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Original Article

Is proton-pump inhibitor effective in preventing postoperative bleeding after esophageal endoscopic submucosal dissection?

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SUMMARY. **Although proton-pump inhibitor (PPI) administration was reported to be effective in preventing delayed bleeding after gastric endoscopic submucosal dissection (ESD), its effectiveness in esophageal ESD is still unknown. We assessed whether PPI or vonoprazan administration was effective in preventing posterior hemorrhage after esophageal ESD. This retrospective cohort study used the Japanese Diagnosis Procedure Combination (DPC) database, and patients who underwent esophageal ESD between January 2012 and December 2020 were enrolled. The participants were divided into two groups: patients who were prescribed PPI or vonoprazan (PPI or vonoprazan group) and those who were not prescribed PPI (no acid suppression). Propensity score matching analysis was performed, and the delayed bleeding rate was compared between the groups. We analyzed 54,345 patients, of whom 8237 (15.16%) were in the no acid suppression group and 46,108 (84.84%) in the PPI or vonoprazan group (PPI: 34,380 and vonoprazan: 11,728). Delayed bleeding occurred in 1126 patients (2.07%). A total of 8237 pairs were created after matching. Delayed bleeding was not significantly different between the no acid suppression group and PPI or vonoprazan group, respectively (odds ratio: 1.20, 95% confidential interval: 0.93–1.54, $P = 0.227$). A sub-analysis according to the dose of PPI or vonoprazan, tumor location, and prescription of antithrombotic or anticoagulant medications was performed, but no significant effects of PPI or vonoprazan administration were found. PPI or vonoprazan did not prevent delayed bleeding; thus, the prescription of PPI and vonoprazan after esophageal ESD may not be recommended for the prevention of delayed bleeding.**

KEY WORDS: **endoscopic submucosal dissection, proton-pump inhibitor, vonoprazan.**

INTRODUCTION

With recent advances in endoscopic equipment and the prevalence of screening endoscopy, digestive cancers are increasingly being detected in their early stages.[1] As lymphatic metastasis is rare for superficial digestive cancers, endoscopic resection, especially endoscopic submucosal dissection (ESD) is widely accepted as a safe and useful treatment for such lesions.[2,3] However, ESD is associated with the risk of postoperative complications.[4,5] In particular, postoperative bleeding is one of the major adverse events related to ESD, and appropriate measures are required.

The bleeding rate after gastric ESD is reported to be 4.1–8.5%, which is higher than that of other gastrointestinal organs, such as the colon, duodenum, and esophagus.[6–8] Therefore, a number of studies have been conducted to analyze the risk factors for postoperative bleeding after gastric ESD and seek its prevention.[6–9] Strong gastric acid suppression, such as oral administration of proton-pump inhibitor (PPI) or vonoprazan was found to be effective in preventing postoperative bleeding after gastric ESD[10,11] and is recommended during the postoperative period of endoscopic procedures in Japanese gastric cancer and EMR/ESD treatment guidelines.[5,12]

However, few studies on postoperative bleeding after esophageal ESD have been conducted, and no studies have examined the efficacy of PPI or vonoprazan administration for the prevention of posterior bleeding. This is because the postoperative

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bleeding rate after esophageal ESD is relatively low (1.3–4.3%),[13–16] and a large sample size is needed. Therefore, in this study, we used a nationwide inpatient database and examined the efficacy of PPI or vonoprazan administration in patients after esophageal ESD.

METHODS

Study design and data source

This retrospective cohort study used the Japanese Diagnosis Procedure Combination (DPC) database to evaluate the effect of PPI or vonoprazan administration on bleeding after esophageal ESD. The DPC database includes data collected from ∼1100 facilities across Japan.[17,18] The data reflect the actual clinical practice in the country. It contains discharge abstracts and administrative reimbursement claim data from inpatient cases collected at participating hospitals. The database includes the following data: disease names, comorbidities at admission, complications during hospitalization coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10),[19] age, sex, medical procedures coded with the Medical Intervention Classification master code (treatment code), names and quantities of medicines administered daily, and unique hospital identifier.

