Investigation of Gastroduodenal Mucosal Injury in Japanese Asymptomatic Antiplatelet Drug Users

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Abstract: Antiplatelet drugs are widely used for the prevention of cardiovascular disease and cerebral vascular disorders. Although there have been several studies on gastroduodenal mucosal injury with gastrointestinal (GI) symptoms such as GI bleeding, in antiplatelet drug users (including low-dose aspirin (LDA)), there have been few reports on the association between antiplatelet drug use and gastroduodenal mucosal injury in asymptomatic antiplatelet drug users. This study was a cross-sectional study elucidating the association between antiplatelet drug use and gastroduodenal mucosal injury in asymptomatic antiplatelet drug users. Subjects were 186 asymptomatic Japanese antiplatelet drug users who underwent a regular health checkup. Subjects were divided into those with and without gastroduodenal mucosal injury endoscopically, and the association between gastroduodenal mucosal injury and other data in asymptomatic antiplatelet drug users was investigated.

The prevalence of males and drinkers were significantly higher in subjects with gastroduodenal mucosal injury than in those without. In addition, the prevalence of proton pump inhibitor (PPI) users was significantly lower in subjects with gastroduodenal mucosal injury than in subjects without gastroduodenal mucosal injury. Logistic regression analysis showed PPI (odds ratios: 0.116; 95% confidence intervals: 0.021–0.638; P < 0.05) was a significant predictor of a decreased prevalence of gastroduodenal mucosal injury and closed-type (C-type) atrophy (3.172; 1.322–7.609; P < 0.01) was a significant predictor of an increased prevalence of severe gastroduodenal mucosal injury in asymptomatic antiplatelet drug users.

Gender and lifestyle, such as drinking, may have an impact on risk of gastroduodenal mucosal injury in asymptomatic subjects taking antiplatelet drugs. Although PPI is a significant predictor of a decreased prevalence of gastroduodenal mucosal injury, including in asymptomatic antiplatelet drug users, status of gastric atrophy should also be considered against severe gastroduodenal mucosal injury.

INTRODUCTION

Antiplatelet drugs have been widely administered for the prevention of cerebrovascular and cardiovascular (CV) diseases in various patient populations.1–3 Although aspirin, an antiplatelet drug, reduces the risk of major CV events,4 it is known to lead to various upper gastrointestinal (GI) complications.5–9 Therefore, the recent increase in number of GI complications, such as GI bleeding, because of the increase in use of antiplatelet drugs, has become problematic. Although there have been many reports on the association between antiplatelet drug use, including low-dose aspirin (LDA), and GI events with symptoms such as GI bleeding and perforation,7–13 there have been few reports on the association between antiplatelet drug use and gastroduodenal mucosal injury in asymptomatic subjects. In this study, the association between antiplatelet drug use and gastroduodenal mucosal injury in asymptomatic Japanese subjects taking antiplatelet drugs was investigated.

METHODS

Study Subjects

Subjects were 7065 Japanese adults aged 21 to 85 years who underwent a regular health checkup, including physical examination, blood test screening, and upper GI endoscopy, at our hospital from April 2010 to March 2013. Most subjects were asymptomatic, healthy adults residing around Takamatsu city. Subjects who had a history of digestive tract surgery, serious hepatic, renal or pulmonary disorders, digestive symptom, such as hematemesis, melena, abdominal pain, epigastralgia, chest...
pain, or back pain, or who were diagnosed with gastric or esophageal cancer at the time of upper GI endoscopy were excluded from this study. Subjects who had been taking antiplatelet drugs (aspirin, clopidogrel, limaprostalfadex, ethylicosapentate, cilostazol, ticlopidine, dipyridamole, beraprost sodium, and sarpogrelate hydrochloride) for at least 3 months before checkup were defined as antiplatelet drug users. The subject who took 81 to 100 mg daily aspirin was defined as taker of LDA in this study. Body weight and height of the participants were measured, and body mass index (BMI) was calculated. Waist circumference (WC) was measured at the umbilical level. Venous blood samples were taken from all subjects at approximately 0900 hours following a 12-h overnight fast, and the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), total cholesterol (T-CHO), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c) (National Glycohemoglobin Standardization Program [NGSP]) were determined by common enzymatic methods using an auto analyzer (TBA-80FR; Toshiba Medical System, Tokyo, Japan). Helicobacter pylori infection was diagnosed by the serological tests for anti-H. pylori immunoglobulin G using an enzyme-linked immunosorbent assay (E Plate ‘Eiken’ H. pylori antibody; Eiken Kagaku, Tokyo, Japan) or histological examination. Presence of H. pylori antibody was considered positive if the antibody level was ≥10 U/ml. All subjects were informed that the clinical data obtained by medical checkup may be retrospectively analyzed, and informed consent was obtained. This study was approved by the Ethics Committees of Kagawa Prefectural Cancer Detection Center.

Upper GI Endoscopy

Upper GI endoscopy was performed in 7065 subjects who underwent a regular health checkup and choose to undergo an upper GI endoscopy rather than an upper GI series for assessment of upper GI. Three endoscopy specialists who had more than 10 years of experience in endoscopy performed the endoscopic procedures. All examiners performed the standard endoscopic examination of the esophagus, stomach, and duodenum without having the subject’s results of the blood test screening, physical, and physiological examinations by using a conventional single-channel endoscope (GIF-H260, -PQ260; Olympus, Tokyo, Japan).

