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ORIGINAL ARTICLE

Recent trends in the occurrence of bleeding gastric and duodenal ulcers under the Japanese evidence-based clinical practice guideline for peptic ulcer disease

Kazunori Nagashima, Keiichi Tominaga, Koh Fukushi, Akira Kanamori, Takako Sasai and Hideyuki Hiraishi

Department of Gastroenterology, Dokkyo Medical University, Tochigi, Japan

Key words
antithrombotic therapy, bleeding gastric and duodenal ulcers, guidelines, low-dose aspirin, proton pump inhibitor.

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Correspondence
Keiichi Tominaga, Department of Gastroenterology, Dokkyo Medical University, 880, Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan.

Email: tominaga@dokkyomed.ac.jp

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Abstract

Background: Gastrointestinal hemorrhage occurs frequently. We reviewed the tendency of occurrence of bleeding gastric and duodenal ulcers and their association with antithrombotic therapy before and after the widespread use of *Evidence-Based Clinical Practice Guidelines for Peptic Ulcer 2009* (1st edition), which was published to improve treatment outcomes and prevent peptic ulcers.
Methods: The study enrolled 1105 patients with bleeding gastric and duodenal ulcers treated at our hospital between January 2000 and March 2016. They were divided into the preguideline group (807 patients treated between January 2000 and December 2010) and the postguideline group (298 patients treated between January 2011 and March 2016). The use of medications, severity, the incidence of *Helicobacter pylori* infection, the presence of any underlying disease, and other factors were compared between the pre- and postguideline groups.
Results: The number of patients receiving antithrombotic therapy was slightly higher in the postguideline group without a significant difference ($P = 0.50$). The incidence of *H. pylori* infection was significantly lower in the postguideline group ($P < 0.001$). The rate of premedication with a proton pump inhibitor (PPI) and the rate of severe ulcers were significantly higher in the postguideline group ($P = 0.001$ and $P < 0.001$, respectively). The rebleeding rate showed no significant difference, whereas the recurrence rate was significantly higher in the postguideline group ($P = 0.041$).
Conclusions: The major cause of hemorrhagic gastroduodenal ulcers seems to be shifting from *H. pylori* infection to the administration of drugs with gastrointestinal risk. Antithrombotic therapy tends to be associated with severe ulcers but without statistical significance.

Introduction

With the recently growing recognition of the importance of medical care, rapid information transfer and medical economic efficiency are required. Thus, treatment with acceptable scientific and objective justification is required, and evidence-based medicine (EBM) has been proposed as a method to support such treatment. In Japan, EBM-based guidelines have been developed for various diseases under the leadership of the Ministry of Health, Labour and Welfare (MHLW) and academic societies.[1–4]

In 2009–2012, the Japanese Society of Gastroenterology published guidelines for six diseases encountered in daily clinical practice. The first edition, *Evidence-Based Clinical Practice Guidelines for Peptic Ulcer 2009*, is one of the guidelines series, and it addresses the management of patients with peptic ulcers, including endoscopic treatment of bleeding gastric and duodenal ulcers, *Helicobacter pylori* eradication, and prevention of drug-induced ulcers. Since publication of the guidelines, the use of proton pump inhibitors (PPIs) was approved for coverage by the Japanese medical insurance system for the prevention of recurrent low-dose aspirin- (LDA) or non-steroidal anti-inflammatory drug (NSAID)-induced ulcers. The guidelines were expected to contribute to the improvement of treatment outcomes, establishment of preventive treatment, and reduction in the number of new patients developing ulcers.[5] The first edition of the guidelines was published in 2009, and the revised edition and English version were published in 2015.[5–7]

Meanwhile, with a rapid increase in the number of elderly people who have various underlying diseases, antithrombotic agents for the secondary prevention of cerebrovascular and cardiovascular events, such as cerebrovascular disorders, ischemic heart disease, and lower-extremity arterial occlusion, and NSAIDs for pain control in patients with orthopedic diseases have widely been used. In addition, two or more such agents are often administered to one patient. As a result, there are concerns

about an increase in the occurrence of critical adverse drug reactions, including gastrointestinal (GI) mucosal injury and bleeding, and the risk of developing more severe conditions.[8–11] The interruption of antithrombotic therapy following GI bleeding is reportedly associated with quite a poor prognosis, and prevention of GI bleeding and treatment when GI bleeding develops have become significant challenges.[12,13]

