

[ORIGINAL ARTICLE]

P2Y12 Inhibitors Exacerbate Low-dose Aspirin-induced Small Bowel Injury in Dual Antiplatelet Therapy

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Abstract:

Objective Antithrombotic drugs are being used increasingly frequently to prevent cardiovascular diseases. Few studies have evaluated small bowel mucosal injury induced by dual antiplatelet therapy (DAPT). The aim of the present study was to evaluate small bowel mucosal injury induced by DAPT compared with other antithrombotics using video capsule endoscopy (VCE).

Methods The study included chronic users of antithrombotics who underwent VCE for obscure gastrointestinal bleeding between January 2007 and July 2018. We evaluated the instances of small bowel injury classified into erosions and ulcers.

Results Overall, 183 patients (114 men and 69 women; mean age, 73.6 years old) were enrolled, and the study groups comprised 49 patients taking low-dose aspirin (LDA) only, 50 taking anticoagulants only, 37 being treated with DAPT, 33 on combined LDA and anticoagulants, and 14 taking P2Y12 inhibitors. Small bowel erosions and ulcers were most frequently observed in the DAPT group, with frequencies of 78.4% and 37.8%, respectively. Exacerbating factors of small bowel ulcers were DAPT [odds ratio (OR) 3.0, 95% confidence interval (CI) 1.2-7.7] and age over 80 years old (OR 2.4, 95% CI 1.1-5.4).

Conclusion P2Y12 inhibitors seem to exacerbate LDA-induced small bowel injury. Preventive strategies for small bowel injury induced by LDA, especially DAPT, are urgently required.

Key words: low-dose aspirin, dual antiplatelet therapy, small bowel injury, capsule endoscopy, obscure gastrointestinal bleeding

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Introduction

Obscure gastrointestinal bleeding (OGIB) is defined as gastrointestinal (GI) bleeding of an unknown origin after a complete evaluation by esophagogastroduodenoscopy (EGD) and colonoscopy. Overt OGIB refers to clinically evident bleeding (melena, or hematochezia), and occult OGIB manifests as iron-deficiency anemia or a positive fecal occult blood test (1). OGIB is responsible for 5% of all GI bleeding cases (2). The small intestine is the leading source of OGIB, accounting for up to 75% of cases (3).

Aspirin causes gastroduodenal mucosal injury as an adverse effect but is regarded as safe beyond the duodenum because of its rapid absorption and lack of enterohepatic re-

circulation (4). Previous studies using new modalities to investigate the small intestine, such as double-balloon endoscopy (5) and small bowel video capsule endoscopy (VCE) (6), have also shown that aspirin can cause mucosal injury in the small intestine (7-10). Although findings have varied by study design, the high prevalence rates of mucosal breaks in the small intestine range from 30% to 91% in patients taking low-dose aspirin (LDA) (11-15).

Percutaneous coronary intervention (PCI) has become a common procedure for coronary stenosis treatment with two basic stent types: bare-metal stents and drug-eluting stents (DESs). Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is basic therapy for patients after PCI (16-18). The recommended duration of DAPT for patients after DES implantation is ≥ 12 months for patients

with acute coronary syndrome and 6 months for patients with stable coronary artery disease (17, 18). Antiplatelet or anticoagulant (antithrombotic) therapy is important for patients with arteriosclerosis; however, the risk of upper GI complications, including small bowel bleeding, has been well-recognized (19, 20).

In our previous preliminary study in patients with OGIB, small bowel mucosal injury was exacerbated by DAPT compared with LDA (21). Conversely, in another previous study in patients after PCI for coronary stenosis, DAPT did not affect LDA-induced small bowel injury (15). The clinical features of the small bowel adverse effects caused by aspirin combined with other antiplatelets or anticoagulants (antithrombotics) have not been revealed.

The present study investigated the effect of antithrombotics on small bowel injury in patients with OGIB using VCE and explored whether or not P2Y12 inhibitors exacerbate LDA-induced small bowel injury.