Endoscopic Evaluation of Gastroduodenal Mucosal Injury and Gastric Atrophy

The grade of gastroduodenal mucosal injury was assessed according to the modified Lanza score (MLS).14-16 In this scoring system, there are 5 grades of gastroduodenal mucosal injury. Five grades of gastroduodenal mucosal injury are from 0 to 4: Grade 0 is normal mucosa; Grade 1 is erythema or petechiae only; Grade 2 is 1 to 2 erosive lesions; Grade 3 is 3 to 10 erosive lesions; Grade 4 is more than 10 erosive lesions or ulcer. Gastroduodenal ulcer was defined by a mucosal break of 3 mm or greater in diameter with unequivocal depth. The longer diameter of the lesion was measured by standard open-biopsy forceps with an opened length of 6 mm. The score of MLS, which was at least Grade 2, was considered as positive of gastroduodenal mucosal injury in this study. In addition, the score of MLS, which was at least Grade 3, was considered as positive of severe gastroduodenal mucosal injury in this study. During endoscopy, more than 30 endoscopic gastroduodenal pictures covering the entire area of the stomach and the duodenum were saved in the database. The MLS was graded and independently validated by a single endoscopy specialist who was blinded to any other information about the subjects. In addition, extension of the endoscopic atrophic border was evaluated, and the grade of atrophy was diagnosed according to the criteria of Kimura and Takemoto.17 If the border was shifted orally and did not exist on the lesser curvature, it was defined as open type. If the border was on the lesser curvature of the stomach, it was defined as closed type.

Statistical Analysis

This study was a cross-sectional study elucidating the association between antiplatelet drug use and gastroduodenal mucosal injury in asymptomatic antiplatelet drug users. All statistical analyses were carried out using Med Calc Software (Broekstraat, Mariakerke, Belgium). Data were expressed as means ± standard deviation (SD) and summarized by the frequency for categorical variables. A probability (P) value considered statistically significance was accepted as less than 0.05. The χ²-test or Student t-test was used to compare and determine differences between two groups for independent samples, and P value was adjusted for confounding variables using analysis of covariance. Factors with a significant influence on the prevalence of gastroduodenal mucosal injury or severe gastroduodenal mucosal injury were then determined by univariate analysis. And age, sex, BMI, and factors that had a P value of less than 0.15 by univariate analysis were then subjected to a multivariate logistic regression analysis. The odds ratios (ORs) and 95% confidence interval (CI) were analyzed for each variable.

RESULTS

Enrollment

Figure 1 shows the flow diagram of the enrolment of subjects in this study. Of the 23,138 subjects who underwent a regular health checkup from April 2010 to March 2013 at our hospital, 7065 (30.5%) subjects underwent upper gastrointestinal endoscopy. Of the 7065 subjects, 200 (2.8%) subjects took some form of antiplatelet drug. Of the 200 subjects, 14 fulfilled the exclusion criteria and were excluded, and the remaining 186 subjects were enrolled in this study.

Subject Characteristics

Subject characteristics are shown in Table 1; the proportion of men was 77.4%, mean age was 63.7 ± 7.5 years, mean BMI was 24.3 ± 3.7 kg/m², and mean WC was 85.7 ± 9.3 cm in all subjects (Table 1). Prevalence of hypertension, dyslipidemia, and impaired glucose tolerance (IGT) was 79.0%, 60.2%, and 29.6%, respectively. The proportion of drinkers and current smokers was 64.5% and 8.1%, respectively. The number of LDA, clopidogrel, ticlopidine, cilostazol, ethylicosapentate, limaprostalfadex, and multiple antiplatelet drugs in antiplatelet drug users was 116, 18, 8, 15, 18, and 22, respectively. The proportion of cerebral vascular disease and ischemic heart disease in underlying disease was 29.0% and 25.3%, respectively.

Comparison of Clinical Characteristics Between Subjects With and Without Gastroduodenal Mucosal Injury

Comparison of clinical characteristics between subjects with and without gastroduodenal mucosal injury is shown in Table 2, in which the adjusted P value was adjusted for
Subjects who underwent a regular health check-up (n=23138)  

(from April 2010 to March 2013 at our hospital)

Subjects who did not undergo upper gastrointestinal endoscopy (n=16073)  

Subjects who underwent upper gastrointestinal endoscopy (n=7065)  

Subjects who did not use anti-platelet drugs (n=6865)  

Subjects who used anti-platelet drugs (n=200)  

Remaining subjects (n=186)

exclusion

FIGURE 1. Flow diagram of subject enrollment in the current study.

gastrointestinal mucosal injury was significantly higher than in those without (P < 0.05). The proportion of PPI users in the subjects with and without gastroduodenal mucosal injury was 3.3% and 14.4%, respectively. The proportion of PPI users in subjects with gastroduodenal mucosal injury was significantly lower than in those without (P < 0.05).

Predictors of Gastroduodenal Mucosal Injury

Univariate and multivariate independent predictors of gastroduodenal mucosal injury in asymptomatic antiplatelet drug users are shown in Table 3. Of the 28 items related to the clinical background of subjects, sex, alcohol consumption, and PPI use were identified as significant factors by univariate analysis. Multiple logistic regression analysis was performed using covariates of age, sex, BMI, and 6 items that had a P-value of less than 0.15 by univariate analysis: HDL-C, AST, presence of H. pylori, alcohol consumption, PPI use, and status of gastric atrophy. Proton pump inhibitor use was a significant and independent predictor of a decreased prevalence of gastroduodenal mucosal injury. The odds ratio (95% confidence interval, P value) for gastroduodenal mucosal injury was as follow: PPI, 0.118 (0.022–0.637, P < 0.05).

