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Vonoprazan or Proton Pump Inhibitor for Gastric Endoscopic Submucosal Dissection in Patients Taking Antithrombotic Agents

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ABSTRACT

Background and Aim: Delayed bleeding is a major concern after gastric endoscopic submucosal dissection (ESD), especially in patients taking antithrombotic agents. The aim of this study was to evaluate the superiority of vonoprazan (VPZ) over proton pump inhibitor (PPI) in preventing delayed bleeding after gastric ESD in patients taking antithrombotic agents.

Methods: A multicenter, open-label, randomized controlled trial was conducted in 10 Japanese centers. Gastric neoplasm patients taking antiplatelets or anticoagulants were enrolled and randomly allocated in a 1:1 ratio to either the VPZ (20 mg per day for 8 weeks) or the PPI group (esomeprazole 20 mg per day for 8 weeks). Antithrombotic agents were managed according to Japanese guidelines. The primary outcome was the delayed bleeding rate within 8 weeks after ESD. Secondary outcomes included the incidence of symptoms after ESD, healing status of ulcers at 8 weeks, safety, and factors related to delayed bleeding.

Results: Of 119 patients (59 in VPZ group, 60 in PPI group), the delayed bleeding rates were 13.6% (8/59) in the VPZ group and 8.3% (5/60) in the PPI group, with no significant difference ($p = 0.36$). Symptoms and adverse events, the healing status of ulcers at 8 weeks, were comparable between the groups. No use of daily antacids and the combination of antiplatelets and anticoagulants were related to delayed bleeding (odds ratio 13.1 and 34.7, $p < 0.01$).

Conclusion: The present study did not demonstrate the superiority of VPZ over PPIs in preventing delayed bleeding after gastric ESD in patients taking antithrombotic agents.

Trial Registration: (UMIN000040641/jRCTs041200045)

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1 | Introduction

Endoscopic submucosal dissection (ESD) is widely accepted to treat early gastric cancer (EGC) [1]. Ulcers after ESD are treated with antacids such as proton pump inhibitors (PPIs), but delayed bleeding occurs in about 5% of cases [2, 3]. Related factors for delayed bleeding include antiplatelet/anticoagulant drugs (antithrombotic agents) usage [3, 4]. Several guidelines allow gastric ESD to be performed while antithrombotic agents are continued, taking into consideration the risk of thromboembolism due to suspension [5–8]. However, the delayed bleeding rate is high in such cases, at around 20% [9–11].

PPIs are generally administered intravenously during the fasting period of gastric ESD (1–2 days) and then orally for up to 8 weeks thereafter [3, 4]. Recently, vonoprazan (VPZ), a potassium ion-competitive acid inhibitor that strongly inhibits acid secretion through a different mechanism, has been reported as an equivalent or better agent to treat gastric ESD ulcers compared to PPIs [12–15]. However, those studies included no or only a small number of patients taking antithrombotic agents. Additionally, because intravenous VPZ is not currently available on the market, PPIs were administered intravenously during the fasting period even in the VPZ group, thus the true effect of VPZ alone is unclear. To date, two studies have investigated the rate of delayed bleeding using oral VPZ in patients under the continuation of antithrombotic agents [16, 17]. One retrospective study included patients taking various antithrombotic agents and reported that the delayed bleeding rate was 31% (18/59) by using intravenous PPIs for 2 days and then oral VPZ for 8 weeks [16]. Another study prospectively studied patients under continuous antiplatelet agents and reported that the delayed bleeding rate was 2% (1/49) by using only VPZ for 4 weeks [17]. Therefore, the therapeutic effect of VPZ alone (without intravenous PPI) in patients taking antithrombotic agents remains unclear. The purpose of this study was to clarify whether VPZ is more effective than PPI for preventing delayed bleeding after gastric ESD in patients taking antithrombotic agents.