This study was approved by the Ethical Committee of Tokyo Medical and Dental University Graduate School of Medicine (M2000-788-28). As all data were anonymous, informed consent was waived. This study conformed to the REporting of studies Conducted using Observational Routinely Collected Health Data statement for PharmacoEpidemiology (RECORD-PE).[20]

Study population

We extracted the data of patients who underwent esophageal ESD (treatment code: K526-22) between April 2012 and March 2020. According to the current ESD/EMR guidelines for esophageal cancer, endoscopic treatment is indicated for cancer with a depth of T1a epithelial/lamina propria (EP/LPM) or T1a-MM/T1b-SM1 (MM/SM1). Also, a lesion more than 20 mm is usually resected by ESD. These treatment guidelines for ESD are generally followed by almost all hospitals in Japan.

Exclusion criteria were as follows: (i) patients who were taking or injected with H2 blockers; (ii) patients taking both PPI and vonoprazan; (iii) patients with missing data; and (iv) patients who underwent the ESD procedure twice during one hospitalization. Patients who started PPI or vonoprazan administration only after the bleeding event were considered no acid suppression patients.

PPI and vonoprazan doses

There were four types of PPI: omeprazole, lansoprazole, rabeprazole, and esomeprazole, with standard daily doses of 20, 30, 10, and 20 mg, respectively. The standard dose of vonoprazan used was 20 mg.

Data collection and variables

We obtained the following data on characteristics of patients and the procedures from the DPC database: sex, age, body mass index (BMI), medications, comorbidities, hospital volume, blood transfusion, and endoscopic hemostasis procedure. We collected information on medications that may affect postoperative bleeding, specifically as follows: antiplatelet agents (APAs) [aspirin, P2Y12 receptor antagonist (P2Y12RA), cilostazol, and other APAs], anticoagulants (ACs) [warfarin, direct oral AC (DOAC), heparin, and other ACs], nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and mucosal protective agents. Patient comorbidities (Charlson comorbidity index) were collected according to the ICD-10 codes. The hospital volume was divided into three categories based on the number of ESDs: small, medium, and large. The number of ESD procedures per year in each category was 0–12, 13–41, and 42–163, respectively.

Outcomes

The primary outcome was delayed bleeding, which was defined as a case that required endoscopic hemostasis and/or blood transfusion ≥2 days after endoscopic treatment.[21] The endpoint was set at 28 days after the treatment because ulcer healing occurred within 4 weeks after esophageal ESD.[22]

Delayed bleeding rates in the following patient groups were compared with those of patients not prescribed PPI or vonoprazan (no acid suppression): (i) versus patients on PPI or vonoprazan (PPI or vonoprazan group); (ii) versus patients on PPI (PPI group); (iii) versus patients on vonoprazan (vonoprazan group); (iv) versus patients on standard or high-dose PPI; and (v) versus patients on standard or high-dose vonoprazan.

In the subgroup analysis, the posterior bleeding rates were compared between the PPI and vonoprazan group and the no acid suppression groups by dividing the location of the lesion into upper, middle, and lower esophagus. Moreover, bleeding rate was analyzed in patients taking antithrombotic or anticoagulant drugs. Matching was performed at each time in each group.

Statistical analysis

Propensity score matching analysis was performed to reduce the effects of confounding factors. The propensity score for each case was calculated using a