Predictors of Severe Gastroduodenal Mucosal Injury

Univariate and multivariate independent predictors of severe gastroduodenal mucosal injury in asymptomatic antiplatelet drug users are shown in Table 4. Of the 186 subjects, 33 had severe gastroduodenal mucosal injury and the proportion of severe gastroduodenal mucosal injury in all subjects was 17.7%. Of the 28 items related to the clinical background of subjects, UA, and status of gastric atrophy were identified as significant factors by univariate analysis. Multiple logistic regression analysis was performed using covariates of age, sex, BMI, and 5 items that had a P value of less than 0.15 by univariate analysis: UA, alcohol consumption, LDA use, PPI use, and status of gastric atrophy. Closed-type (C-type) gastric atrophy was a significant and independent predictor of an increase prevalence of severe gastroduodenal mucosal injury. The odds ratio (95% confidence interval, P value) for severe gastroduodenal mucosal injury was as follow: C-type, 3.172 (1.322–7.609, P < 0.01).

DISCUSSION

This study aimed to explore the association between antiplatelet drug use and gastroduodenal mucosal injury in asymptomatic antiplatelet drug users. Antiplatelet drugs, including LDA, have been known to reduce the risk of CV disease.13 Use of antiplatelet drugs has increased with the recent rise in the number of elderly individuals in developed countries, including in Japan. In addition, an increase in incidence of GI complications, such as hematemesis, melena, and ulcers, in antiplatelet drug users has become problematic.18–22 Although there have been many reports on the association between antiplatelet drug use and GI events with symptoms such as GI bleeding and perforation, the association between antiplatelet drugs and gastroduodenal mucosal injury in asymptomatic antiplatelet drug users remains unclear. To our knowledge, this study is the first to demonstrate that in asymptomatic antiplatelet drug users, the proportion of men and drinkers was significantly higher in subjects with gastroduodenal mucosal injury than in those without. In addition, PPI use was a significant predictor of a decreased prevalence of
gastroduodenal mucosal injury and C-type gastric atrophy was a significant predictor of an increased prevalence of severe gastroduodenal mucosal injury in asymptomatic antiplatelet drug users.

Antiplatelet drugs have been known to easily cause GI bleeding.1,23,24 Derry et al reported that the odds ratio of GI bleeding in taking LDA was 1.51 to 1.68 against a placebo in a metaanalysis of randomized controlled trials.25 An odds ratio of 7.7 was reported for upper GI bleeding among LDA users in a recent Japanese case-controlled multicenter study.7 Moreover, the cumulative incidence of recurrent bleeding in subjects with healed ulcers was reported to be 8.6 % among patients who received clopidogrel, and 0.7 % among those who received aspirin plus esomeprazole.11 A 12 % incidence rate of GI bleeding after a median follow-up of 1 year was reported in patients who received clopidogrel and who had had previous peptic ulcer disease.12 In addition, several studies have identified the use of nonsteroid anti-inflammatory drugs (NSAIDs), LDA, and antithrombotic drugs as being a significant cause of gastroduodenal ulcers.7,26–30 Therefore, the use of antiplatelet therapy may be limited by the possibility of GI bleeding and ulcers in patients with a history of GI events. Of the 33 subjects with severe gastroduodenal mucosal injury, 17 had endoscopically observable gastroduodenal ulcers, and the prevalence of endoscopically observable gastroduodenal ulcers in all subjects was 9.1% in the current study. There, however, was no

TABLE 1. Subject Characteristics

| Number | 186 |
|---|---|
| Sex (men/women) (% men) | 144/42 (77.4%) |
| Age (years) | 63.7 ± 7.5 |
| BMI (kg/m²) | 24.3 ± 3.7 |
| WC (cm) | 85.7 ± 9.3 |
| SBP (mmHg) | 127.8 ± 14.5 |
| DBP (mmHg) | 76.8 ± 10.3 |
| Hypertension (+/−) (% positive) | 147/39 (79.0%) |
| T-CHO (mg/dl) | 190.0 ± 33.0 |
| TG (mg/dl) | 124.1 ± 104.9 |
| HDL-C (mg/dl) | 59.2 ± 15.5 |
| LDL-C (mg/dl) | 115.1 ± 28.7 |
| Dyslipidemia (+/−) (% positive) | 112/74 (60.2%) |
| UA (mg/dl) | 5.8 ± 1.4 |
| FPG (mg/dl) | 108.4 ± 22.9 |
| HbA1c (% NGSP) | 6.0 ± 0.7 |
| IGT (+/−) (% positive) | 55/131 (29.6%) |
| Hb (g/dl) | 14.2 ± 1.4 |
| MCV (fl) | 92.1 ± 4.7 |
| ALT (IU/l) | 24.6 ± 13.3 |
| AST (IU/l) | 24.1 ± 8.0 |
| GGT (IU/l) | 46.3 ± 46.5 |
| Presence of Helicobacter pylori (+/−) (% positive) | 71/115 (38.2%) |
| Drinker/nondrinker (% drinker) | 120/66 (64.5%) |
| Past history of smoking (+/−) (% positive) | 112/74 (60.2%) |
| Current smoker (+/−) (% positive) | 15/171 (8.1%) |
| Kind of antiplatelet drug (LDA/clopidogrel/ticlopidine/cilostazol/ethyl icosapentate/limaprostalfadex/others/multiple antiplatelet drugs) | 116/18/22 (10.2%)/10/22/22/10 |
| Gastric agents (+/−) (% positive) (PPI/H2-RA) | 30/156 (16.1%)/19 (10.2%)/11 (5.9%) |
| Underlying diseases | |
| Ischemic heart disease | 47 (25.3%) |
| Cardiac dysrhythmias | 17 (9.1%) |
| Other cardiac disease | 5 (2.7%) |
| Cerebral vascular disease | 54 (29.0%) |
| Other vascular disease | 5 (2.7%) |
| Renal disease | 13 (7.0%) |
| Orthopedic disease | 18 (9.7%) |
| Collagen disease | 3 (1.6%) |
| Other disease | 4 (2.2%) |
| Data are mean ± SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; H2-RA, histamine type 2-receptor antagonist; HbA1c, hemoglobin A1c;Hb, hemoglobin; LDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LDA, low dose aspirin; LDL-C, low-density lipoprotein cholesterol; MCV, mean corpuscular volume; NGSP, National Glycohemoglobin Standardization Program; PPI, proton pump inhibitor; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