2 | Methods

2.1 | Study Design

This study was a multicenter, randomized, open-label, superiority study conducted in 10 Japanese centers, including one university hospital, one prefectural cancer center, and eight community hospitals. We hypothesized that VPZ would be superior to oral PPI in the prevention of delayed bleeding in high-risk patients after gastric ESD. The study was approved by the Nagoya University Clinical Research Review Board (approval number CRB4180004) and the ethics committees at each participating site. This study was registered in Japan Registry of Clinical Trials (Identifier: jRCTs041200045) and University Hospital Medical Information Network Clinical Trials Registry (Identifier: UMIN000040641).

2.2 | Participation and Randomization

Inclusion criteria were (a) patients with gastric neoplasms scheduled for ESD, (b) currently taking antiplatelets or anticoagulants, (c) the neoplasm meets the Japanese criteria for ESD [differentiated type intramucosal carcinoma (cT1a) without ulcer findings (UL), differentiated type cT1a 3 cm or less with UL, undifferentiated type cT1a 2 cm or less without UL], (d) 20 years or older, (e) Eastern cooperative oncology group performance status of 0–2, (f) serum hemoglobin level ≥ 9 g/dL, (g) platelet count $\geq 100\,000/mm^3$, (h) aspartate aminotransferase and alanine aminotransferase ≤ 100 IU/L, and (i) prothrombin time-international normalized ratio ≤ 2.0. Exclusion criteria were (a) simultaneous treatment of esophageal or duodenal neoplasm, (b) previous endoscopic treatment within 31 days before gastric ESD, (c) pregnancy or lactating women, (d) allergic to or cannot take oral VPZ or esomeprazole, and (e) concomitant infectious disease. All eligible patients provided informed consent before study randomization.

Randomization was centrally managed by the University Hospital Medical Information Network Internet Data and Information Center for Medical Research. Randomization was performed via the block method. The stratification factor was institution. Patients and physicians were not blinded to the allocated treatment group.

2.3 | Study Protocol and Interventions

Since there was no difference in delayed bleeding rate between patients treated by oral PPI only or 2-days infusion followed by oral PPI [14, 15, 17, 18], both VPZ and PPIs were administered orally in this study. Gastric ESD was performed in accordance with the Japanese guidelines [1]. Starting from the day before gastric ESD, patients took either VPZ 20 mg daily or esomeprazole 20 mg daily for 8 weeks. Periprocedural management of antithrombotic agents was decided by the physician in charge, referring to the Japanese guidelines [6]. Antithrombotic agents in this study were aspirin, ticlopidine, cilostazol, clopidogrel, warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, prasugrel, and combinations of these agents.

2.4 | Outcomes

Primary endpoint was the delayed bleeding rate up to 8 weeks after gastric ESD. Delayed bleeding was defined as hematemesis or tarry stools together with bleeding from the ESD ulcer confirmed by endoscopy. Preventive hemostasis during second-look endoscopy without active bleeding was not defined as delayed bleeding. Secondary endpoints were (a) incidence of symptoms according to the Frequency Scale for the Symptoms of gastroesophageal reflux disease (F-scale) [19], (b) incidence of pain after gastric ESD (VAS score) [20], (c) healing status of gastric ESD ulcers at 8 weeks, (d) incidence of adverse events, and (e) factors related to delayed bleeding.

We used the F-scale to assess upper gastrointestinal symptoms after ESD at a cutoff score of 8 points. The F-scale includes 12 questions to assess (1) heartburn, (2) feeling of fullness after meals, (3) bloated feeling, (4) regurgitation, (5) pain in the upper abdomen, (6) nausea, (7) difficulty swallowing, (8) bitter taste in the mouth, (9) burping, (10) feeling of something

stuck in the throat, (11) chest pain, and (12) discomfort when bending over. Pain was assessed according to a VAS score of 4 points or more, which indicated pain as a therapeutic objective.