The numbers of patients with peptic ulcers and deaths due to peptic ulcers in 2014 were compared with those in 1996, when the number of patients with gastric ulcers was the highest since 1990, using the MHLW Specified Reports of Vital Statistics. The number of patients with peptic ulcers was 1.124 million in 1996 and 0.311 million in 2014; the number of deaths due to peptic ulcers was 4514 in 1996 and 3110 in 2014. The number of patients with peptic ulcers decreased to approximately 30%, whereas the number of deaths did not significantly decrease. The number of deaths relative to the number of patients with peptic ulcers was 0.40% in 1996 and increased to 0.89% in 2014.[14] The increased mortality rate may represent more serious clinical manifestations of ulcers.[15] While the rate of infection with *H. pylori* has decreased recently in young people, and the number of patients who have previously been treated with eradication therapy is increasing, peptic ulcers are likely to manifest more serious conditions, including those caused by antithrombotic therapy, which have become common in an aging Japanese population.[16]

In the present study, we reviewed the occurrence of bleeding gastric and duodenal ulcers and their association with antithrombotic therapy before and after the first edition of *Evidence-Based Clinical Practice Guidelines for Peptic Ulcer* achieved widespread use.

Materials and methods

Patients. Between January 2000 and March 2016, at Dokkyo Medical University Hospital, 1786 patients underwent emergency upper GI endoscopy because of suspected symptoms of upper GI bleeding, such as hematemesis and melena, and were diagnosed with upper GI bleeding. Of these, 1105 patients were diagnosed with bleeding gastric and duodenal ulcers and were included in this study. The follow-up period for these subjects was until April 2017. They included inpatients, outpatients from the emergency department, and patients transported by ambulance.

This study was approved by the ethics committee of Dokkyo Medical University Hospital. The number of the ethics committee is 28 140.

Pre- and postguideline groups. In October 2009, *Evidence-Based Clinical Practice Guidelines for Peptic Ulcer 2009* (1st edition) was published by the Japanese Society of Gastroenterology.[5] The use of these guidelines was thought to have become more widespread by 2010. The 1105 patients were divided into the preguideline group (807 patients treated between January 2000 and December 2010) and the postguideline group (298 patients treated between January 2011 and March 2016). As the guidelines included *H. pylori* eradication and prevention of drug-induced ulcers, the postguideline group was expected to show improvement in treatment outcomes and reduction in the incidence of ulcers.

Endoscopic procedures and clinical course. Endoscopic therapy was our first-line treatment for peptic ulcer bleeding. If active bleeding or visible vessels were identified on endoscopic examinations, hemostatic procedures were performed. Procedure types were selected at the discretion of the endoscopist depending on the bleeding condition. However, endoscopic clipping was primarily used for hemostasis because endoscopic clipping is associated with a lower rebleeding rate. For hemostasis, clipping or argon plasma coagulation was used; if needed, topical injection of hypertonic saline and epinephrine and thrombin spray were used. Hemostatic procedures were indicated for all cases with Forrest Ia, Ib, and IIa ulcers. For other bleeding stigmata, no hemostatic procedures were performed, or thrombin was sprayed at the discretion of the endoscopist. A sedative agent (midazolam) was used in patients who could not rest, and this was used only when their blood pressure levels and respiratory states were stable. Patients who needed hemostatic procedures underwent endoscopic re-examination. Eating was allowed when hemostasis was confirmed; when bleeding was observed, they underwent additional procedures, similar to those used for the emergency endoscopy. An endoscopic re-examination was performed the day after every additional procedure. Oral intake was initiated with a liquid diet, followed at 1-day intervals by rice porridge with a rice-to-water ratio of 1:20, then 1:10, then 1:5, and finally a regular diet. In the cases of NSAID- or antithrombotic-related ulcers, those agents were discontinued, and lansoprazole or omeprazole was administered intravenously.

In patients with a higher risk of infarction or embolism on the basis of consultations with cardiology or neurology specialists, antithrombotic agents were continued at a reduced dose without interruption or were switched to another antithrombotic agent.

In patients who could have their antithrombotic therapy interrupted, the interruption was limited to as short a period as possible, and its administration was resumed within a week after hemostasis was confirmed.