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TABLE 2. Comparison of Clinical Characteristics Between Asymptomatic Antiplatelet Drug Users With and Without Gastroduodenal Mucosal Injury

|                          | Mucosal Injury (+) (N = 61) | Mucosal Injury (−) (N = 125) | P Value \(^a\) (adjusted \(^b\)) |
|--------------------------|-----------------------------|------------------------------|--------------------------------|
| Age (years)              | 63.7 ± 8.0                  | 63.8 ± 7.3                   | NS                             |
| Sex (men/women) (% men)  | 53/8 (86.9%)                | 91/34 (72.8%)                | <0.05                          |
| BMI (kg/m²)              | 24.3 ± 3.6                  | 24.3 ± 3.8                   | NS                             |
| WC (cm)                  | 86.0 ± 8.3                  | 85.5 ± 9.7                   | NS                             |
| SBP (mmHg)               | 127.5 ± 15.8                | 128.0 ± 13.9                 | (NS)                           |
| DBP (mmHg)               | 76.6 ± 9.5                  | 77.0 ± 10.7                  | (NS)                           |
| Hypertension (+/−) (% positive) | 48/13 (78.7%)             | 99/26 (79.2%)                | (NS)                           |
| T-CHO (mg/dl)            | 186.6 ± 30.5                | 191.7 ± 34.1                 | (NS)                           |
| TG (mg/dl)               | 117.4 ± 65.0                | 127.4 ± 119.7                | (NS)                           |
| HDL-C (mg/dl)            | 58.1 ± 14.0                 | 59.8 ± 16.2                  | (NS)                           |
| LDL-C (mg/dl)            | 113.5 ± 25.6                | 115.9 ± 30.2                 | (NS)                           |
| Dyslipidemia (+/−) (% positive) | 39/22 (63.9%)             | 73/52 (58.4%)                | (NS)                           |
| UA (mg/dl)               | 6.2 ± 1.3                   | 5.6 ± 1.4                    | (<0.05)                        |
| FPP (mg/dl)              | 109.0 ± 28.6                | 108.1 ± 19.6                 | (NS)                           |
| HbA1c (% NGSP)           | 6.0 ± 0.8                   | 5.9 ± 0.6                    | (NS)                           |
| IGT (+/−) (% positive)   | 15/46 (24.6%)               | 40/85 (32.0%)                | (NS)                           |
| WBC (μl)                 | 6090 ± 2183                 | 5699 ± 1398                  | (NS)                           |
| Hb (g/dl)                | 14.3 ± 1.2                  | 14.1 ± 1.4                   | (NS)                           |
| MCV (fl)                 | 92.5 ± 3.5                  | 91.8 ± 5.2                   | (NS)                           |
| ALT (IU/l)               | 25.4 ± 13.8                 | 24.3 ± 13.1                  | (NS)                           |
| AST (IU/l)               | 25.3 ± 8.6                  | 23.6 ± 7.7                   | (NS)                           |
| GGT (IU/l)               | 46.7 ± 44.9                 | 46.0 ± 47.4                  | (NS)                           |
| Drinker/nondrinker (% drinker) | 46/15 (75.4%)           | 74/51 (59.2%)                | <0.05                          |
| Current smoker (+/−) (% positive) | 6/55 (9.8%)                | 9/116 (7.2%)                 | NS                             |
| Presence of Helicobacter pylori (+/−) (% positive) | 18/43 (29.5%)             | 53/72 (42.4%)                | (NS)                           |
| LDA (+/−) (% positive)   | 42/19 (68.9%)               | 74/51 (59.2%)                | (NS)                           |
| Multiple antiplatelet drugs (+/−) (% positive) | 6/55 (9.8%)                | 17/108 (13.6%)               | (NS)                           |
| Anticoagulant drug (+/−) (% positive) | 4/57 (6.6%)                | 7/118 (5.6%)                 | (NS)                           |
| Gastric atrophy (C-type/O-type) (% C-type) | 22/39 (36.1%)             | 30/95 (24.0%)                | (NS)                           |
| Past history of peptic ulcer (+/−) (% positive) | 13/48 (21.3%)             | 22/103 (17.6%)               | (NS)                           |
| PPI (+/−) (% positive)    | 2/59 (3.3%)                 | 18/107 (14.4%)               | (<0.05)                        |
| H2-RA (+/−) (% positive)  | 5/56 (8.2%)                 | 6/119 (4.8%)                 | (NS)                           |

Data are mean ± SD.
\(^a\) P value is based on the \(\chi^2\) test or Student t-test. Significant is at the 5% level.
\(^b\) Adjusted for age, sex, BMI, WC, alcohol consumption, and smoking habit. AST, aspartate aminotransferase; AUT, alanine aminotransferase; BMI, body mass index; C-type, closed type; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT \(\gamma\)-glutamyl transpeptidase; H2-RA, histamine type 2-receptor antagonist; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LDA, low dose aspirin; LDL-C, low-density lipoprotein cholesterol; MCV, mean corpuscular volume; NGSP, National Glycohemoglobin Standardization Program; NS, not significant; O-type, open type; PPI, proton pump inhibitor; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WBC, white blood cell; WC, waist circumference.
the general population, had underlying disease, underwent regular medical checkup, or underwent upper GI endoscopy, and differences in lifestyle backgrounds.