2.5 | Statistical Analysis

The delayed bleeding rate of gastric ESD in average-risk patients was 5% (0–13) for PPI and 5% (0–5.4) [12, 14, 15, 18, 21–23] for VPZ. Based on the analysis of 10,000 cases of gastric ESD in Japan, the reported frequency of antithrombotic agent usage was aspirin 9%, thienopyridine 4%–5%, cilostazol 2%–3%, warfarin 3%, and direct oral anticoagulant 2%–3% [3]. Thus, the delayed bleeding rate after gastric ESD in patients taking antithrombotic agents while using PPI was estimated to be 8%–26.6%. Considering other papers that investigated delayed bleeding after gastric ESD in patients taking antithrombotic agents, we assumed that the incidence of delayed bleeding after gastric ESD using PPI was 20% [10, 11, 16, 24, 25]. The delayed bleeding rate of gastric ESD using VPZ in patients on antiplatelets was 2%, and 31% in patients on various anticoagulants [16, 17], in which there was considerable difference. Thus, we assumed the delayed bleeding rate in patients under antithrombotic agents for VPZ was 8%, which is the lowest level estimated for PPI. The necessary sample size was initially calculated as 204 patients, with 102 patients per group, to achieve 80% power with a one-sided alpha of 5%. In July 2023, 3 years after the beginning of enrolment, the sample size was revised because the recruitment of patients was unsatisfactory due to the COVID-19 pandemic. Based on a study which reported that there was a −14.6% difference in the delayed bleeding rate of gastric ESD between PPI and VPZ [26], we assumed the delayed bleeding rate for VPZ as 5%, and the revised sample size was calculated as 118 patients, with 59 patients per group. The target number of cases was set at 124 patients in consideration of dropouts.

We analyzed all outcomes using an intention-to-treat analysis. For the primary endpoint, Fisher's exact test was used with one-sided $p < 0.05$ indicating statistical significance. Comparisons of continuous variables were performed using the Mann–Whitney *U* test. A multivariate logistic regression analysis was performed by adjusting the variables with a *p*-value < 0.01 by univariate analysis. Statistical analyses were performed using JMP statistical analysis software (version 18.0.1; JMP Statistical Discovery LLC, Cary, NC).

3 | Results

3.1 | Study Recruitment

Between September 2020 and October 2023, 125 patients were enrolled, of whom 63 and 62 patients were assigned to VPZ and PPI groups, respectively (Figure 1). After excluding six patients (ESD was not performed 2, consent withdrawal 3, and duplicate registration 1), 119 patients were included in the analysis. The baseline patient and lesion characteristics were well balanced between the two groups, except for body mass index (23 vs. 24, $p = 0.04$) (Table 1). In both groups, the majority of

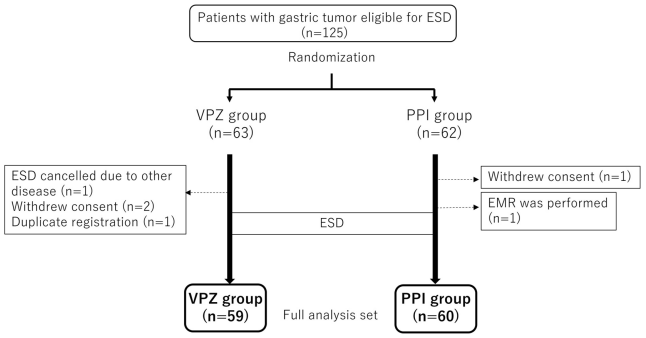


FIGURE 1 | Study flow chart.

patients took one kind of agent (88% vs. 77%, $p = 0.10$), and 27% of patients had no suspension of antithrombotic agents during the periprocedural period. Most patients (80% vs. 77%, $p = 0.69$) routinely took antacid treatment before the ESD. Main tumor size was similar between the groups, and the majority of patients (90% vs. 87%, $p = 0.59$) underwent gastric ESD for a single lesion.

