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Investigation of Gastroduodenal Mucosal Injury in Japanese Asymptomatic Antiplatelet Drug Users

Masahiro Sogabe, MD, PhD, Toshiya Okahisa, MD, PhD, Masahiko Nakasono, MD, PhD, Yasuteru Fujino, Yasuhiro Mitsui, Yoshihumi Takaoka, Tetsuo Kimura, MD, PhD, Koichi Okamoto, MD, PhD, Naoki Muguruma, MD, PhD, and Tetsuji Takayama, MD, PhD

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.

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Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, C-type = closed-type, CV = cardiovascular, DBP = diastolic blood pressure, FPG = fasting plasma glucose, GGT = γ-glutamyl transpeptidase, GI = gastrointestinal, *H. pylori* = *Helicobacter pylori*, 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, MLS = modified Lanza score, NGSP = National Glycohemoglobin Standardization Program, NS = not significant, NSAID = nonsteroid antiinflammatory drug, OR = odds ratio, O-type = open-type, *P* = probability, PPI = proton pump inhibitor, SBP = systolic blood pressure, SD = standard deviation, T-CHO = total cholesterol, TG = triglyceride, UA = uric acid, WBC = white blood cell, WC = waist circumference.

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.[5,6] 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

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From the Department of General Medicine and Community Health Science, Institute of Health, Biosciences, Tokushima University Graduate School (MS, TO); Department of Gastroenterology and Oncology, Institute of Health Biosciences, Tokushima University Graduate School, Tokushima (MS, TO, YF, YM, YT, TK, KO, NM, TT); Department of Gastroenterology, Kagawa Prefectural Cancer Detection Center, Takamatsu, Japan (MS); Department of Internal Medicine, Tsurugi Municipal Handa Hospital, Tokushima, Japan (MN).
Reprints: Masahiro Sogabe, MD, Department of General Medicine and Community Health, Science, Institute of Health Biosciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima city, Tokushima 770–8503, Japan (e-mail: tokushimakenananshi@yahoo.co.jp).
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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, ethyl icosapentate, 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 $\geq$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 over the body, antrum, and proximal duodenum. 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 $\pm$ 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 χ^2-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 $24.3 \pm 3.7\,kg/m^2$, 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, ethyl icosapentate, limaprostalfadex, and multiple antiplatelet drugs in antiplatelet drug users was 116, 18, 8, 15, 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

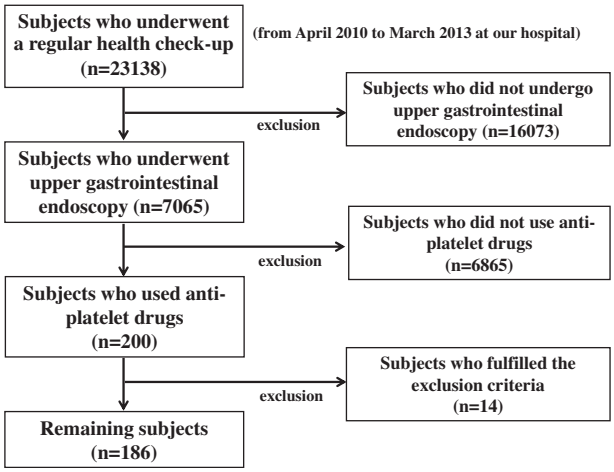

FIGURE 1. Flow diagram of subject enrollment in the current study.

confounding variables, including age, BMI, WC, alcohol consumption, and smoking habit. Of the 186 subjects, 61 had gastroduodenal mucosal injury and the proportion of gastroduodenal mucosal injury in all subjects was 32.8%. The proportion of men in the subjects with and without gastroduodenal mucosal injury was 86.9% and 72.8%, respectively. The proportion of men was significantly higher in subjects with gastroduodenal mucosal injury than in those without ($P < 0.05$). The mean age in the subjects with and without gastroduodenal mucosal injury was 63.7 ± 8.0 years and 63.8 ± 7.3 years, respectively. The mean BMI in the subjects with and without gastroduodenal mucosal injury was $24.3 \pm 3.6\,kg/m^2$ and $24.3 \pm 3.8\,kg/m^2$, respectively. The mean WC in the subjects with and without gastroduodenal mucosal injury was 86.0 ± 8.3 cm and 85.5 ± 9.7 cm, respectively. There was no significant difference in age, BMI, and WC between subjects with and without gastroduodenal mucosal injury. The prevalence of hypertension in the subjects with and without gastroduodenal mucosal injury was 78.7% and 79.2%, respectively. The prevalence of dyslipidemia in the subjects with and without gastroduodenal mucosal injury was 63.9% and 58.4%, respectively. The prevalence of IGT in the subjects with and without gastroduodenal mucosal injury was 24.6% and 32.0%, respectively. There was no significant difference in the prevalence of hypertension, dyslipidemia, or IGT between subjects with and without gastroduodenal mucosal injury. Uric acid in the subjects with and without gastroduodenal mucosal injury was 6.2 ± 1.3 mg/dl and 5.6 ± 1.4 mg/dl, respectively. Uric acid was significantly higher in subjects with gastroduodenal mucosal injury than in those without ($P < 0.05$). The proportion of current smokers in the subjects with and without gastroduodenal mucosal injury was 9.8% and 7.2%, respectively. The proportion of LDA users in the subjects with and without gastroduodenal mucosal injury was 68.9% and 59.2%, respectively. The proportion of anticoagulant drug users in the subjects with and without gastroduodenal mucosal injury was 6.6% and 5.6%, respectively. There was no significant difference in the proportion of current smokers, LDA users, or anticoagulant drug users between subjects with and without gastroduodenal mucosal injury. The proportion of drinkers in the subjects with and without gastroduodenal mucosal injury was 75.4% and 59.2%, respectively. The proportion of drinkers in subjects with gastroduodenal 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.[1,3] 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

TABLE 1. Subject Characteristics

Number	186
Sex (men/women) (% men)	144/42 (77.4%)
Age (years)	63.7 ± 7.5
BMI (kg/m^2)	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)	116/18/8/15/15/18/18/22
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; 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; PPI, proton pump inhibitor; SBP, systolic blood pressure; T-CHO, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

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 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* (adjusted†)
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/m^2)	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)
FPG (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.