Materials and Methods

Subjects

The study included patients taking antithrombotics who underwent VCE for OGIB between January 2007 and July 2018. For every patient, abdominal ultrasonography, upper GI endoscopy, and total colonoscopy were performed within one month before VCE, and the origin of GI bleeding was not diagnosed. All patients with at least a 3-month history of the usage of 100 mg enteric-coated aspirin (Bayer Health Care, Osaka, Japan) and/or antithrombotics were included. Recent and present users of non-steroidal anti-inflammatory drugs (NSAIDs) were excluded. Patients were also excluded if they had been identified as having lesions causing small bowel bleeding, such as malignant, tumorous, inflammatory, or vascular lesions, except for ulcers or erosions.

The study was approved by the Research Ethics Committee of Kawasaki Medical School, Okayama, Japan. The study protocol was consistent with the ethical guidelines of the 1975 Declaration of Helsinki as reflected in its prior approval by the institution's human research committee, and the patients were informed using posters and our website (https://h.kawasaki-m.ac.jp/data/dept_022/ekigaku_s_dtl/). An opportunity to opt out was always available.

The assessment and evaluation of clinical data

We retrospectively collected patients' clinical data based on clinical records and evaluated the small bowel injury using VCE findings. Underlying diseases and concomitant medications were corroborated with medical prescription and refill records based on electronic health records. The most commonly evaluated medicines were those continued for more than three years, and all evaluated medicines were confirmed to be unchanged from others within three months. Gastroprotective drugs that had been prescribed or changed just before endoscopy were not evaluated. We assessed the

effects of antithrombotics, including antiplatelets (LDA, P2Y12 inhibitor: ticlopidine or clopidogrel), anticoagulants (warfarin, apixaban, rivaroxaban, dabigatran, and edoxaban), or any combination thereof. Chronic renal failure was defined as receiving hemodialysis or peritoneal dialysis.

Small bowel VCE and the evaluation of small bowel injury

We performed capsule endoscopy with the PillCam SB, SB2, and SB3 (Given Diagnostic Imaging System; Given Imaging, Tokyo, Japan) in this study. The subjects swallowed the video capsule after a 12-h fast. Two experienced gastroenterologists blinded to the subjects' groups separately reviewed each procedure and identified all suspected lesions by recording them as thumbnail photographs using a Rapid Reader (Given Diagnostic Imaging System; Given Imaging). When discrepancies in the interpretation occurred, they discussed suspected lesions until a consensus was reached. The patients were asked to repeat VCE if the procedure was incomplete because of a large quantity of residue or blood and persistence of the capsule in the upper GI tract.

VCE findings associated with antithrombotics were categorized into four types of small bowel lesions, as previously reported: redness, small erosions, large erosions, and ulcers (Fig. 1) (22). We evaluated the small bowel injury classified into erosions and ulcers. To analyze the distribution of small bowel injuries, the small bowel was classified into three parts (proximal, middle, and distal) based on the small bowel transit time.

Statistical analyses

Continuous and normally distributed values are expressed as the mean with the standard deviation (SD), and non-normally distributed continuous values are expressed as the median with the 25th-75th percentile. Categorical data are expressed as counts with percentages and analyzed using the chi-square test. Continuous data were compared between two groups using the unpaired *t* test and Mann-Whitney U test. In multiple comparisons among the five groups, the Kruskal-Wallis one-way analysis and a one-way factorial analysis of variance were used. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by a binomial regression analysis. A *p* value <0.05 was considered statistically significant.

All statistical calculations were performed using the SPSS software program (version 25 for Windows; SPSS, Chicago, USA).