3.2 | Primary Outcome (Table 2)

The incidence of bleeding was 8 of 59 (13.6%) in the VPZ group and 5 of 60 (8.3%) in the PPI group ($p = 0.39$). There was no significant difference in terms of perforation rate, procedure time, en bloc resection rate, and pathological lesion characteristics between the two groups. Preventive hemostasis during second-look endoscopy was performed in 5% and 22% of patients in the VPZ and PPI groups, respectively, with a significant difference ($p = 0.01$). Immediate closure of the ESD ulcer was not performed in 90% and 95% of the VPZ and PPI groups, respectively.

3.3 | Secondary Outcomes

The healing status of gastric ESD ulcers at 8 weeks was scarring stage in 76% and 80% of patients in the VPZ and PPI group, with no significant difference. One case of cerebral infarction occurred on the day after ESD in the VPZ group, in which rivaroxaban was suspended only on the day of ESD. The patient was immediately treated with thrombectomy and recovered well. One case of drug allergy was observed in the PPI group. There were no other serious adverse events (Table 2).

Table 3 presents the results of symptoms according to the F-scale before and after ESD for 3 days. There were no differences in the median points of the F-scale between the groups. Although there was a significant difference in the rate of patients having ≥8 points before ESD in the PPI group, there were no differences after ESD between the groups. In regard to pain according to the VAS score, there were no differences in the median VAS score for 3 days after ESD. There were 10% and 11% of patients who had pain with ≥4 points at Day 1 after ESD, with no significant difference.

Table 4 shows the univariate analyses of factors related to delayed bleeding. The use of antiplatelets was related to no

TABLE 1 | Baseline characteristics of patients.

Characteristics		Vonoprazan ($n=59$)	PPI ($n=60$)	p
Age, median, (IQR)		77 (74–80)	78 (75–83)	0.21
Male gender, *n* (%)		43 (73)	50 (83)	0.17
Performance status, *n* (%)	0	54 (92)	57 (95)	0.45
	1–2	5 (8)	3 (5)	
Body mass index (kg/m^2), median, (IQR)		23 (21–26)	24 (23–26)	0.04
Comorbidities, *n* (%)	Hypertension	37 (63)	43 (72)	0.29
	Diabetes	16 (27)	23 (38)	0.19
	Ischemic heart disease	17 (29)	27 (45)	0.07
	Chronic renal disease	2 (3)	0	—
	Liver cirrhosis	0	0	—
H. pylori status, *n* (%)	Positive	16 (27)	18 (30)	0.08
	Eradicated	21 (36)	17 (28)	0.40
	Negative	8 (14)	11 (18)	0.48
	Unknown	14 (24)	14 (23)	0.96
Antithrombotic agent				
Aspirin, *n* (%)		26 (44)	33 (55)	0.23
P2Y12-receptor inhibitor, *n* (%)		10 (17)	18 (30)	0.09
Cilostazol, *n* (%)		5 (8)	5 (8)	0.98
Warfarin, *n* (%)		5 (8)	1 (2)	0.09
Direct oral anticoagulants, *n* (%)		19 (32)	16 (27)	0.51
Number of antithrombotic agents, *n* (%)				
One kind of agent		52 (88)	46 (77)	0.10
Multiple kinds of agents		7 (12)	14 (23)	
Suspension of agents, *n* (%)				
One kind of agent		39 (66)	36 (60)	0.49
Multiple kinds of agents		4 (7)	8 (13)	0.24
No suspension		16 (27)	16 (27)	0.96
Days of suspension, *n* (%)				
1 day		5 (8)	5 (8)	0.98
2 days		5 (8)	3 (5)	0.45
3–5 days		11 (19)	9 (15)	0.60
6–9 days		15 (25)	15 (25)	0.96
10 days		3 (5)	9 (15)	0.07
Antacid treatment before ESD, *n* (%)		47 (80)	46 (77)	0.69
PPI		31 (53)	25 (42)	0.23
Vonoprazan		13 (22)	15 (25)	0.70
H2-receptor blocker		3 (5)	6 (10)	0.31
Type of institution				