Low-dose aspirin, an antiplatelet drug, can cause mucosal injury and potential bleeding directly as well as by COX inhibition.33 Although antiplatelet drugs, including LDA, have a possibility of causing GI bleeding, the prevalence of GI bleeding is lower in users of antiplatelet drugs other than LDA. Hallas et al13 reported that administration of clopidogrel, an antiplatelet drug, did not have a significant risk of causing GI bleeding in a case-controlled study. On the contrary, the use of clopidogrel in patients with previous peptic ulcer disease was reported to have a high incidence of GI bleeding.12 The association between antiplatelet drug use and GI mucosal injury in asymptomatic subjects has been unclear. Although there have been many reports on the association between antiplatelet drug use and GI injury, most reports did not make a distinction between subjects with and without symptoms. Thus, to clarify possible differences between subjects with and without gastroduodenal mucosal injury, we simply divided asymptomatic antiplatelet drug users into those with or without gastroduodenal mucosal injury, using upper GI endoscopy during a normal medical checkup. In the current study, the prevalence of gastroduodenal mucosal injury was 32.8%, and the prevalence of endoscopically gastroduodenal ulcer was 9.1%. LDA use was not a significant factor for prevalence of gastroduodenal mucosal injury in asymptomatic antiplatelet drug users. Of the 17 subjects who, however, had an endoscopically observable gastroduodenal ulcer, 12 (88.2%) were LDA users. These results suggest that LDA use may increase the risk of deep mucosal injury compared with other antiplatelet drugs.

The association between H. pylori infection and GI injury among antiplatelet drug users has remained controversial. Shiotani et al14 reported that there was no association between H. pylori infection and the presence of peptic ulcers among patients taking LDA. An Italian study, however, reported that...

### TABLE 3. Results of Univariate and Multivariate Analyses: Independent Predictors of Gastroduodenal Mucosal Injury in Asymptomatic Antiplatelet Drug Users

|                        | Mucosal Injury (+) (N = 61) | Mucosal Injury (-) (N = 125) | P Value * | Multivariate Analysis |
|------------------------|-----------------------------|-----------------------------|-----------|----------------------|
| Age (≥ 65/65 years)    | 27/34                       | 59/66                       | NS        | 0.970 0.495–1.901    | NS |
| Sex (men/women)        | 53/8                        | 91/34                       | <0.05     | 1.749 0.650–4.711    | NS |
| BMI (≥ 25/25 kg/m²)    | 20/41                       | 50/75                       | NS        | 0.643 0.315–1.312    | NS |
| WC (≥ 85/85 cm)        | 35/26                       | 69/56                       | NS        |                      |    |
| SBP (≥ 130/130 mmHg)   | 29/32                       | 53/72                       | NS        |                      |    |
| DBP (≥ 90/90 mmHg)     | 6/55                        | 13/112                      | NS        |                      |    |
| Hypertension (+/-)     | 48/13                       | 99/26                       | NS        |                      |    |
| T-CHO (≥ 220/220 mg/dl)| 7/54                        | 25/100                      | NS        |                      |    |
| TG (≥ 150/150 mg/dl)   | 13/48                       | 31/94                       | NS        |                      |    |
| HDL-C (<40/40 mg/dl)   | 8/53                        | 6/119                       | NS        | 3.571 0.937–13.61    | NS |
| LDL-C (≥ 140/140 mg/dl)| 9/52                        | 25/100                      | NS        |                      |    |
| Dyslipidemia (+/-)     | 39/22                       | 73/52                       | NS        |                      |    |
| UA (≥ 7.0/7.0 mg/dl)   | 18/43                       | 24/101                      | NS        |                      |    |
| FPG (≥ 110/110 mg/dl)  | 15/46                       | 38/87                       | NS        |                      |    |
| HbA1c (≥ 6.2/6.2 % NGSP)| 16/45                      | 30/95                       | NS        |                      |    |
| IGT (+/-)              | 15/46                       | 40/85                       | NS        |                      |    |
| ALT (≥ 31/31 IU/l)     | 15/46                       | 25/100                      | NS        |                      |    |
| AST (≥ 31/31 IU/l)     | 15/46                       | 18/107                      | NS        | 1.836 0.759–4.442    | NS |
| GGTY (≥ 51/51 IU/l)    | 16/45                       | 31/94                       | NS        |                      |    |
| Presence of Helicobacter pylori (+/-) | 18/43 | 53/72 | NS | 0.684 0.319–1.467 | NS |
| Drinker/nondrinker     | 46/15                       | 74/51                       | <0.05     | 1.255 0.549–2.871    | NS |
| Current smoker (+/-)   | 6/55                        | 9/116                       | NS        |                      |    |
| LDA (+/-)              | 42/19                       | 74/51                       | NS        |                      |    |
| Anticoagulant (+/-)    | 4/57                        | 7/118                       | NS        |                      |    |
| PPI (+/-)              | 2/59                        | 18/107                      | <0.05     | 0.118 0.022–0.637    | <0.05 |
| H2-RA (+/-)            | 5/56                        | 6/119                       | NS        |                      |    |
| Gastric atrophy (C-type/O-type) | 22/39 | 30/95 | NS | 1.843 0.842–4.035 | NS |
| Past history of peptic ulcer (+/-) | 13/48 | 22/103 | NS |                      |    |

*P value is based on the univariate analysis.