Results

Among the 880 patients who underwent VCE between January 2007 and July 2018 in our department, 286 taking antithrombotics underwent VCE for OGIB. Of these, 103 patients were excluded for taking NSAIDs (*n*=30), repeated VCE (*n*=29), incomplete procedure (*n*=10), lack of visualization of the entire small intestine owing to active bleeding

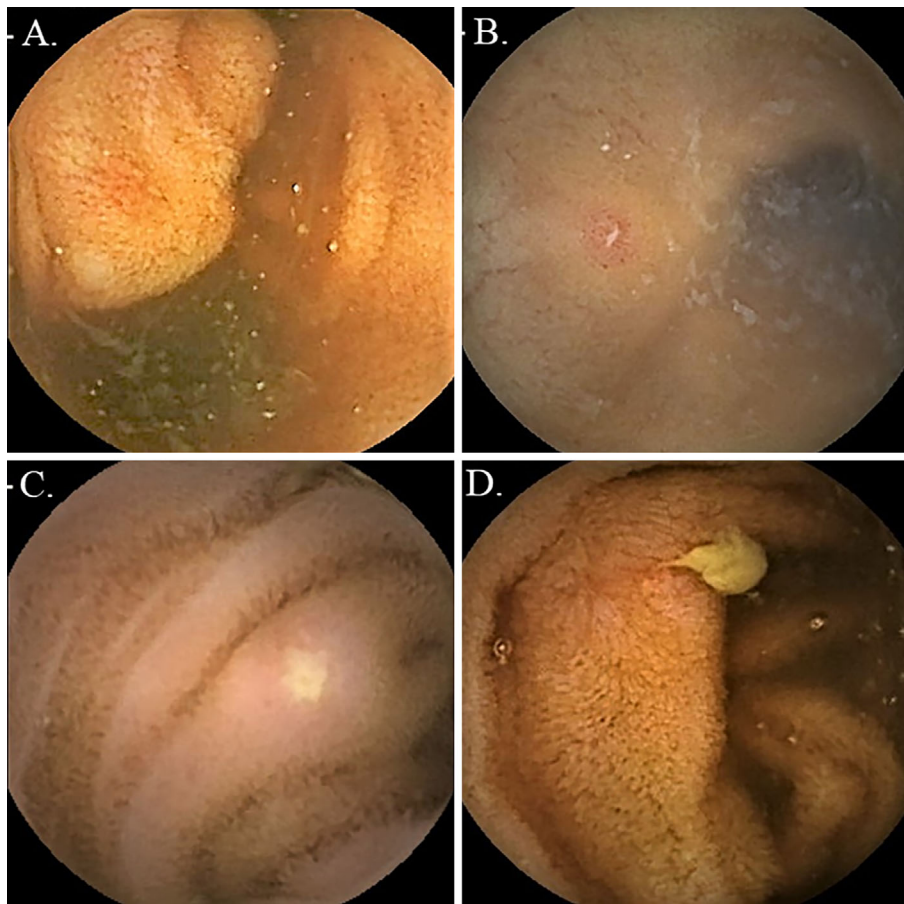


Figure 1. Capsule endoscopy images showing small bowel injuries. (A) Redness, (B) small erosions, (C) large erosions, and (D) ulcers.