(Continues)

TABLE 1 | (Continued)

Characteristics		Vonoprazan ($n=59$)	PPI ($n=60$)	p
Cancer center		6 (10)	11 (18)	0.20
University hospital		18 (31)	14 (23)	0.38
Community hospital		35 (59)	35 (58)	0.91
Number of lesions, *n* (%)	Single	53 (90)	52 (87)	0.59
	Multiple	6 (10)	8 (13)	
Endoscopic tumor size[a], mm (IQR)		15 (10–24)	15 (10–22)	0.90
Tumor location[a], *n* (%)	Upper third	11 (19)	11 (18)	0.97
	Middle third	18 (30)	24 (40)	0.28
	Lower third	30 (51)	25 (42)	0.32
Macroscopic type[a], *n* (%)	0-I	4 (7)	9 (15)	0.15
	0-IIa	25 (42)	26 (43)	0.92
	0-IIb, 0-IIc, 0-III	30 (51)	25 (42)	0.32
Ulcerative findings of tumor[a], *n* (%)	Positive	5 (8.5)	4 (6.7)	0.71

[a]Characteristics of main tumor.
Abbreviations: ESD, endoscopic submucosal dissection; *H. pylori*, *Helicobacter pylori*; PPI, proton pump inhibitor.

bleeding ($p=0.04$), and the combination of antiplatelets and anticoagulants was related to delayed bleeding ($p<0.001$). In the bleeding group, the rate of patients who restarted antithrombotic agents on Day 4 was higher compared to the non-bleeding group (54% vs. 24%, $p=0.02$). The rate of patients who daily took antacids before ESD was 82% in the non-bleeding group compared to 46% in the bleeding group, with a significant difference ($p=0.003$). Considering confounding factors, variables with a p-value of <0.01 by univariate analysis; the combination of antiplatelets and anticoagulants and the use of daily antacids were selected for multivariate logistic regression analysis. Both factors were independent predictors for delayed bleeding (Table 5).

4 | Discussion

The overall delayed bleeding rate after gastric ESD is 4%–5% [2, 3]. Delayed bleeding is particularly common on the day and the day after ESD; therefore, intravenous PPI is often administered for 2 days, including the day of ESD. VPZ has several advantages compared to PPIs. It is stable across a wide pH range, reaches its maximum plasma concentration in a shorter time, increases the intragastric pH to above 4.0 within 4 h, and provides prolonged suppression of gastric acid secretion. Additionally, the pharmacokinetics of VPZ are not affected by CYP2C19 polymorphism [27, 28]. Due to these advantages, VPZ was expected to be more useful for the treatment of gastric ESD ulcer. In previous systematic reviews comparing VPZ and PPI, one reported that VPZ had better ulcer healing rates [29], another reported no difference in rates of ulcer healing and delayed bleeding [30], and only one reported the efficacy of VPZ in reducing delayed bleeding [31]. Moreover, it was unclear whether those reviews included oral or intravenous administration of PPI and how many patients were on antithrombotic agents.

Patients taking antithrombotic agents currently account for approximately 20% of Japanese patients receiving gastric ESD [2, 3]. Patients taking antithrombotic agents are considered high-risk for delayed bleeding, with a rate of up to 30% [3, 10, 11, 16]. This study prospectively evaluated oral VPZ with PPI in patients taking antithrombotic agents, without using intravenous PPI. The overall delayed bleeding rate in this study was 13/119 cases (10.9%), with 8/59 cases (13.6%) in the VPZ group and 5/60 cases (8.3%) in the PPI group, which were comparable to previous studies [10, 11, 16, 24, 25]. From our results, we could not conclude that VPZ is superior to PPI to prevent delayed bleeding after ESD in patients on antithrombotic agents.