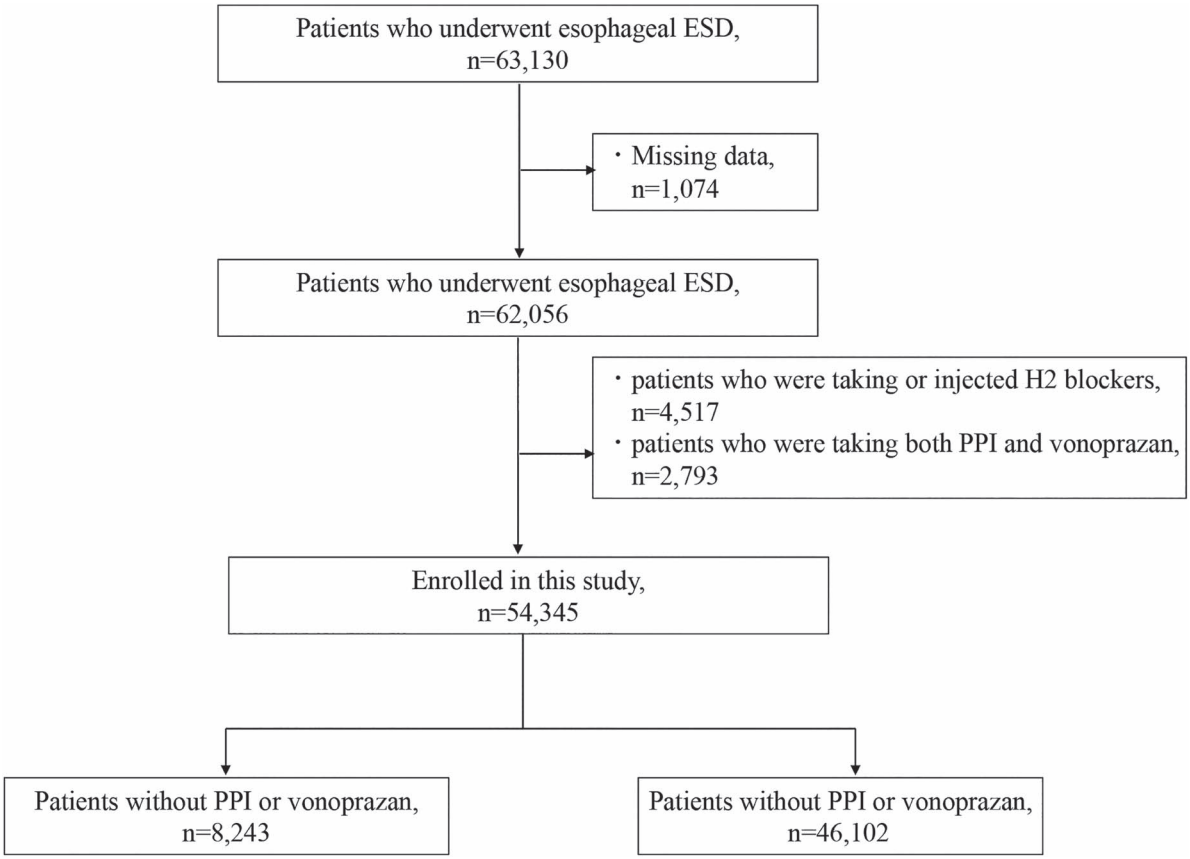

Fig. 1 A flowchart of the study population enrolment.

logistic regression model with covariates including age, sex, BMI, comorbidities, drugs, and annual hospital volume. A one-to-one matching of PPI and control group cases was performed using the nearest neighbor method with a 0.2 caliper width of the standard deviation of the propensity score logit. Model discrimination was evaluated using *c-statistics*. Furthermore, we used standardized differences (SDs) to evaluate the balance of the baseline characteristics between the two groups; an SD < 0.1 denotes a good balance of covariates.[23] After matching, the delayed posterior bleeding rates were compared between the groups. Moreover, propensity score matching was performed in each subgroup analysis. Categorical data were compared using Fisher's exact test or the chi-squared test, and continuous data were compared using the Mann–Whitney U test. Statistical significance was set at $P < 0.05$. All statistical analyzes were performed using STATA version 16 (StataCorp, College Station, TX, USA).

Sensitivity analysis

To check the robustness of the results, a stratified analysis was performed as a sensitivity analysis. We checked whether age (65 years and older vs. younger) and hospital volume changed the results for the main outcome.

RESULTS

Baseline characteristics of patients

Among the 63,130 patients who underwent esophageal ESD, 54,345 patients were included in the current study, of which 8237 (15.16%) patients were in the no acid suppression group and 46,108 (84.84%) were in the PPI or vonoprazan group (PPI: 34,380 and vonoprazan: 11,728) (Fig. 1, Table 1). The number of patients taking oral antithrombotic drugs and anticoagulants was 4056 (7.46%) and 3928 (7.23%), respectively. Delayed bleeding occurred in 1126 patients (2.07%).