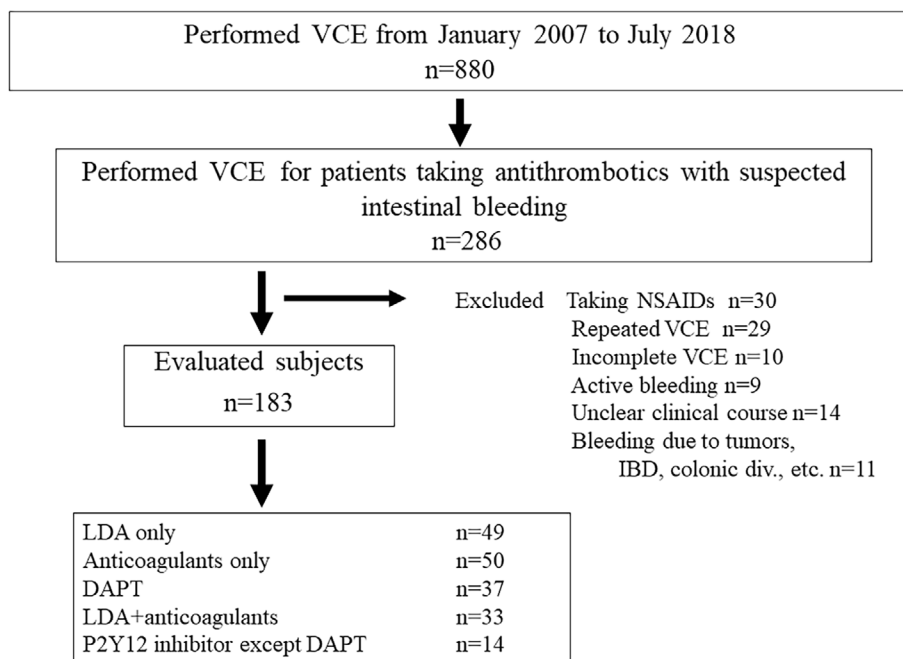


Figure 2. Flow chart of the study subjects.

(n=9), unclear clinical course (n=14), and bleeding owing to causes besides small bowel enteropathy (e.g., tumors, inflammatory bowel disease, angioectasia, and colonic diver-

ticulum; n=11). The remaining 183 patients (114 men and 69 women; mean age, 73.6 years old) were enrolled. Of these, 49 patients were taking LDA alone, 50 were taking

Table 1. Patient Demographic and Clinical Characteristics.

	LDA alone n=49	Anti- coagulants alone n=50	DAPT n=37	LDA+anti- coagulants n=33	P2Y12 inhibitors* n=14	p
Age (SD)	74.1 (8.8)	72.6 (11.0)	71.1 (10.8)	78.0 (7.3)	72.4 (10.9)	
Over 80 yr of age (%)	13 (26.5)	13 (26.0)	10 (27.0)	17 (51.5)	5 (35.7)	0.098
Sex, men (%)	30 (61.2)	28 (56.0)	28 (75.7)	19 (57.6)	9 (64.3)	0.403
Drinking (%)	15 (34.9)	11 (23.9)	10 (30.3)	4 (14.8)	3 (25.0)	0.428
Smoking (%)	7 (16.3)	6 (13.0)	8 (24.2)	2 (7.1)	2 (27.3)	0.330
Ischemic heart disease (%)	19 (39.6)	3 (6.0)	32 (86.5)	16 (48.5)	6 (42.9)	<0.001
AF or valvular heart disease (%)	10 (20.8)	40 (80.0)	10 (27.0)	21 (63.6)	7 (50.0)	<0.001
Cerebrovascular disease (%)	17 (35.4)	11 (22.0)	5 (13.59)	11 (33.3)	7 (50.0)	0.043
Chronic renal failure (%)	8 (16.7)	11 (22.0)	5 (13.5)	8 (24.2)	3 (21.4)	0.771
Diabetes mellitus (%)	13 (26.5)	8 (16.0)	7 (18.9)	5 (15.2)	2 (14.3)	0.626
Liver cirrhosis (%)	2 (4.1)	1 (2.0)	0 (0)	0 (0)	1 (7.1)	0.405
PPIs (%)	26 (53.1)	26 (52.0)	22 (59.5)	20 (60.6)	8 (57.1)	0.916
H2-RA (%)	8 (16.3)	3 (6.0)	4 (10.8)	6 (18.2)	2 (14.3)	0.451
Mucosal protective agent (%)	14 (28.6)	19 (38.0)	19 (27.0)	6 (18.2)	4 (28.6)	0.417
NSAIDs for external use (%)	3 (6.1)	1 (2.0)	1 (2.7)	0 (0)	1 (7.1)	0.505

* 2 patients taking cilostazol and 3 patients taking warfarin. p values was calculated by Pearson's Chi-square test.