†P value is based on the multivariate logistic regression analysis. Significant is at the 5% level. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; C-type, closed type; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; H2-RA, histamine type 2-receptor antagonist; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LDA, low dose aspirin; LDL-C, low-density lipoprotein cholesterol; NGSP, National Glycohemoglobin Standardization Program; NS, not significant; OR, odds ratio; O-type, open type; PPI, proton pump inhibitor; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.
TABLE 4. Results of Univariate and Multivariate Analyses: Independent Predictors of Severe Gastroduodenal Mucosal Injury in Asymptomatic Antiplatelet Drug Users

|                                | Severe Mucosal Injury (+) (N = 33) | Mucosal injury (−) (N = 125) | P Value* | OR   | 95% CI | P Value† |
|--------------------------------|------------------------------------|-----------------------------|----------|------|-------|---------|
| Age (≥ 65/<65 years)           | 13/20                              | 59/66                       | NS       | 1.099 | 0.449–2.688 | NS      |
| Sex (men/women)                | 29/4                               | 91/34                       | NS       | 1.702 | 0.465–6.229 | NS      |
| BMI (≥ 25/< 25 kg/m²)          | 9/24                               | 50/75                       | NS       | 0.459 | 0.180–1.169 | NS      |
| WC (≥ 85/<85 cm)               | 19/14                              | 69/56                       | NS       | 0.144 | 0.017–1.207 | NS      |
| SBP (≥ 130/<130 mmHg)          | 15/18                              | 53/72                       | NS       | 2.158 | 0.822–5.667 | NS      |
| DBP (≥ 90/<90 mmHg)            | 2/31                               | 13/112                      | NS       | 0.419 | 0.017–3.055 | NS      |
| Hypertension (+/−)             | 24/9                               | 99/26                       | NS       | 2.170 | 0.823–5.685 | NS      |
| T-CHO (≥ 220/<220 mg/dl)       | 4/29                               | 25/100                      | NS       | 0.803 | 0.383–1.774 | NS      |
| TG (≥ 150/<150 mg/dl)          | 8/25                               | 31/94                       | NS       | 0.144 | 0.017–1.207 | NS      |
| LDL-C (≥ 140/<140 mg/dl)       | 6/27                               | 25/100                      | NS       | 0.144 | 0.017–1.207 | NS      |
| Dyslipidemia (+/−)             | 21/12                              | 73/52                       | NS       | 0.419 | 0.305–5.055 | NS      |
| UA (≥ 7.0/<7.0 mg/dl)          | 13/20                              | 24/101                      | <0.05    | 2.158 | 0.822–5.667 | NS      |
| FPG (≥ 110/<110 mg/dl)         | 7/26                               | 38/87                       | NS       | 0.419 | 0.305–5.055 | NS      |
| HbA1c (≥ 6.2/<6.2 % NGSP)       | 6/26                               | 30/95                       | NS       | 0.419 | 0.305–5.055 | NS      |
| IGT (+/−)                      | 7/26                               | 40/85                       | NS       | 0.419 | 0.305–5.055 | NS      |
| ALT (≥ 31/<31 IU/l)            | 7/26                               | 25/100                      | NS       | 0.419 | 0.305–5.055 | NS      |
| AST (≥ 31/<31 IU/l)            | 7/26                               | 18/107                      | NS       | 0.419 | 0.305–5.055 | NS      |
| GGT (≥ 51/<51 IU/l)            | 7/26                               | 31/94                       | NS       | 0.419 | 0.305–5.055 | NS      |
| Presence of Helicobacter pylori (+/−) | 11/22                          | 53/72                       | NS       | 1.131 | 0.419–3.055 | NS      |
| Drinker/nondrinker             | 25/8                               | 74/51                       | NS       | 0.144 | 0.017–1.207 | NS      |
| Current smoker (+/−)           | 4/29                               | 9/116                       | NS       | 0.144 | 0.017–1.207 | NS      |
| LDA (+/−)                      | 26/7                               | 74/51                       | NS       | 0.144 | 0.017–1.207 | NS      |
| Anticoagulant (+/−)            | 2/31                               | 7/118                       | NS       | 0.144 | 0.017–1.207 | NS      |
| PPI (+/−)                      | 1/32                               | 18/107                      | NS       | 0.144 | 0.017–1.207 | NS      |
| H2-RA (+/−)                    | 3/30                               | 6/119                       | NS       | 0.144 | 0.017–1.207 | NS      |
| Gastric atrophy (C-type/O-type) | 16/17                           | 30/95                       | <0.05    | 3.172 | 1.322–7.609 | <0.01  |
| Past history of peptic ulcer (+/−) | 7/26                           | 22/103                      | NS       | 3.172 | 1.322–7.609 | <0.01  |

*P value is based on the univariate analysis.
†P value is based on the multivariate logistic regression analysis. Significant is at the 5% level. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; C-type, closed type; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; H2-RA, histamine type 2-receptor antagonist; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LDA, low dose aspirin; LDL-C, low-density lipoprotein cholesterol; NGSP, National Glycogenolipid Standardization Program; NS, not significant; OR, odds ratio; O-type, open type; PPI, proton pump inhibitor; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