Delayed bleeding rate in the PPI or vonoprazan group

Before matching, the delayed bleeding rate was 1.40% (116/8237) and 2.19% (1010/46,108) in the no acid suppression and the PPI or vonoprazan groups, respectively. After matching, 8237 pairs of no acid suppression and PPI or vonoprazan groups were created. The *c*-statistic of this propensity score model was 0.6439.

Delayed bleeding was seen in 116 (1.41%) and 139 (1.69%) patients in the no acid suppression and PPI or vonoprazan groups, respectively ($P = 0.147$) (Table 2). There was no significant difference between the two groups. In addition, delayed bleeding occurred

Table 1 Patient characteristics before propensity score matching

	Before PS matching			After PS matching		
	No acid suppression $n=8237$	PPI or vonoprazan $n=46,108$	*P* value	No acid suppression $n=8237$	PPI or vonoprazan $n=8237$	*P* value
Age (y), median, (P25–P75)	69 (64–76)	69 (64–76)	0.669	70 (64–76)	69 (64–76)	0.101
Gender, male, *n* (%)	7054 (85.6)	38,736 (84.0)	0.000	7052 (85.6)	7074 (85.8)	0.336
BMI (kg/m^2), median (P25–P75)	21 (19–24)	22 (20–24)	0.000	21 (19–24)	22 (20–24)	0.000
CCI, median (P25–P75)	0.8 (0–1)	0.9 (0–1)	0.000	0.8 (0–1)	0.9 (0–1)	0.134
Hemodialysis, *n* (%)	50 (0.6)	313 (0.6)	0.459	50 (0.6)	51 (0.6)	0.843
Hospital stay, median (P25–P75)	8 (7–10)	8 (7–10)	0.000	8 (7–10)	8 (7–10)	0.000
Hospital volume, *n* (%)			0.000			0.000
Low	2223 (26.9)	15,948 (34.5)		2223 (26.9)	1887 (22.9)	
Intermediate	2464 (29.p)	15,777 (34.2)		2464 (29.9)	2770 (33.6)	
High	3552 (43.1)	14,381 (31.1)		3550 (43.1)	3580 (43.4)	
Drug						
Aspirin	207 (2.5)	2450 (5.3)	0.000	207 (2.5)	157 (1.9)	0.021
P2Y12RA	74 (0.9)	955 (2.0)	0.000	74 (0.9)	71 (0.8)	0.093
Cilostazol	99 (1.2)	957 (2.0)	0.000	99 (1.2)	94 (1.1)	0.113
Other antiplatelet drugs	11 (0.1)	80 (0.1)	0.436	11 (0.1)	10 (0.1)	0.133
Warfarin	90 (1.0)	723 (1.5)	0.001	90 (1.0)	89 (1.0)	0.241
DOAC	121 (1.4)	1397 (3.0)	0.000	121 (1.4)	90 (1.0)	0.228
Heparin	441 (5.3)	2007 (4.3)	0.000	441 (5.3)	475 (5.7)	0.275
NSAIDs	831 (10.1)	2835 (6.1)	0.000	829 (10.0)	1014 (12.3)	0.000
Mucosal protective agents	3969 (48.2)	29,670 (64.3)	0.000	3969 (48.2)	3378 (41.0)	0.000
Corticosteroids	482 (5.8)	4328 (9.4)	0.000	482 (5.8)	369 (4.5)	0.052

PS, propensity score; SD, standardized difference; PPI, proton-pump inhibitor; BMI, body mass index; CCI, Charlson comorbidity index; DOAC, direct oral anticoagulant; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2 Delayed bleeding rate

	Delayed bleeding	Delayed bleeding rate (%)	Odds ratio	95% CI	*P* value
No acid suppression group $n=8237$	116	1.41	Reference		
PPI or vonoprazan $n=8237$	139	1.69	1.20	0.93–1.54	0.147
PPI $n=6261$	107	1.71	1.21	0.93–1.58	0.146
Vonoprazan $n=1976$	32	1.61	1.16	0.88–1.53	0.264

PPI, proton-pump inhibitor; CI, confidence interval.

in 107 patients (1.71%) in the PPI group and 32 patients (1.61%) in the vonoprazan group. In these groups, no significant difference was observed compared with the no acid suppression group ($P=0.146$ and 0.264, respectively) (Table 2).