* *P* value is based on the χ^2 test or Student *t*-test. Significant is at the 5% level.

† 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 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; 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.

incidence of bleeding during upper GI endoscopy. In addition, the prevalence of endoscopically observable gastroduodenal ulcers was 40% in subjects with a history of previous peptic ulcer disease, demonstrating that the current results were similar to previous reports.

Gastric mucosal injury induced by antiplatelet drugs has been known to be not necessarily associated with gastric events and digestive symptoms, such as hematemesis, melena, and abdominal pain. In addition, most endoscopically determined peptic ulcers induced by long-term NASID treatment including antiplatelet drugs, have been known to be generally asymptomatic or minimally symptomatic.[20,31,32] If overt bleeding signs, such as hematemesis and melena, and/or digestive symptoms, such as abdominal pain, occur in patients taking antiplatelet drugs, it is likely that most of these patients would go to a medical institution. Asymptomatic gastroduodenal mucosal injury induced by antiplatelet drugs, however, may easily be missed because of the absence of bleeding signs and digestive symptoms. The frequency of gastroduodenal mucosal injury observed in the current study may be similar to the real frequency of gastroduodenal mucosal injury without digestive symptoms, because participants in the current study underwent upper GI endoscopy and had no digestive symptoms or events. The range in frequency of abdominal symptoms in antiplatelet drug users has been reported to be very wide. In the current study, 6% of antiplatelet drug users had digestive symptoms and underwent a regular health checkup (data not shown). This discrepancy in the proportion of antiplatelet drug users with abdominal symptoms may be because of differences between studies, including whether the subjects were representative of

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

	Univariate Analysis			Multivariate Analysis		
	Mucosal Injury (+) (N = 61)	Mucosal Injury (−) (N = 125)	*P* Value*	OR	95% CI	*P* Value†
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/m^2)	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
GGT (≧ 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.

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 al[13] 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 al[34] 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 4. Results of Univariate and Multivariate Analyses: Independent Predictors of Severe Gastroduodenal Mucosal Injury in Asymptomatic Antiplatelet Drug Users

	Univariate Analysis			Multivariate Analysis		
	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/m^2)	9/24	50/75	NS	0.459	0.180–1.169	NS
WC (≧ 85/<85 cm)	19/14	69/56	NS			
SBP (≧ 130/<130 mmHg)	15/18	53/72	NS			
DBP (≧ 90/<90 mmHg)	2/31	13/112	NS			
Hypertension (+/−)	24/9	99/26	NS			
T-CHO (≧ 220/<220 mg/dl)	4/29	25/100	NS			
TG (≧ 150/<150 mg/dl)	8/25	31/94	NS			
HDL-C (< 40/≧ 40 mg/dl)	2/31	6/119	NS			
LDL-C (≧ 140/<140 mg/dl)	6/27	25/100	NS			
Dyslipidemia (+/−)	21/12	73/52	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			
HbA1c (≧ 6.2/<6.2 % NGSP)	6/26	30/95	NS			
IGT (+/−)	7/26	40/85	NS			
ALT (≧ 31/<31 IU/l)	7/26	25/100	NS			
AST (≧ 31/<31 IU/l)	7/26	18/107	NS			
GGT (≧ 51/<51 IU/l)	7/26	31/94	NS			
Presence of *Helicobacter pylori* (+/−)	11/22	53/72	NS			
Drinker/nondrinker	25/8	74/51	NS	1.131	0.419–3.055	NS
Current smoker (+/−)	4/29	9/116	NS			
LDA (+/−)	26/7	74/51	NS	2.170	0.803–5.865	NS
Anticoagulant (+/−)	2/31	7/118	NS			
PPI (+/−)	1/32	18/107	NS	0.144	0.017–1.207	NS
H2-RA (+/−)	3/30	6/119	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			

* *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.

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.[35] 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.[12] The current study showed that in antiplatelet drug users, there was no significant difference in the prevalence of *H. pylori* infection between those with and without gastroduodenal mucosal injury. In addition, in LDA users, there was no significant difference in the prevalence of *H. pylori* infection between those with and without gastroduodenal mucosal injury (data not shown). The discrepancy between *H. pylori* infection and presence of peptic ulcers or gastric mucosal injury in antiplatelet drug users may be because of differences in the severity of *H. pylori* gastritis, and topography of the gastritis among the subjects of each study.[36] Antral-predominant gastritis is associated with increased acid secretion, which may increase gastric mucosal injury, whereas corpus-predominant gastritis is associated with reduced acid secretion and thus may reduce gastric mucosal injury.[36,37] Interestingly, 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.[38] 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

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.[37,39] 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.[40] Shiotani et al[34] 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,[41] a previous study reported that in NSAID users, the risk of upper GI bleeding in nondrinkers was higher than in light drinkers.[42] Light drinking in NSAID users may induce adaptive cytoprotection, a mechanism of protection against upper GI bleeding.[43,44] 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 regular health 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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