LDA: low dose aspirin, DAPT: dual antiplatelet therapy, NSAIDs: non-steroidal anti-inflammatory drugs, SD: standard deviation, AF: atrial fibrillation, PPIs: proton pump inhibitors, H2-RA: histamine-2-receptor antagonist

Table 2. Frequencies of Erosion and Ulcer in Each Group.

	Erosion (%)	Ulcer (%)
LDA alone n=49	29 (59.2)	9 (18.4)
Anticoagulants alone n=50	27 (54.0)	4 (8.0)
DAPT n=37	29 (78.4)	14 (37.8)
LDA+anticoagulants n=33	23 (69.7)	7 (21.2)
P2Y12 inhibitor n=14	7 (50.0)	2 (14.3)
p values	0.115	0.015

LDA alone group, patients taking 100mg of enteric-coated aspirin, Anticoagulants alone group, patients taking warfarin or direct oral anticoagulants neither LDA nor P2Y12 inhibitor. DAPT group, patients taking LDA and P2Y12 inhibitor. Twelve patients additionally taking anticoagulants.

p values was calculated by Pearson's Chi-square test.

LDA: low dose aspirin, DAPT: dual antiplatelet therapy

anticoagulants alone (neither aspirin nor P2Y12 inhibitor), 37 were taking LDA and P2Y12 inhibitor, 33 were being treated with LDA and anticoagulants, and 14 were taking P2Y12 inhibitor (without aspirin). The flow chart of the study subjects is illustrated in Fig. 2.

The demographic and clinical characteristics of the five study groups are shown in Table 1. The most frequent indications for antithrombotic therapy were ischemic heart disease (86.5%) in the DAPT group and cerebrovascular diseases in the LDA alone group (35.4%) and LDA+anticoagulants group (33.3%). Other cardiac diseases, mainly atrial fibrillation or cardiac valvular disease, were prominent indications in the anticoagulants alone group (80%). However, there were no significant differences in other clinical charac-

teristics, including chronic renal failure and proton pump inhibitors use, among groups.

Among the five groups, erosions (78.4%) and ulcerative lesions (37.8%, $p=0.015$) were observed predominantly in the DAPT group (Table 2). The number of ulcers was significantly higher ($p=0.004$) in the patients taking DAPT than in those receiving other treatments, but not the number of erosions ($p=0.380$) (Fig. 3). Regarding the distribution of mucosal lesions, there were no significant differences in the location of erosions or ulcers among the groups (Supplementary material).

Smoking was associated with small bowel erosion. Subjects over 80 years old and with ischemic heart disease were significantly associated with ulcers (Table 3). A multivariate logistic regression analysis revealed that the exacerbating factors for small bowel ulcer were DAPT (adjusted OR 3.0; 95% CI 1.2-7.7, $p=0.024$) and age over 80 years old (adjusted OR 2.4; 95% CI 1.1-5.4, $p=0.028$) (Table 4).

Discussion

In the present study, mucosal injury was observed most frequently in the DAPT group among patients taking antithrombotics. The combination of aspirin with a P2Y12 inhibitor seems to exacerbate small bowel injury. The previous preliminary studies reported that the concomitant use of antiplatelet drugs with LDA tended to exacerbate LDA-induced small bowel injury (21, 23). In a study including 13 patients taking DAPT, small bowel ulcers were more frequently observed in the DAPT group (46.2%, $p=0.01$) than in the thienopyridine (12.5%), aspirin (9.1%), and warfarin