Delayed bleeding rate according to the dose of PPI and vonoprazan

When PPI and vonoprazan were restricted to standard/high doses, the bleeding rates for the PPI and vonoprazan groups were 1.77% and 1.60%, respectively (Table 3). Compared to the no acid suppression group, no significant differences were observed in each group ($P=0.061$ and 0.518, respectively).

Delayed bleeding rate according to the location of the lesion

The delayed bleeding rates in the upper, middle, and lower esophagus in the PPI or vonoprazan groups were 1.78%, 1.57%, and 2.28%, respectively (Table 4), and no significant difference was observed compared to the no acid suppression group ($P=1.000$, 0.804, and 0.513, respectively).

The results were almost the same in the PPI and vonoprazan groups (no data).

Delayed bleeding in patients with oral antithrombotic and anticoagulant drugs

When patients were restricted to those who took oral antithrombotic or anticoagulant medications, the delayed bleeding rates in the PPI or vonoprazan groups were 1.46% and 3.62%, respectively (Table 5). There was no significant difference compared with that in the no acid suppression group ($P=0.761$ and 0.753, respectively).

Sensitivity analysis

The results of the stratified analyzes were consistent with the main results (Table 6). For instance, delayed bleeding in the PPI and vonoprazan groups showed

Table 3 Delayed bleeding rate according to the dose of PPI and vonoprazan

		Delayed bleeding	Delayed bleeding rate (%)	Odds ratio	95%CI	*P* value
PPI	No acid suppression group $n=8202$	115	1.40	Reference		
	Standard/high dose $n=8202$	145	1.77	1.26	0.98–1.61	0.061
Vonoprazan	Mo acid suppression group $n=6454$	94	1.46	Reference		
	Standard/high dose $n=6454$	103	1.60	1.09	0.82–1.45	0.518

PPI, proton-pump inhibitor; CI, confidence interval.

Table 4 Delayed bleeding rate according to the location of the lesion

		Delayed bleeding	Delayed bleeding rate (%)	Odds ratio	95%CI	*P* value
Ut	No acid suppression group $n=393$	7	1.78	Reference		
	PPI or vonoprazan group $n=393$	7	1.78	1.00	0.34–2.87	1.000
Mt	No acid suppression group $n=2168$	32	1.48	Reference		
	PPI or vonoprazan group $n=2168$	34	1.57	1.06	0.65–1.72	0.804
Lt	No acid suppression group $N=923$	17	1.84	Reference		
	PPI or vonoprazan group $N=923$	21	2.28	1.24	0.65–2.36	0.513

PPI, proton-pump inhibitor, CI, confidence interval.

Table 5 Delayed bleeding rate in patients with oral antithrombotic and anticoagulant drugs

		Delayed bleeding	Delayed bleeding rate (%)	Odds ratio	95%CI	*P* value
Antithrombotic drugs	No acid suppression group $n=342$	6	1.75	Reference		
	PPI or vonoprazan group $n=342$	5	1.46	0.83	0.25–2.74	0.761
Anticoagulant drugs	No acid suppression group $N=552$	22	3.99	Reference	—	—
	PPI or vonoprazan group $N=552$	20	3.62	0.90	0.48–1.67	0.753

PPI, proton-pump inhibitor; CI, confidence interval.

no significant interaction across groups stratified by age and hospital volume.

DISCUSSION

In this study, using the DPC database, we evaluated the efficacy of PPI and vonoprazan in preventing delayed bleeding after esophageal ESD with a propensity score matching analysis. Before this study was performed, we predicted that the bleeding rate in patients prescribed PPI or vonoprazan would be significantly lower than patients who were not prescribed them. However, contrary to our prediction, the results showed no significant difference in the rate of delayed bleeding between patients prescribed and not prescribed PPI or vonoprazan.