Data analysis. This study was a single-center retrospective cohort study.

The antithrombotic therapy included LDA, other antiplatelet agents (thienopyridine and cilostazol), and anticoagulant agents (warfarin and direct oral anticoagulants [DOACs]). Patients receiving LDA were not included with patients receiving oral NSAIDs.

The severity of bleeding ulcers was objectively assessed using the Forrest classification. Type I (spurting blood [Ia] and oozing blood [Ib]) was defined as severe, and types II and III were defined as mild. *H. pylori* infection was diagnosed with an *H. pylori*–IgG antibody blood test and an *H. pylori* antigen stool test. Patients with rebleeding were defined as those who developed bleeding gastric and duodenal ulcers again within 72 h after the diagnosis of bleeding gastric and duodenal ulcers was confirmed. Patients with recurrence were defined as those who developed bleeding gastric and duodenal ulcers again at least 72 h after the diagnosis of bleeding gastric and duodenal ulcers was confirmed. Cardiovascular events were included among the underlying cardiac diseases.

The use of medications, severity, incidence of *H. pylori* infection, and rebleeding and recurrence rates were compared

between the pre- and postguideline groups. In addition, risk factors involved in either severe or recurrent cases were evaluated.

Statistical analysis. This study was a single-center retrospective cohort study. Data analysis was performed using statistical software (IBM SPSS Statistics 21, IBM Japan, Ltd.). Data on age were analyzed using the Student's *t*-test. Comparisons between the pre- and postguideline groups were made using chi-square tests, except when expected cells were found to be ≤5, in which case, Fisher's exact tests were used. For data on severe cases, univariate and multivariate analyses were used. A *P*-value <0.05 was considered to indicate statistical significance.

Results

Overall subjects. A total of 1786 patients were treated at our hospital between 2000 and 2016. Patients with Mallory-Weiss syndrome, bleeding from gastric cancer or gastrointestinal stromal cell tumors, gastroesophageal variceal hemorrhage, and postendoscopic procedure (endoscopic submucosal dissection/endoscopic mucosal resection) bleeding were excluded from the study, and the remaining 1105 patients were included in the study (Fig. 1).

Table 1 shows the baseline characteristics of the 1105 patients (723 men and 382 women) with bleeding gastric and duodenal ulcers. The mean age was 64 years. Of these, 801 (72.5%) patients had gastric ulcers. The mean yearly incidence was 67.

Antithrombotic therapy was administered to 321 (29.0%) patients. Of these, 220 (68.5%) received monotherapy; 123 received an LDA alone, 53 received an oral antiplatelet agent alone, and 44 received an anticoagulant agent (warfarin or DOAC) alone. The percentage of patients receiving NSAIDs was 17.1%.

The incidence of *H. pylori* infection was 77.6%, and the incidence of multiple ulcers was 31.3%. The rate of premedication with a PPI was 8.0%. Hemostatic procedures were performed during endoscopy in 783 (70%) patients. Severe ulcers were detected in 254 (23.0%) patients. The rebleeding rate was 7.4%, and the recurrence rate was 5.4%. The rebleeding rate was 20.4% in the Forrest Ia, 8.8% in the Forrest Ib, and 7.6% in the Forrest IIa cases; the corresponding recurrence rates were 8.0%, 4.7%, and 5.9%, respectively. The underlying diseases included hypertension (n = 354 [32.0%]), heart disease (n = 254 [23.0%]), cerebrovascular disorders (n = 164 [14.8%]), chronic kidney disease (CKD) (n = 226 [20.4%]), and previous peptic ulcers (n = 301 [27.2%]).