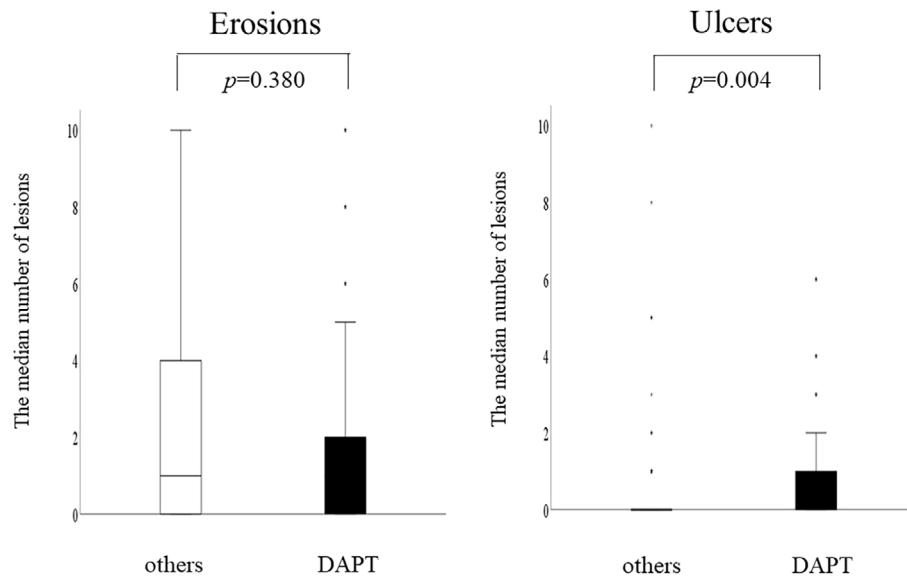


Figure 3. Comparisons of the median number of erosions and ulcers between patients taking DAPT and those taking other antithrombotics. p values according to the Mann-Whitney U analysis of variance. DAPT: dual antiplatelet therapy

Table 3. CE Findings and Clinical Characteristics.

	Erosion			Ulcer		
	negative	positive	p	negative	positive	p
Over 80 yr. of age (%)	15 (25.4)	42 (36.5)	0.140	15 (25.4)	17 (47.2)	0.029
Sex, men (%)	40 (67.8)	69 (60.0)	0.314	40 (67.8)	21 (58.3)	0.351
Drinking (%)	14 (26.4)	25 (25.0)	0.848	14 (26.4)	9 (27.3)	0.930
Smoking (%)	13 (24.1)	10 (10.2)	0.022	13 (24.1)	5 (15.2)	0.319
Ischemic heart disease (%)	23 (39.0)	50 (43.9)	0.538	23 (39.0)	22 (61.1)	0.036
AF or Valvular heart disease (%)	31 (52.5)	55 (48.2)	0.592	31 (52.5)	12 (33.3)	0.068
Cerebrovascular disease (%)	15 (25.4)	33 (28.9)	0.624	15 (25.4)	9 (25.0)	0.963
Chronic renal failure (%)	12 (20.3)	21 (18.4)	0.761	12 (20.3)	7 (19.4)	0.916
Diabetes mellitus (%)	12 (20.3)	20 (17.4)	0.635	12 (20.3)	8 (22.2)	0.827
Liver cirrhosis (%)	4 (100)	0 (0)	-	4 (100)	0 (0)	-
PPIs (%)	38 (64.4)	60 (52.2)	0.124	38 (64.4)	20 (55.6)	0.391
H2-RA (%)	6 (10.2)	15 (13.0)	0.582	6 (10.2)	8 (22.2)	0.108
Mucosal protective agent (%)	22 (37.3)	27 (23.5)	0.055	22 (37.3)	10 (27.8)	0.341
NSAIDs for external use (%)	3 (5.1)	2 (1.7)	0.216	3 (5.1)	2 (5.6)	0.631

p values by Pearson's Chi-square test. CE: capsule endoscopy, AF: atrial fibrillation, PPIs: proton pump inhibitors, NSAIDs: non-steroidal anti-inflammatory drugs, H2-RA: histamine-2-receptor antagonist

(0%) groups, although there was no significant difference in the frequency of erosions among the groups. Conversely, in another small study including 10 patients taking DAPT after PCI, LDA-induced small-intestinal mucosal injury was not worsened by DAPT (15). However, in this prospective study, the number of ulcers was not described, and the mean hemoglobin level was more than 14 g/dL indicating that the mucosal injury seemed to be less severe than in our study. This difference might be due to variations in selected subjects; a prospective large-scale study will thus be required to confirm the exacerbation of bowel mucosal injuries by P2Y12 inhibitors.