Kakushima *et al*. conducted a randomized controlled trial to evaluate the efficacy of PPI therapy after esophageal ESD.[24] The primary endpoint of this study was the proportion of patients with GERD-like symptoms after ESD, which was not significantly different between patients with and without PPI. Although, the sample size in this study was too small to compare the rate of postoperative bleeding, which is relatively rare, the bleeding rates in the PPI and no acid suppression groups were 0% and 3%, respectively. These figures are almost similar to those of the present study. Although our study was retrospective, a significantly larger number of cases was analyzed compared with that in the study of Kakushima *et al*. (62,056 vs. 229). Therefore, we were able to assess the impact of PPI and vonoprazan on the occurrence of posterior hemorrhage in this study.

Table 6 Sensitivity analysis

		Delayed bleeding rate (%) No acid suppression group vs. PPI or vonoprazan group	Odds ratio	95% CI	*P* value
Age	<64	1.33 vs. 1.44	1.17	0.86–1.59	0.30
	≥65	1.61 vs. 1.75	1.11	0.68–1.79	0.66
Hospital volume	Low	2.23 vs. 2.23	1.19	0.78–1.82	0.40
	Middle	1.01 vs. 0.97	0.98	0.54–1.76	0.95
	High	1.31 vs. 1.42	1.14	0.76–1.72	0.51

PPI, proton-pump inhibitor; CI, confidence interval.

The current ESD/EMR guidelines for esophageal cancer do not recommend oral PPI after esophageal ESD, and the results of the current study strongly support that recommendation.[4] In terms of gastric ESD, PPI administration has been reported to reduce the risk of postoperative bleeding.[9] This means that controlling gastric acid exposure to the postoperative ulcer is a key factor in preventing delayed bleeding. Regarding the esophagus, since gastric acid reflux is mainly confined to the lower esophagus, we predicted that PPI administration would be effective only in the lower esophagus. However, in the present study, no significant differences were found at any site, including the lower esophagus. In addition, the analysis according to the dose of PPI and limited to patients with antithrombotic or anticoagulant medications was also performed, but no significant effects of PPI and vonoprazan were found in either category. In other words, PPI administration may not be effective in preventing postoperative bleeding, regardless of dosage, and location of the lesion. The results of the sensitivity analysis showed a similar result, which makes the results of this study reliable. Ota *et al*. reported that the type of ER (EMR or ESD), the length of the resected specimen, and the circumference of the ulcer did not affect ulcer healing in relation to PPI treatment.[24] Moreover, Kanaoka *et al*. found that PPI administration was not associated with accelerated ulcer healing after esophageal ESD.[25] Similarly, the present study suggests that PPI administration may not have a significant impact on ulcers after esophageal ESD.

This study also revealed the percentage of patients who were prescribed PPI or vonoprazan after esophageal ESD. Surprisingly, 84.8% of post-esophageal ESD patients were prescribed PPI or vonoprazan even if it is not recommended by the current ESD/EMR guidelines for esophageal cancer.[4] These drugs are recommended for gastric ESD, and hence, most doctors may prescribe them after esophageal ESD. Doctors should adhere to the guideline statements, which have been strengthened by the current findings that PPI or vonoprazan is ineffective after esophageal ESD.

Abe *et al*. compared the efficacy of PPI and vonoprazan administration for postoperative bleeding after EMR and ESD using DPC data similar to the present study.[26] The results showed that vonoprazan was significantly more effective than PPI in preventing delayed bleeding after esophageal ESD, especially in the middle and lower esophagus. However, in the present study, there was no significant difference in the rate of postoperative bleeding between the no acid suppression and PPI groups. In an additional analysis, no significant difference in posterior bleeding rates was found between the PPI and vonoprazan groups using the present study data (no table shown). The period of the previous study was from April 2014 to March 2019, whereas the present study dealt with the data between January 2012 and December 2020, which is ~4 years longer. It also included a period during which vonoprazan was not in the market. Therefore, the difference in the study period may be the one reason for the different results. In addition, although a significant difference in the effectiveness of vonoprazan and PPI was observed in esophageal ESD in the study by Abe *et al*., the 95% confidence interval was 0.55–0.99, which is quite close to 1.0. This means that the presence or absence of significance can easily change due to slight fluctuations in the volume of data.