In the comparison between the bleeding group and non-bleeding group, univariate and multivariate analyses showed that the combination of antiplatelets and anticoagulants was significantly related to delayed bleeding. In a multicenter study, multiple antithrombotic agents and direct oral anticoagulants (DOACs) have also been reported as factors related to delayed bleeding [3]. In that study, the suspension of antithrombotic drugs was also related to decreasing the risk of delayed bleeding. Although our study did not show that the suspension of antithrombotic agents was related to delayed bleeding, it would be better to suspend them among patients taking multiple agents if their condition is acceptable for temporary suspension.

Ulcer closure or shielding the ulcer by polyglycolic acid (PGA) sheets with fibrin glue has been reported to be effective in reducing the rate of delayed bleeding in patients under antithrombotic agents [24, 25, 32, 33]. In our study, no closure was performed in 90% of cases, and there was no case of shielding with a PGA sheet. Possible reasons may include the time, cost, and effort involved in the closure method, and the fact that the method itself is not standardized.

TABLE 2 | Results of gastric-ESD in patients under antithrombotic agents.

		VPZ ($n=59$)	PPI ($n=60$)	p–value
Procedure time, min, median, (IQR)		70 (26–141)	53 (27–105)	0.29
En bloc resection, *n* (%)		59 (100)	60 (100)	—
Number of resected specimens, *n* (%)	Single	54 (91.5)	52 (86.7)	0.39
	Multiple	5 (8.5)	8 (13.3)	
Diameter of specimen[a], mm, median, (IQR)		35 (27–50)	33 (25–43)	0.33
Pathological tumor depth[a], *n* (%)	Mucosal	49 (83.1)	54 (90.0)	0.26
	Submucosal	10 (16.9)	6 (10.0)	
Histology of tumor[a], *n* (%)	Differentiated	58 (98.3)	58 (96.7)	0.57
	Undifferentiated	1 (1.7)	2 (3.3)	
Second-look endoscopy, *n* (%)	Yes	36 (61.0)	41 (68.3)	0.40
Preventive hemostasis during SLE, *n* (%)	Yes	3 (5)	13 (22)	0.01
Closure of ESD ulcer, *n* (%)	No	53 (89.8)	57 (95.0)	0.28
	Partially/completely	2/4	2/1	
Delayed bleeding, *n* (%)		8 (13.6)	5 (8.3)	0.39
Perforation, *n* (%)		2 (3.4)	1 (1.7)	0.54
Other adverse events, *n* (%)		1 (1.7)	3 (5.0)	0.32
	Cerebral infarction	1	0	
	Drug allergy	0	1	
	Aspiration pneumonia	0	1	
	Traffic accident	0	1	
Ulcer stage at 8 weeks	Healing, *n* (%)	12 (20.3)	11 (18.3)	0.74
	Scarring, *n* (%)	45 (76.2)	48 (80.0)	
	Not evaluated	2	1	

[a]Characteristics of main tumor.
Abbreviations: ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; SLE, second-look endoscopy; VPZ, vonoprazan.

TABLE 3 | Symptoms after ESD: (a) F-scale, (b) VAS score.

(a) F-scale

F-scale, median (IQR)	Before ESD		Day 1		Day 2		Day 3	
PPI	0 (0–3)		1 (0–4)		1 (0–4)		0 (0–2.5)	
VPZ	0 (0–3)		1 (0–3)		0 (0–2.8)		1 (0–2)	
Patients with ≥8 points		p		p		p		p
PPI, *n* (%)	2 (3)	0.01	5 (8)	0.73	4 (7)	0.49	4 (7)	0.18
VPZ, *n* (%)	10 (17)		6 (10)		6 (10)		1 (2)	

(b) VAS

VAS score, median (IQR)	Day 1		Day 2		Day 3	
PPI	0 (0–3)		0 (0–2)		0 (0–2)	
VPZ	1 (0–3)		0 (0–2)		0 (0–2)	
Patients with ≥4 points		p		p		p
PPI, *n* (%)	11 (18)	0.84	13 (22)	0.68	5 (8)	0.52
VPZ, *n* (%)	10 (17)		11 (19)		7 (12)	

Abbreviations: ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; VAS, visual analogue scale; VPZ, Vonoprazan.