Pre- and postguideline groups. Table 1 shows patient characteristics and results in the pre- and postguideline groups. The mean age was significantly higher in the postguideline group (P < 0.006). The percentage of patients who received antithrombotic therapy was slightly higher in the postguideline group without a statistically significant difference (P = 0.50). The percentage of patients receiving NSAIDs was higher in the postguideline group, but the difference was not statistically significant (P = 0.59). The incidence of *H. pylori* infection was significantly lower in the postguideline group (P < 0.001), whereas the incidence of multiple ulcers was significantly higher

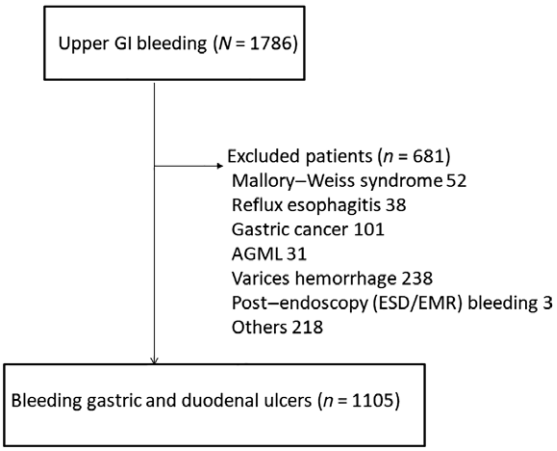

Figure 1 Flow diagram of this study.

in the postguideline group (P < 0.001). The rate of premedication with PPI was significantly higher in the postguideline group (13.4% *vs* 5.9%, P = 0.001), although both rates still remained low. The incidence of severe ulcers was higher in the postguideline group (P = 0.01). The rebleeding rate showed no significant difference between the groups, whereas the recurrence rate was significantly higher in the postguideline group (P = 0.041). The rate of combination antithrombotic therapy was higher in the postguideline group (35.2%) without a statistically significant difference.

Table 2 shows the results of the analysis for antithrombotic therapy. In the postguideline group, the rate of anticoagulant monotherapy increased significantly, and the rate of antiplatelet monotherapy decreased significantly. No significant differences were found in combination therapies, although the combined use of LDA and antiplatelet agents was noted to be increasing.

Severe and recurrent cases. As the numbers of patients with severe ulcers and those with recurrence significantly increased in the postguideline group, various factors involved in the severe and recurrent cases were evaluated. The factors evaluated were age, gender, premedication with a PPI, antithrombotic therapy, and underlying disease (kidney disease, heart disease, cerebrovascular disorders, and previous peptic ulcer). On univariate analysis, age (≥70 years, P = 0.085) and antithrombotic therapy (P = 0.061) were likely to be associated with severe ulcers, but no factors showed a significant difference (Table 3). Univariate analysis for recurrent cases showed no factors with a statistical difference (Table 4).

Discussion

This study demonstrated that, despite the recent decrease in the number of patients with bleeding gastric and duodenal ulcers, the numbers of patients with drug-induced ulcers, elderly patients, and more severe cases are increasing. After the widespread use of *Evidence-Based Clinical Practice Guidelines for Peptic Ulcer*, the number of patients with peptic ulcer disease decreased because of the increased rate of premedication with a PPI in high-risk patients receiving oral agents, and the incidence of

