2.6%)	8 (5.4%)	
H. pylori infection status	1 (1.2%)	2 (1.3%)	6 (4.0%)	
<i>H. pylori</i> infection status	14 (41.2%)	18 (40.9%)	27 (46.6%)	0.813

GI, gastrointestinal.

ences were statistically significant ( $p=0.001$ ). The rate of gastroduodenal mucosal injury in the ASA+clopidogrel group, 57.7% was higher than that in the control group, 29.3% ( $p=0.001$ ) and in the ASA group, 42.9% ( $p=0.012$ ) (Table 2, Fig. 1). In addition, the rate of gastroduodenal mucosal injury in the ASA group was higher than in the control group ( $p=0.049$ ). Gastrointestinal bleeding occurred in 22 patients (5.7%); 2.4% (2 of 82 patients) of the control group, 3.8% (6 of 156 patients) of the ASA group and 9.4% (14 of 149 patients) of the ASA+clopidogrel group. There was no statistical difference among three groups (Table 2). However, when each group was compared with the control group, incidence of bleeding in the ASA+clopidogrel group was significantly higher than that of the control group (9.4% and 2.4%, respectively,  $p=0.048$ ) (Fig. 2). The gastroscopic findings in the 13 cases with upper GI bleeding showed active bleeding in five patients (38.5%), exposed vessels in two pa-



**Fig. 1.** Incidence of gastroduodenal mucosal injury such as acute erosive gastritis, hemorrhagic gastritis, and gastroduodenal ulcer for different medications.



**Fig. 2.** Incidence of gastrointestinal bleeding for different medications.

tients (15.4%) and adherent blood clots in six patients (46.1%), all in the stomach. Among the nine cases with lower GI bleeding, one patient had angiodysplasia with oozing into the cecum. In the remaining eight patients the bleeding focus was thought to be the small bowel because they had no abnormal endoscopic findings in the stomach, duodenum and colon in spite of definite melena or hematochezia with decrease of hemoglobin  $\geq 2$  g/dL.

### 3. Factors associated with gastrointestinal bleeding

When the risk factors for GI bleeding were analyzed according to the age, gender, use of NSAIDs, steroids, warfarin, a COX-2 inhibitor, smoking, alcohol, *H. pylori* infection, location of the ulcer, number of co-morbidities, the duration of aspirin use, age and at least of two co-

morbidities were significant factors associated with gastrointestinal bleeding (Table 3). A statistically significant difference was found for age (64.7 years in the bleeding group and 59.0 years in the no bleeding group) ( $p=0.042$ ) and in patients with more than two comorbidities (50% in the bleeding group and 28.9% in the no bleeding group without bleeding) (Table 3). However, when multivariate analysis was performed this significance disappeared.

## DISCUSSION

Low-dose enteric coated aspirin is effective for preventing and treating cardiovascular events. In the past, a high-dose aspirin regimen was used to prevent cardiovascular disease (up to a maximum dose of 1,000 mg/day). In recent years, however, a low-dose regimen ranging from 81-325 mg/day has been reported to have a similar efficacy as high-dose regimens.<sup>12</sup> In the USA, 100 mg of aspirin is recommended to prevent cardiovascular disease and cerebrovascular accidents. However, even a small dose (75 mg, 150 mg or 300 mg) of aspirin can cause mucosal injuries, and can further increase the risk for peptic ulcer bleeding.<sup>13</sup> NSAIDs have a direct effect on the defensive system of the gastric mucosa. Their use causes an increase in intestinal permeability, and inhibition of prostaglandin synthesis.<sup>1</sup> When the generation of prostaglandins is suppressed, secretion of bicarbonate from the mucus of the epithelial layer decreases, the blood supply to the mucous membranes is reduced, proliferation of the epithelial cells deteriorates, and the resistance of the mucous membranes against injuries decreases. Once resistance of the mucous membrane is reduced, injuries by gastric acid, pepsin, bile salt, or externally administered NSAIDs increase. Thus, a reduction of the concentration of prostaglandins in the gastrointestinal mucous membranes influences the occurrence of injuries to the gastrointestinal mucous membranes.<sup>1,14</sup> A dose of aspirin of 10 mg reduces the concentration of thromboxane A<sub>2</sub> in the blood by 75%,<sup>15</sup> suggesting that the concentration of thromboxane A<sub>2</sub> in the blood goes down in proportion to the quantity of aspirin. Similarly, with a low dose of aspirin such as 10 mg, the concentration of prostaglandin in the gastric mucous membranes is also decreased. At doses of 81 mg and 325 mg, the concentration of prostaglandin in the duodenum is further decreased.<sup>16</sup> Thus, although there was a report suggesting injury to the gastric mucous membranes at a dose of 10 mg of aspirin, the injuries to the gastric mucous membrane generally increase in proportion to the dose of aspirin.