TABLE 4 | Univariate analyses of factors related to delayed bleeding.

		Bleeding ($n=13$)	No bleeding ($n=106$)	p-value
Age, median (IQR)		78 (74–81)	78 (74–82)	0.98
Male, *n* (%)		11 (84.6)	82 (77.4)	0.55
Performance status, *n* (%)	0	12 (92.3)	99 (93.4)	0.88
	1–2	1 (7.7)	7 (6.6)	
Body mass index, median (IQR)		23.9 (19.7–26.2)	23.6 (21.7–26.0)	0.96
Comorbidities, *n* (%)				
Hypertension		10 (77)	70 (66)	0.43
Diabetes		4 (31)	35 (33)	0.87
Ischemic heart disease		4 (31)	40 (38)	0.62
Chronic renal failure		0	2 (1.8)	—
H. pylori, status, *n* (%)	Positive	6 (46.2)	28 (26.4)	0.14
	Eradicated/negative	3 (23.1)	54 (50.9)	0.06
	Unknown	4 (30.8)	24 (22.6)	0.51
Antithrombotic agents, *n* (%)				
Antiplatelet monotherapy		4 (31)	64 (60)	0.04
Multiple antiplatelets		0 (0)	10 (9)	—
Anticoagulant monotherapy		4 (31)	27 (25)	0.68
Combination of antiplatelets and anticoagulants		5 (38)	5 (5)	<0.001
Suspension of agents, *n* (%)				
One kind of agent		7 (53.8)	68 (64.2)	0.47
Two kinds of agents		3 (23.1)	8 (7.5)	0.19
Three kinds of agents		1 (7.7)	0 (0)	0.21
No suspension		2 (15.4)	30 (28.3)	0.32
Restart of antithrombotic agents, *n* (%)				
Day 0–1		3 (23)	49 (46)	0.19
Day 2–3		3 (23)	32 (30.2)	0.83
Day 4		7 (54)	25 (23.6)	0.02
Daily antacids, yes, *n* (%)		6 (46.2)	87 (82.1)	0.003
Multiple lesions resected, *n* (%)		1 (7.7)	12 (11.3)	0.94
Diameter of specimen[a], mm, median (IQR)		36 (33–58)	33.5 (25–45)	0.06
Lower stomach localization, *n* (%)		8 (61.5)	47 (44.3)	0.24
No closure of ESD, *n* (%)		12 (92.3)	98 (92.5)	0.59
Preventive hemostasis during SLE		2 (15)	14 (13)	0.83

[a]Main tumor.
Abbrevistions: ESD, endoscopic submucosal dissection; *H. pylori*, *Helicobacter pylori*; SLE, second-look endoscopy.

Second-look endoscopy was performed in 61% of the VPZ and 68% of the PPI group, and more patients underwent preventive hemostasis during second-look endoscopy in the PPI group. However, preventive hemostasis during second-look endoscopy was not a significant factor related to delayed bleeding in the univariate analysis. Previously, second-look endoscopy did not show a decrease in delayed bleeding for patients with an average bleeding risk [34]. Even in patients at high risk for bleeding, second-look endoscopy may be omitted if there are no clinically suspicious bleeding symptoms.

The rate of patients who daily took antacids before ESD was significantly higher in the non-bleeding group. A systematic review on four randomized controlled studies (RCTs) concluded that the use of PPI before ESD had no advantage for the prevention of delayed bleeding [35]. However, patients at high risk

TABLE 5 | Multivariate analysis of factors associated with delayed bleeding.