The prevalence of peptic ulcers was significantly higher among *H. pylori*-positive subjects than among *H. pylori*-negative subjects in elderly, symptomatic chronic users of LDA. In addition, it was reported that there was no significant difference in the prevalence of previous *H. pylori* infection between with and without GI bleeding in patients with previous peptic ulcer disease. The current study showed that there was a tendency of increased prevalence of C-type atrophy in subjects with gastroduodenal mucosal injury (36.1%) than in those without (24.0%) and C-type atrophy was a significant and independent predictor of an increased prevalence of severe gastroduodenal mucosal injury. In addition, the prevalence of gastroduodenal mucosal injury in subjects with C-type atrophy was significantly higher than in subjects with O-type atrophy among antiplatelet drug users with *H. pylori* infection in current study (data not shown). It was reported that the effect of *H. pylori* infection on the aspirin-induced gastropathy was biphasic depending on the individual gastric acid secretion. In other words, the presence of sufficient amounts of gastric acid, *H. pylori* infection, and aspirin may cause a synergistically damage gastric mucosal. Our results suggest that C-type atrophy may increase the risk of severe gastric mucosal injury, whereas corpus-predominant gastritis is associated with reduced acid secretion and thus may reduce gastric mucosal injury.
mucosal injury than O-type atrophy because of increased acid secretion in even antiplatelet drugs users. Furthermore, studies are needed to elucidate the mechanism of association between gastric acid secretion level, status of gastric atrophy, H. pylori infection, and antiplatelet drugs, because gastric acid secretion levels were not measured in the current study.

Although there have been no prospective clinical trials showing PPI use significantly preventing NSAID-associated upper GI complications, PPIs are effective at reducing the risk of endoscopic peptic ulcer. In addition, an epidemiological study reported that PPI use was associated with an 80% decrease in the risk of upper GI bleeding in LDA users. Shiotani et al reported that in LDA users, the proportion of PPI users was significantly lower in those with peptic ulcer than in those without. The current study showed that in asymptomatic antiplatelet drug users, the proportion of PPI users was significantly lower in those with gastroduodenal mucosal injury (3.3%) than in those without (14.4%), and that PPI use was a significant predictor of a decreased prevalence of gastroduodenal injury, in confirmation with previous studies.

The association between drinking and gastric mucosal injury, including peptic ulcers, remains controversial. Although excess alcohol consumption is believed to cause GI injury, a previous study reported that in NSAID users, the risk of upper GI bleeding in nondrinkers was higher than in light drinkers. Light drinking in NSAID users may induce adaptive cytoprotection, a mechanism of protection against upper GI bleeding. The current study, however, showed that subjects with gastroduodenal mucosal injury had a higher proportion of drinkers than in those without gastroduodenal mucosal injury. In addition, alcohol consumption was not a significant protective factor against gastroduodenal mucosal injury in asymptomatic antiplatelet drug users.

There were several limitations to the current study. First, full evaluation of the cause-and-effect relationship between gastroduodenal mucosal injury and use of antiplatelet drugs was not performed, because the current study was of a cross-sectional design. Second, of the 23,138 subjects who underwent a medical checkup, 16,073 subjects did not undergo upper GI endoscopy (Fig. 1), because the Japanese who undergo a medical checkup often choose to undergo an upper gastrointestinal series rather than an upper GI endoscopy. Third, there was a possibility of selection bias, because most participants in the current study were healthy individuals who underwent a normal medical checkup. Furthermore studies are needed to resolve these limitations.

In conclusion, the current study showed that in asymptomatic antiplatelet drug users, there were significant differences in sex, UA, proportion of drinkers, and PPI users between those with and without gastroduodenal mucosal injury. Although PPI use is an important protective factor against gastroduodenal mucosal injury, including in antiplatelet drug users without digestive symptoms, status of gastric atrophy should also be considered against severe gastroduodenal mucosal injury.

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REFERENCES
1. Antithrombotic Trialists’ Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Br Med J. 2002;324:71–86.
2. Patrono C, García Rodriguez LA, Landolfi R, et al. Low-dose aspirin for the prevention of atherothrombosis. Engl J Med. 2005;353:2373–2383.
3. Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. Arch Intern Med. 2002;162:2197–2202.
4. Pearson TA, Blair SN, Daniels SR, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation. 2002;106:388–391.
5. Antithrombotic Trialists’ (ATT) CollaborationBaigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849–1860.
6. MAGIC Study GroupUemura N, Sugano K, et al. Risk factor profiles, drug usage, and prevalence of aspirin-associated gastroduodenal injuries among high-risk cardiovascular Japanese patients: the results from the MAGIC study. J Gastroenterol. 2014;49:814–824.
7. Sakamoto C, Sugano K, Ota S, et al. Case-control study on the association of upper gastrointestinal bleeding and nonsteroidal antiinflammatory drugs in Japan. Eur J Clin Pharmacol. 2006;62:765–772.
8. Shiotani A, Kamada T, Haruma K. Low-dose aspirin-induced gastrointestinal diseases: past, current, and future. J Gastroenterol. 2008;43:581–588.
9. Collaborative Group of the Primary Prevention Projectede Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet. 2001;357:89–95.
10. Laine L. Approaches to nonsteroidal antiinflammatory drug use in the high-risk patient. Gastroenterology. 2001;120:594–606.
11. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med. 2005;352:238–244.
12. Ng FH, Wong SY, Chang CM, et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. Aliment Pharmacol Ther. 2003;18:443–449.
13. Hallas J, Dall M, Andries A, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. Br Med J. 2006;333:726–728.
14. Naito Y, Iinuma S, Yagi N, et al. Prevention of indomethacin-induced gastric mucosal injury in Helicobacter pylori-negative healthy volunteers: a comparison study rebamipide vs famotidine. J Clin Biochem Nutr. 2008;43:34–40.
15. Lanza FL, Graham DY, Davis RE, et al. Endoscopic comparison of cimetidine and sucralfate for prevention of naproxen-induced acute gastroduodenal injury. Effect of scoring method. Dig Dis Sci. 1990;35:1494–1499.
16. Lanza F. An endoscopic comparison of GD injury with over-the-counter doses of ketoprofen and acetaminophen. Am J Gastroenterol. 1998;93:1051–1054.
17. Kimura K, Satoh K, Ido K, et al. Gastritis in the Japanese stomach. Scand J Gastroenterol (Suppl). 1996;214:17–20 discussion 21–23.
18. Ito Y, Sasaki M, Noguchi S, et al. Effect of aspirin cessation before endoscopy in Japanese patients with low-dose-aspirin-associated gastroduodenal mucosal injury. United European Gastroenterol J. 2013;1:259–264.
19. Grove EL, Würtz M, Schwarz P, et al. Gastrointestinal events with clopidogrel: a nationwide population-based cohort study. *J Gen Intern Med.* 2013;28:216–222.