Table 1 Baseline characteristics

	Total *n* = 1105	Pre *n* = 807	Post *n* = 298	Odds ratio (95 %CI)	*P*-value
Age, years	64 ± 15	63 ± 15	67 ± 15	0.98	0.002
Sex (male)	723	603	220	0.95 (0.70–1.30)	0.76
Mean number of patients/year	67	73	58	—	—
Gastric ulcer/duodenal ulcer	801 (72.5%)/ 304 (27.5%)	582 (72.1%)/ 225 (27.9%)	219 (73.5%)/ 79 (26.5%)	1.07 (0.79–1.45)	0.65
Antithrombotic therapy	321 (29.0%)	230 (28.5%)	91 (30.5%)	1.10 (0.83–1.47)	0.50
Incidence of multiple ulcers	346 (31.3%)	206 (25.5%)	140 (47.0%)	2.59 (1.96–3.41)	<0.001
Monotherapy/combination	220 (68.5%)/ 101 (31.5%)	161 (70.0%)/ 69 (30.0%)	59 (64.8%)/ 32 (35.2%)	1.27 (0.76–2.12)	0.37
Low-dose aspirin alone	123 (11.1%)	93 (11.5%)	30 (10.1%)	1.38 (0.83–2.30)	0.22
Anti-platelets alone	53 (4.8%)	44 (5.5%)	9 (3.0%)	0.46 (0.22–1.00)	0.04
Anti-coagulants alone	44 (4.0%)	24 (3.0%)	20 (6.7%)	0.41 (0.22–0.79)	0.007
NSAIDs	189 (17.1%)	135 (16.7%)	54 (18.1%)	1.10 (0.78–1.56)	0.59
Incidence of *Helicobacter pylori*	857 (77.6%)	686 (85.0%)	171 (57.4%)	0.24 (0.18–0.32)	<0.001
Rate of premedication with a PPI	88 (8.0%)	48 (5.9%)	40 (13.4%)	2.45 (1.58–3.82)	<0.001
Rate of premedication with a H2RA	117 (10.6%)	103 (12.8%)	14 (4.7%)	0.34 (0.19–0.60)	<0.001
Rate of premedication with a steroid	59 (5.3%)	40 (5.0%)	19 (6.4%)	1.31 (074–2.30)	0.35
Forrest I/II and III	259 (23.0%)/ 846 (77%)	(21.4%)/(78.6%)	(28.0%)/(72.0%)	1.49 (1.10–2.01)	0.01
Re-bleeding rate/recurrence rate	7.4%/5.4%	7.2%/4.6%	8.1%/7.7%	1.13 (0.69–1.86)/ 1.74 (1.02–3.00)	0.62/0.041
Cardiovascular disease (heart disease/HT)	254 (23.0%)/ 354 (32.0%)	173 (21.5%)/ 221 (27.4%)	81 (27.2%)/ 133 (44.6%)	1.37 (1.01–1.86)/ 2.14 (1.62–2.82)	0.04/<0.001
Cerebrovascular disease	164 (14.8%)	124 (15.4%)	40 (13.4%)	0.85 (0.58–1.25)	0.42
Chronic kidney disease (CKD)/Hemo Dialysis (HD)	125 (20.4%)/ 46 (4.2%)	84 (10.4%)/ 37 (4.6%)	41 (13.8%)/9 (3.0%)	1.37 (0.92–2.05)/ 0.65 (0.31–1.36)	0.12/0.25
Previous peptic ulcer	301 (27.2%)	216 (26.8%)	85 (28.5%)	1.09 (0.81–1.47)	0.56

Table 2 Anti-thrombotic agents in the pre- and postguideline groups

	Preguideline *n* = 230	Postguideline *n* = 91	Odds ratio (95 %CI)	*P*-value
Low-dose aspirin (LDA) alone	93 (40.4%)	30 (33.0%)	1.38 (0.83–2.30)	0.22
Anti-platelets alone	44 (19.1%)	9 (9.9%)	0.46 (0.22–1.00)	0.04
Anti-coagulants alone	24 (10.4%)	20 (22.0%)	0.41 (0.22–0.79)	0.007
LDA+ Anti-platelets	37 (16.1%)	22 (24.2%)	0.60 (0.33–1.10)	0.09
LDA+ Anti-coagulants	16 (6.9%)	2 (2.2%)	0.30 (0.07–1.33)	0.10
Two other agents	5 (2.2%)	1 (1.1%)	0.50 (0.06–0.34)	0.52
Anti-platelets + anti-coagulants	6 (2.6%)	3 (3.3%)	1.27 (0.31–5.20)	0.74
Three agents	5 (2.2%)	4 (4.4%)	0.48 (0.13–1.84)	0.28

H. pylori infection decreased with the implementation of *H. pylori* eradication.[11,15,17,18]

In addition, the combination of antithrombotic therapy with an antiplatelet agent has become more common, although this difference was not significant, and combination antithrombotic therapy may increase the bleeding risk and cause multiple ulcers.

Although the rate of premedication with a PPI increased, the incidence of multiple ulcers increased because of increased anticoagulation therapy or antithrombotic combination therapy.

In the present study, no factors associated with severe or recurrent cases were identified. The recurrence rate was significantly higher in the postguideline group. We considered that a combination of factors such as anticoagulant therapy and older age, rather than a single factor, was associated with the increased rate of recurrence in the postguideline group.