The precise mechanisms underlying the small bowel mu-

cosal injuries exacerbated by P2Y12 inhibitors are unknown. P2Y12 inhibitors are thought to have no effect on COX-1 activity or the inhibition of prostaglandin production in the small intestine. Previous animal studies have revealed that platelet adenosine diphosphate-receptor antagonists, such as ticlopidine, impair the healing of gastric ulcers by suppressing the release of platelet-derived growth factors (24). Treatment with ticlopidine significantly delays ulcer healing and modulates serum levels of endostatin and vascular endothelial growth factor (VEGF) released from platelets (24). VEGF is a highly specific mitogen for vascular endothelial cells that promotes endothelial proliferation and migration (25), and it significantly accelerates ulcer healing (26).

Table 4. Relationship between Ulcer in Small Bowel and Clinical Factors Based on Multivariate Logistic Regression Analysis.

	p	Odds ratio	95% CI
DAPT	0.024	3.0	1.2 to 7.7
Over 80 yr of age	0.028	2.4	1.1 to 5.4
Ischemic heart diseases	0.301	1.6	0.7 to 3.8

The adjusted OR and 95% CI by multiple logistic regression analysis after adjustment for the other factors. DAPT: dual antiplatelet therapy

Endostatin is one of the most potent endogenous inhibitors of angiogenesis (27), and it directly inhibits endothelial growth and migration, promotes apoptosis, and antagonizes the angiogenesis-promoting effects of VEGF (28). Platelets play a pivotal role in wound healing by releasing a number of growth factors promoting angiogenesis, which is an essential process for ulcer healing (29-32). P2Y12 inhibitors may exacerbate LDA-induced mucosal injury owing to impaired ulcer healing by suppressing the release of platelet-derived growth factors.

In our present study, the frequency of erosions and ulcers was highest in the DAPT group (78.4% and 37.8%, respectively), and the prevalence of small bowel ulcer was 18.4% in the LDA alone group and 14.3% in the P2Y12 inhibitor group. The previously reported prevalence of small bowel injury in long-term LDA users was 88.5-100%, which is higher than that in our study. Enteropathy is generally evaluated based on VCE findings, such as multiple petechiae/red spots; loss of villi; scars; mucosal erosions; and round, irregular, or punched-out ulcers (11, 13, 33). Differences in the prevalence of small bowel injury may be due to differences in the definition of small bowel injury. The DAPT group showed a significant difference in the number and frequency of ulcer lesions, but not erosive lesions, from the other groups. This may be because it is difficult to accurately evaluate the number of mucosal lesions using VCE, especially small erosions.

Advanced age (>80 years old) was another significant exacerbating factor of small bowel ulcer in our study. According to previous large-scale clinical studies, advanced age is the most consistent risk factor for major bleeding or GI bleeding after PCI (34-38). Nadatani et al. (39) also reported that advanced age (≥ 75 years old) was a significant risk factor for bleeding throughout the GI tract in patients on LDA after PCI.

Several limitations associated with the present study warrant mention. First, this was a single-center study, and the number of subjects in each group was small. The findings regarding the capsule were retrospectively evaluated. It is difficult to accurately evaluate the number of mucosal lesions, especially small erosions. Anticoagulant administration was continued until VCE was performed, whereas LDA was suspended in some patients after GI bleeding, especially in the DAPT group. The small erosions might have been

cured after suspension when performing VCE. However, elucidating the characteristics of small bowel injury associated with antithrombotics will aid in the development of novel strategies for preventing small bowel injury. Thus, further studies are required to confirm the mechanisms underlying mucosal injury in patients taking DAPT.

In conclusion, P2Y12 inhibitors seem to exacerbate LDA-induced small bowel injury. The establishment of preventive strategies for small bowel injury induced by LDA, especially DAPT, is thus urgently required.

The authors state that they have no Conflict of Interest (COI).

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