		Odds ratio	95% CI	*p*-value
Daily antacids	No	13.07	2.9–93.7	0.001
	Yes	1		
Combination of antiplatelets and anticoagulants	Yes	34.69	5.7–326.2	0.006
	No	1		

of bleeding, such as patients taking antithrombotic agents and those with chronic renal failure or liver cirrhosis, were excluded from three RCTs. Therefore, there have been no studies that investigated the effect of PPI before ESD specifically in patients taking antithrombotic agents. The results of our study showed that preoperative PPI administration may contribute to the prevention of delayed bleeding in patients taking antithrombotic agents. Further studies with larger sample sizes are needed on this matter.

In this study, post-ESD symptoms were also evaluated using the F-scale and VAS. Previous studies have focused on bleeding and perforation [2, 3], so the frequency of these symptoms was unknown. In this study, 9% (11/119) of the patients had a score of 8 or more on the F-scale, and 18% (21/119) had a score of 4 or more on the VAS scale, with no difference between the VPZ and PPI groups. On the third day after ESD, the proportion of symptomatic cases has halved. We consider that these findings will help improve perioperative management of gastric ESD.

This study has some limitations. First, the sample size was relatively small. Thus, the number of patients taking warfarin or DOACs, which are considered the highest risk factor for delayed bleeding [3], was small. Second, delayed bleeding was defined as clinical evidence of bleeding from the gastric ESD ulcer requiring blood transfusion or intervention. The definition of delayed bleeding may differ among previous studies and the present study. Some studies included a >2 g/dL decrease in serum hemoglobin. However, a >2 g/dL decrease is sometimes observed in patients when they receive intravenous drip during the periprocedural period of ESD. Thus, the findings of endoscopy were considered necessary to mitigate potential measurement bias. Third, the patients included various backgrounds with different antithrombotic agents. Since the possible suspension period of antithrombotic agents varies depending on the patient's comorbidities, no uniform suspension period was established in this study. Patients on antithrombotic agents often take daily antacids to prevent peptic ulcer bleeding; therefore, we did not standardize the use of antacids for inclusion in this study. The performance of second-look endoscopy differed among institutions; therefore, randomization was performed with stratification by institution. As a result, there was no difference between the two groups in terms of antithrombotic agent suspension, the number of agents suspended, and the duration of agent suspension. There was also no difference in the ratio of daily antacids and the performance of second-look endoscopy. Fourth, a washout period of previous antacids is necessary to truly see the effects of VPZ and PPI. In Japan, PPIs are indicated for the prevention of peptic ulcers during low-dose aspirin administration. Routine administration of antacids is also common for patients requiring anticoagulants or dual antiplatelet therapy. The fact that patients in this study were elderly and mostly affected by *Helicobacter pylori* may also have contributed to the high incidence of routine intake of antacids. Since this study included 27% of patients who did not suspend anticoagulants, routine antacids before ESD were not stopped. Indeed, there was no significant difference in the use of routine antacids between the VPZ and PPI groups. However, there is a possibility that this study yielded negative results because most patients had already taken antacids before study enrollment. From our results, in cases where patients are taking antithrombotic drugs with daily antacids, either PPI or VPZ can be selected, and there is no need to switch to VPZ for routine users of PPI.

In conclusion, the present study did not demonstrate the superiority of VPZ over PPIs in preventing delayed bleeding after gastric ESD in patients under antithrombotic agents.

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Ethics Statement

The study was approved by the Nagoya University Clinical Research Review Board (approval number CRB4180004) and the ethics committees at each participating site. All eligible patients provided informed consent before study randomization. This study was registered in the Japan Registry of Clinical Trials (Identifier: jRCTs041200045) and University Hospital Medical Information Network Clinical Trials Registry (Identifier: UMIN000040641).

Conflicts of Interest

M.F. received lecture honoraria from Takeda pharmaceutical company. All other authors disclose no conflicts.

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