For antithrombotic therapy in patients with peptic ulcers, risk of bleeding and developing severe conditions as well as risks due to the withdrawal of agents should carefully be considered. In particular, prevention of bleeding with PPI premedication is important.[19]

The number of patients with cerebrovascular disorders and those with cardiovascular disease has recently increased, and the need for antithrombotic therapy has also increased as the

Table 3 Factors associated with severe cases in the pre- and postguideline group

	Preguideline				Postguideline			
	Severe *n* = 173	Non-severe *n* = 634	Odds ratio (95 %CI)	*P*-value	Severe *n* = 86	Non-severe *n* = 212	Odds ratio (95 %CI)	*P*-value
Age (years)	63.5 ± 14.0	63.1 ± 15	1.32	0.77	69.1 ± 14.1	67.0 ± 13.8	1.78	0.23
Age ≥ 70 years	63 (36.4%)	230 (36.3%)	1.01 (0.71–1.43)	0.97	48 (55.8%)	95 (44.8%)	1.56 (0.94–2.58)	0.085
Sex (male)	142 (82.1%)	461 (72.7%)	1.72 (1.12–2.63)	0.012	63 (73.3%)	157 (74.1%)	0.96 (0.54–1.69)	0.89
Premedication with a PPI	10 (5.8%)	38 (6.0%)	0.96 (0.47–1.97)	0.92	14 (16.3%)	26 (12.3%)	1.39 (0.69–2.81)	0.36
Anti-thrombotic therapy	54 (31.2%)	176 (27.8%)	1.18 (0.82–1.70)	0.37	33 (38.4%)	58 (27.4%)	1.65 (0.97–2.81)	0.061
Chronic kidney disease	19 (11.0%)	65 (10.3%)	1.08 (0.63–1.86)	0.78	13 (15.1%)	28 (13.2%)	1.17 (0.58–2.38)	0.67
Cardiovascular disease	44 (25.4%)	129 (20.4%)	1.34 (0.90–1.98)	0.15	24 (27.9%)	57 (26.9%)	1.05 (0.60–1.84)	0.86
Cerebrovascular disease	29 (16.8%)	95 (15.0%)	1.14 (0.73–1.80)	0.57	14 (16.3%)	26 (12.3%)	1.39 (0.69–2.81)	0.36
Previous peptic ulcer	58 (33.5%)	158 (24.9%)	1.52 (1.06–2.19)	0.02	24 (27.9%)	61 (28.8%)	0.96 (0.55–1.67)	0.88

Table 4 Factors associated with recurrence cases in the pre- and postguideline group

	Preguideline				Postguideline			
	Recurrence *n* = 37	Non-recurrence *n* = 770	Odds ratio (95 %CI)	*P*-value	Recurrence *n* = 23	Non-recurrence *n* = 275	Odds ratio (95 %CI)	*P*-value
Age (years)	62.1 ± 15.9	63.2 ± 15.4	2.59	0.66	64.1 ± 13.1	67.9 ± 13.9	3.02	0.21
Age ≥ 70 years	13 (35.1%)	280 (36.4%)	0.95 (0.48–1.89)	0.88	8 (34.8%)	135 (49.1%)	0.55 (0.23–1.35)	0.19
Sex (male)	29 (78.4%)	574 (74.5%)	1.24 (0.56–2.75)	0.60	15 (65.2%)	205 (74.6%)	0.64 (0.26–1.58)	0.33
Premedication with a PPI	5 (13.5%)	43 (5.6%)	2.64 (0.98–7.12)	0.062	1 (4.4%)	39 (14.2%)	0.28 (0.04–2.10)	0.18
Anti-thrombotic therapy	13 (35.1%)	217 (28.2%)	1.38 (0.69–2.76)	0.36	4 (17.4%)	87 (31.6%)	0.46 (0.15–1.38)	0.15
Chronic kidney disease	7 (18.9%)	77 (10.0%)	2.10 (0.89–4.94)	0.083	4 (17.4%)	37 (14.5%)	1.35 (0.44–4.20)	0.60
Cardiovascular disease	9 (24.3%)	164 (21.3%)	1.19 (0.55–2.57)	0.66	3 (13.0%)	78 (28.4%)	0.38 (0.11–1.31)	0.11
Cerebrovascular disease	5 (13.5%)	119 (15.5%)	0.86 (0.33–2.24)	0.75	3 (13.0%)	26 (13.5%)	0.97 (0.27–3.41)	0.96
Previous peptic ulcer	13 (35.1%)	203 (26.4%)	1.51 (0.76–3.03)	0.24	7 (30.4%)	78 (28.4%)	1.11 (0.44–2.79)	0.83

population ages.[20] In the present study, combined use of LDA and an antiplatelet agent, including dual antiplatelet therapy, was on the rise. Although combination therapy was not associated with severe cases, it may increase the bleeding risk.[21]