**Table 3.** Risk Factors for Gastrointestinal Bleeding

	No bleeding (n=365)	Bleeding (n=22)	P- value
Age (yr)	59.0 $\pm$ 10.5	64.7 $\pm$ 11.5	
$\geq 60$	171 (46.8%)	14 (63.6%)	<b>0.042</b>
$< 60$	194 (53.2%)	8 (36.4%)	
Sex			
Male	209 (57.3%)	17 (77.3%)	0.076
Female	156 (42.7%)	5 (22.7%)	
NSAID			
No	356 (97.5%)	21 (95.5%)	0.447
Yes	9 (2.5%)	1 (4.5%)	
Steroid			
No	349 (95.6%)	21 (95.5%)	0.990
Yes	16 (4.4%)	1 (4.5%)	
Warfarin			
No	346 (94.8%)	21 (95.5%)	0.99
Yes	19 (5.2%)	1 (4.5%)	
COX2 inhibitor			
No	362 (99.2%)	21 (95.5%)	0.209
Yes	3 (0.8%)	1 (4.5%)	
Smoking			
No	200 (60.2%)	12 (54.5%)	0.820
Yes	132 (39.8%)	10 (45.5%)	
Alcohol			
No	196 (53.7%)	12 (54.5%)	0.990
Yes	136 (46.3%)	10 (45.5%)	
<i>H. pylori</i> infection			
No	72 (57.1%)	5 (50.0%)	0.746
Yes	54 (42.9%)	5 (50.0%)	
Location of ulcer			
Non-antrum	14 (46.7%)	5 (62.5%)	0.693
Antrum	16 (53.3%)	3 (37.5%)	
Number of comorbidities			
$< 2$	259 (71.1%)	11 (50.0%)	<b>0.049</b>
$\geq 2$	106 (28.9%)	11 (50.0%)	

When clopidogrel is added to aspirin, the combination is more effective for ischemic heart disease. However, recent reports suggest that antithrombotic agents, which impair antiplatelet activities, increase the risk of upper GI bleeding. Conflicting results have been reported regarding the bleeding risk of combined administration of aspirin and clopidogrel. One report showed no statistically significant difference in bleeding between these two treatments, that is aspirin and clopidogrel.<sup>17</sup> However, when aspirin and clopidogrel were combined reports have shown a significant increase in bleeding.<sup>18,19</sup> The results of this study for an acute gastric injury such as acute ulcer, erosive gastritis and hemorrhagic gastritis, showed that 100 mg of aspirin alone caused significant damage, and the addition of clopidogrel further increased the damage. In case of gastrointestinal bleeding, a significant increase was found when clopidogrel was added to the aspirin. However, there was no significant difference in cases treated with 100 mg of enteric coated aspirin alone. These results suggest that addition of clopidogrel to aspirin should be done with caution in patients who are at high risk for gastrointestinal bleeding.

The risk factors associated with NSAIDs-induced gastric and duodenal ulcer have been reported to be a previous ulcer history, combined use of steroids or anticoagulation, use of a large quantity of NSAIDs and a poor general condition associated with systemic disease. *H. pylori* infection, drinking, and smoking were also classified as possible risk factors.<sup>20</sup> Among these variables, an old age over 60 years and more than two comorbid conditions were significant risk factors for GI bleeding in the study reported here. Most studies have documented that the risk of NSAIDs-associated GI complications increase with age. The multivariate analysis in the MUCOSA trial indicated an OR of 2.5 (95% CI, 1.5-4.1) for patients over 75 years compared with younger patients.<sup>21</sup> A meta-analysis of eight case-control studies reported that NSAIDs use in patients over 60 was associated with an OR of 5.5 (95% CI, 4.6-6.6) for GI events. However, a review of three case control studies showed an OR of 1.7 (95% CI, 1.1-2.5) for NSAIDs users under the age of 60.<sup>22</sup> In a recent large-scale study, an age over 75 was the most important risk factor.<sup>23</sup> An increase of age causes several physiological changes in the gastrointestinal tract, in particular a reduction of prostaglandins in the stomach and intestines. Weakening of the defensive system of the gastric mucous membranes, rather than an abnormality of intestinal factors such as gastric acid or pepsin, lowers the recovery ability of the gastric mucous membranes, thus causing an increase in gastrointestinal injuries in the

elderly. Therefore, in elderly patients taking NSAIDs, combined use of a prophylactic proton-pump inhibitor should be considered especially if there are gastrointestinal symptoms, and esophagogastroduodenoscopy should be performed even if there are no gastrointestinal symptoms.

However, many believe that it is not the physiologic changes of the elderly patients but rather the comorbidities, that are often found in elderly patients and the medicines they take, that are the important risk factors. The results of our study showed that more than two comorbid disorders were a risk factor for gastrointestinal bleeding in addition to an old age. One prior report showed that elderly patients, with systemic disease, were likely to have gastric and duodenal ulcers and gastrointestinal bleeding with doses of aspirin less than 325 mg.<sup>5</sup> The results of this study showed that the combined use of other NSAIDs, warfarin or steroids, *H. pylori* infection, the location of the ulcer, alcohol, and smoking were not significant risk factors. *H. pylori* infection has been reported as a possible risk factor, together with drinking and smoking. However, recent well-designed studies report no correlation,<sup>24-28</sup> similar to the present study.

This study has several limitations. First of all, the initial study pool was small. This was mainly originated from the practical difficulty of the endoscopic follow-up. Most subjects refused to participate in this continuous follow-up study, especially when they were offered endoscopy without gastrointestinal bleeding or dyspeptic symptom. Secondly, the number of patients with gastrointestinal bleeding was too small to perform a more comprehensive analysis of the risk factors. This few bleeding patients is primarily caused by the low rate of gastrointestinal bleeding with the use of low-dose enteric coated aspirin and/or clopidogrel. In spite of these limitations, this is the first prospective report in Korea or even in Asia regarding the safety of 100 mg of enteric coated aspirin. In addition, our results showed two risk factors for gastrointestinal bleeding, advanced age ( $\geq 60$  year-old) and the presence of more than two comorbid disorders, even these differences disappeared in the multivariate analysis mainly because of many variables in the small pool of bleeding patients.

In conclusion, low-dose enteric coated aspirin is safe for gastrointestinal bleeding. However, the addition of clopidogrel increased the rate of gastrointestinal bleeding, suggesting that the combined use of clopidogrel with aspirin should be done with caution in patient ( $\geq 60$  year-old) or with at least two comorbid disorders.

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