This study had several limitations. First, this was a retrospective study and did not evaluate comorbid endoscopic findings. For example, patients with a hiatal hernia and gastroesophageal reflux disease may experience severe gastric acid reflux. Thus, PPI administration may be effective in such patients; however, this cannot be verified in this study. In addition, as the DPC database does not include information about cancer histology, we could not evaluate the delayed bleeding rate according to cancer type, such as Barrett's esophageal cancer and squamous cell carcinoma. However, Watanabe *et al*. reported that the proportion of esophagogastric junction cancer among all esophageal cancer cases resected by endoscopic treatment was 8.6%, and reduced to 3.3% when limited to Barrett's esophageal cancer.[27] Thus, we believe that the proportion of Barrett's esophagus cancer in the present study was extremely small, and

therefore, its impact on the results is likely to be minimal. Second, PPI may be introduced in patients who are more likely to experience delayed bleeding. In other words, the PPI group may include a large number of patients at high risk of delayed bleeding, such as those who underwent esophageal ESD for a large lesion. Actually, in some analysis of this study, the OR of PPI and vonoprazan group was higher than that of the no acid suppression group, despite no significant difference. Thus, to eliminate this bias, we limited our analysis to low volume centers because we believe that large esophageal lesions are mainly treated in high volume centers. However, the results were similar, showing no effectiveness of PPI administration in delayed bleeding. Although this analysis does not eliminate all the bias in this study, we are confident that it did not significantly affect the results of this study. Third, we used an in-hospital database; therefore, postoperative bleeding after discharge was not included. Fourth, in this study, we analyzed the data using the first dose of PPI prescribed after hospitalization. Thus, changes in dose were not considered in this study. Fifth, although propensity score matching was performed to eliminate selection bias, the SD of mucosal protective agents was above 0.1, which means that more patients in the no acid suppression group were prescribed the drug. Thus, we cannot eliminate the impact of mucosal protective agents on delayed bleeding. However, based on our clinical experience, the impact of this medication on delayed bleeding after esophageal ESD seems minimal. Also, even considering gastric ESD, which has a higher rate of delayed bleeding than esophageal ESD, there have been no studies on the effectiveness of mucosal protective agents on delayed bleeding after gastric ESD.[11,28] In addition, we divided the patients into two groups: one with and one without mucosal protective agents and performed propensity score matching, but no significant difference in delayed bleeding was observed between patients with and without PPI in each group (group without mucosal protective agents: $P = 0.321$ and group with mucosal protective agents: $P = 0.08$). This means that the main results of this study did not change even after dividing the patients into two groups based on the prescription of mucosal protective agents. Therefore, mucosal protective agents may not have much influence on the rate of delayed bleeding.

CONCLUSION

In conclusion, this is the first study to investigate the necessity of PPI and vonoprazan administration for delayed bleeding after esophageal ESD, using nationwide data. There was no effect of PPI or vonoprazan oral administration on the prevention of posterior bleeding, regardless of PPI dose, the site of the lesion treated by esophageal ESD, or whether the patients were taking antithrombotic or anticoagulant medications. PPI prescription after esophageal ESD may not be recommended for the prevention of delayed bleeding.

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AUTHORS' CONTRIBUTIONS

Ippei Tanaka (Conceptualization, Methodology, Formal analysis and investigation, Writing—original draft), Kunio Tarasawa (Acquisition of data), Hiroaki Saito, Dai Hirasawa, Kunio Tarasawa, Kenji Fujimori, Kiyohide Fushimi, and Tomoki Matsuda (Writing—critical review and editing) and Kenji Fujimori, Dai Hirasawa, and Tomoki Matsuda (Supervision).

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to legal restrictions.

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