20. Yeomans ND, Lanas A, Talley NJ, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. *Aliment Pharmacol Ther.* 2005;22:795–801.

21. García Rodríguez LA, Hernández-Díaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. *Br J Clin Pharmacol.* 2001;52:563–571.

22. Niv Y, Battler A, Abuksis G, et al. Endoscopy in asymptomatic minidose aspirin consumers. *Dig Dis Sci.* 2005;50:78–80.

23. Harrington RA, Becker RC, Ezekowitz M, et al. Antiplatelet therapy for coronary artery disease: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest.* 2004;126:5138–548S. 

24. Tsai YW, Wen YW, Huang WF, et al. Cardiovascular and gastrointestinal events of three antiplatelet therapies: clopidogrel, clopidogrel plus proton-pump inhibitors, and aspirin plus proton-pump inhibitors in patients with previous gastrointestinal bleeding. *J Gastroenterol.* 2011;46:39–45.

25. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *Br Med J.* 2000;321:1183–1187.

26. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol.* 2012;107:345–360.

27. Kim Y, Yokoyama S, Watari J, et al. Endoscopic and clinical features of gastric ulcers in Japanese patients with or without *Helicobacter pylori* infection who were using NSAIDs or low-dose aspirin. *J Gastroenterol.* 2012;47:904–911.

28. Sugano K, Matsumoto Y, Itabashi T, et al. Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. *J Gastroenterol.* 2011;46:724–735.

29. Origasa H, Goto S, Shimada K, et al. MAGIC Investigators. Prospective cohort study of gastrointestinal complications and vascular diseases in patients taking aspirin: rationale and design of the MAGIC Study. *Cardiovasc Drugs Ther.* 2011;25:551–560.

30. Chan FK, Goto S, Wu MS, et al. Burden of nonsteroidal antiinflammatory and antiplatelet drug use in Asia: a multidisciplinary working party report. *Clin Gastroenterol Hepatol.* 2012;10:753–760.

31. Singh G, Ramey DR, Morfeld D, et al. Gastrointestinal tract complications of nonsteroidal antiinflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch Intern Med.* 1996;156:1530–1536.

32. Miyake K, Kusunoki M, Ueki N, et al. Implication of antiplatelet agents on potential bleeding from endoscopically determined peptic ulcers, incidentally detected as surrogate markers for nsaids-associated ulcers complication. *Dig Endosc.* 2013;25:25–31.

33. Tran H, Anand SS. Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease. *J Am Med Assoc.* 2004;292:1867–1874.

34. Shiotani A, Sakakibara T, Yamanaka Y, et al. Upper gastrointestinal ulcer in Japanese patients taking low-dose aspirin. *J Gastroenterol.* 2009;44:126–131.

35. Pilotto A, Franceschi M, Longoa MG, et al. *Helicobacter pylori* infection and the prevention of peptic ulcer with proton pump inhibitors in elderly subjects taking low-dose aspirin. *Dig Liver Dis.* 2004;36:666–670.

36. Shiotani A, Graham DY. Pathogenesis and therapy of gastric and duodenal ulcer disease. *Med Clin North Am.* 2002;86:1447–1466viii.

37. Shiotani A, Yamaoka Y, El-Zimaity HM, et al. NSAID gastric ulceration: predictive value of gastric pH, mucosal density of polymorphonuclear leukocytes, or levels of IL-8 or nitrite. *Dig Dis Sci.* 2002;47:38–43.

38. Iijima K, Ara N, Abe Y, et al. Biphasic effects of *H. pylori* infection on low-dose aspirin-induced gastropathy depending on the gastric acid secretion level. *J Gastroenterol.* 2012;47:1290–1297.

39. Investigators of the Asociación Española de Gastroenterología (AEG) Lanas A, García-Rodríguez LA, Arroyo MT, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal antiinflammatory drugs, antiplatelet agents, and anticoagulants. *Am J Gastroenterol.* 2007;102:507–515.

40. Lanas A, Bajador E, Serrano P, et al. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med.* 2000;343:834–839.

41. Kelly JP, Kaufman DW, Koff RS, et al. Alcohol consumption and the risk of major upper gastrointestinal bleeding. *Am J Gastroenterol.* 1995;90:1058–1064.

42. Kaufman DW, Kelly JP, Wohlen BE, et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. *Am J Gastroenterol.* 1999:94:3189–3196.

43. Chaudhury TK, Robert A. Prevention by mild irritants of gastric necrosis produced in rats by sodium taurocholate. *Dig Dis Sci.* 1980;25:830–836.

44. Kokoska ER, Smith GS, Deshpande Y, et al. Adaptive cytoprotection induced by ethanol in human intestinal cells: role of prostaglandins and calcium homeostasis. *Ann Surg.* 1998;228:123–130.