One study reported that discontinuation of antiplatelet therapy was associated with a risk of cerebrovascular disorders and recurrence of cardiovascular events and resulted in a quite poor prognosis.[22] Another randomized, controlled trial was conducted in Hong Kong on patients who developed bleeding ulcers while receiving LDA for cardiovascular or cerebrovascular diseases and underwent endoscopic hemostasis. In that study, risk of GI rebleeding on continuous LDA and risk of recurrence of the primary disease following LDA withdrawal were evaluated.[12]

Recurrent ulcer bleeding within 30 days was 10.3% in the continuous LDA group, which was not significantly different from that in the LDA withdrawal group (5.4%). The all-cause mortality rate within 8 weeks in the LDA withdrawal group was 12.8%, which was significantly higher than that in the continuous LDA group (1.3%). In that report, the risk of the recurrence of primary disease following withdrawal of LDA was higher than the risk of recurrent ulcer bleeding in patients who developed ulcer bleeding while receiving LDA. The results suggested that risks due to withdrawal of LDA should be carefully considered in those patients. To avoid a long-term interruption and resume antithrombotic therapy soon, safe and adequate hemostatic therapy is necessary.

Many clinical trials have demonstrated the efficacy of PPIs for secondary prevention of gastric mucosal injury due to LDA. In Japan, PPIs were first approved for the additional indication of prevention of recurrent LDA-induced ulcers in 2010.[23–25] PPIs and histamine 2-receptor antagonists are also reported to be effective for primary prevention.[26–28]

The present study demonstrated that the rate of premedication with a PPI has increased since the publication of *Evidence-Based Clinical Practice Guidelines for Peptic Ulcer*. Although the number of patients with recurrence increased in the postguideline group, proper premedication with a PPI is important to prevent peptic ulcers in patients receiving antithrombotic therapy, as previously reported.[29]

The number of patients with peptic ulcers is decreasing; however, the incidence of severe bleeding peptic ulcers is increasing, and the mortality rate related to bleeding peptic ulcers is rising.[30,31] Antithrombotic therapy is thought to be a risk factor for bleeding, although it was not a risk factor for severe cases in our study. PPIs to prevent GI bleeding are believed to result in a good prognosis.

Our study has several limitations. It was a single-center, retrospective study. Performing an optimal analysis was difficult because the ages and changes in the agents for antithrombotic therapy were inconsistent. Ideally, we should conduct studies after matching cases and conditions among multiple institutions. The endoscopic skills varied between gastroenterologists and between the time periods. Severe ulcers were defined only based on the Forrest classification; neither degrees of anemia nor

requirements for blood transfusion were evaluated. A long-term, multicenter, prospective study is necessary to confirm the results.

In conclusion, the major cause of hemorrhagic gastroduodenal ulcers seems to be shifting from *H. pylori* infections to a variety of drugs with gastrointestinal risk.

Antithrombotic therapy tends to be associated with severe ulcers but without statistical significance. Because the follow-up period was until April 2017, the length of follow-up in the preguideline group differed from that of the postguideline group. The subjects included patients with upper GI bleeding referred from clinics and hospitals where the guidelines were not well established. Thus, the rate of PPI premedication was low. This low rate of PPI premedication was also explained by the use of PPIs not being covered by the Japanese medical insurance system for the prevention of recurrent LDA- or NSAID-induced ulcers before 2010. Minimal data on the interruption of antithrombotic therapy and the interruption period were collected because the information was not documented in sufficient detail in the data source, that is, medical charts. As the assessment of interruption/continuation of antithrombotic therapy had too much missing data, it was difficult to include all the data. The rate of continuation was approximately 50%, apparently similar to the rate of interruption, to the extent that we were able to examine this issue. The antithrombotic therapy was resumed at the discretion of the treating doctor; however, an endoscopic re-examination was performed the day after every hemostatic procedure. The antithrombotic therapy was resumed within 3 days after the interruption in nearly all evaluable patients. As the overall re-bleeding or recurrence rates were low, antithrombotic therapy needs to be resumed as soon as possible after adequate hemostatic is achieved.

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