Vonoprazan versus proton pump inhibitors for post-endoscopic submucosal dissection bleeding in the stomach: A multicenter population-based comparative study

Abstract

Background and Aims: The effectiveness of vonoprazan relative to that of proton pump inhibitors (PPIs) after gastric endoscopic submucosal dissection (ESD) is unclear. Although previous studies used post-ESD ulcer healing as the outcome measure, post-ESD bleeding rate is the most objective and appropriate outcome measure as it has less ascertainment bias. We aimed to compare the post-ESD bleeding rates between vonoprazan and PPIs.

Methods: This nationwide population-based retrospective cohort study was conducted between 2014 and 2018 and involved nine hospitals. After two days of intravenous PPI administration, either vonoprazan or PPI was administrated from postoperative day 2 to day 30.

Results: Overall, data of 1,715 patients (627 patient pairs) were analyzed through propensity score matching. The vonoprazan group had significantly lower post-ESD bleeding rates than the PPI group (overall: 11.9% vs. 17.2%, P=0.008; bleeding between days 2 and 30: 7.8% vs. 11.8%, P=0.015). The readmission rate due to post-ESD bleeding was lower in the vonoprazan group (2.4% vs. 4.1%, P=0.081). Blood

transfusion (2.1% vs. 3.0%, P=0.15) and additional surgery due to delayed perforation (0.5 vs. 1.0%, P=0.32) were not significantly different between the two groups. No deaths within 30 days occurred in both groups. On Cox regression analysis, vonoprazan use, lesion location (antrum), aspirin use, direct oral anticoagulant use, and Charlson Comorbidity Index (≥2) were associated with an increased risk of post-ESD bleeding within 30 days.

Conclusions: Vonoprazan has a lower post-ESD bleeding rate than PPIs. Further prospective studies are required to confirm these results.

Keywords: endoscopic submucosal dissection; stomach neoplasms; bleeding; gastrointestinal endoscopy; proton pump inhibitors

Introduction

Gastric endoscopic submucosal dissection (ESD) is an advanced endoscopic procedure primarily used for the treatment of early gastric neoplasms. Its use has been expanding worldwide. One of the adverse effects of ESD is post-ESD gastric ulcer bleeding. To reduce the risk of post-ESD bleeding, proton pump inhibitors (PPIs) are administered to patients.[1]

PPI use was demonstrated to reduce post-ESD bleeding by 11% in a randomized control trial, as compared with H2-receptor antagonists.[2] However, this magnitude of reduction is insufficient for patients at a high risk of bleeding, such as those on antithrombotic medications.[3-6]

Vonoprazan, a novel oral potassium-competitive acid blocker, has been used in Japan since 2014. It is a stronger, faster-acting, and longer-lasting gastric acid suppression agent than conventional PPIs.[7,8] Several studies have reported the superiority of vonoprazan over PPIs for treating post-ESD ulcers.[9-19] However, there is limited evidence on the effect of vonoprazan in reducing the bleeding risk post-ESD.[20]

This study compared the post-ESD bleeding rates between vonoprazan and PPIs in a large multicenter cohort. The effect of vonoprazan and PPIs in reducing post-ESD bleeding risk was also evaluated in high-risk populations, including patients receiving antiplatelet and anticoagulant medications.

Methods

Patients and study design

This was a multicenter, retrospective cohort study conducted in Japan using the Japanese Diagnosis Procedure Combination database of personal academic groups. This

database contains information from St. Luke's International Hospital, Tokyo University, Nagasaki Harbor Medical Center, Fukui Prefectural Hospital, Ishikawa Prefectural Central Hospital, Tonan Hospital, Toyonaka Municipal Hospital, Shuto General Hospital, and Nerima Hikarigaoka Hospital. Data were collected from January 2014 (the year in which vonoprazan use was approved in Japan) to December 2018. The database includes data on patients' age, sex, comorbidities based on the International Classification of Diseases, Tenth Revision (ICD-10) codes, medications, and procedures according to the original Japanese codes. Personal identifiers were removed from the data. This study was approved by the Institutional Review Board of the University of Tokyo Hospital (approval no. 2019161NI), and the need for informed consent was waived due to the retrospective study design. The study was done in accordance with the guidelines laid down by the Declaration of Helsinki (1964) and its subsequent amendments.

ESD was performed on patients with gastric carcinoma with a low risk of lymph node metastasis or patients preoperatively diagnosed with gastric adenoma, as per indications.[21] After resection, the occurrence of post-ESD ulcer was carefully examined, and any visible vessels were coagulated using hemostatic forceps. After 2 days (day 0 to day 1) of intravenous omeprazole (20 mg) administration during fasting, vonoprazan (20 mg) or PPI was administered perorally after a meal was started (day 2 after ESD). We did not use vonoprazan for patients with a history of allergy to the drug. In hospitals that routinely performed second endoscopic evaluation (five institutions), the second evaluation was conducted on day 1.

A total of 3,598 cases were extracted from the database using the procedure code K653-2. Regarding the patients who underwent ESD more than once during the study period,

data from the second and any subsequent ESDs were excluded. Patients with duplication of medications with vonoprazan and PPIs, on multiple anti-acid medications, and with missing data related to propensity score matching (PSM) analysis were also excluded. The patients were stratified into vonoprazan and PPI groups. The time interval from ESD and bleeding events was counted on a daily basis.

Gastric acid suppressant use was defined as treatment starting on day 2 after ESD, and continuing for >30 days. PPIs included esomeprazole, rabeprazole, lansoprazole, and omeprazole. Antithrombotic agent use was defined as the administration of an antithrombotic agent before undergoing ESD (day 0). Post-ESD bleeding was defined as cases that required an endoscopic hemostasis for overt bleeding within 30 days using the procedure code K654. Since prophylactic endoscopic hemostasis is counted as a hemostatic event in facilities that perform a second endoscopic evaluation, the overall bleeding rate may be high. Therefore, post-ESD bleeding after day 2, which was not affected by the second endoscopic evaluation, was also assessed. Additional surgery due to delayed perforation was defined by the diagnosis of delayed perforation and the performance of additional surgical procedures within 30 days. Since prior studies have reported that post-ESD ulcers may heal within 4 weeks,[4,5] the observation duration was set at 30 days. Details of the ICD-10 codes are provided in Supplementary Table 1.

Outcomes

The primary outcomes of this study were post-ESD bleeding and readmission due to post-ESD bleeding within 30 days. Secondary outcomes included blood transfusion, additional surgery due to delayed perforation, and mortality. In the subgroup analyses, post-ESD bleeding rates of patients on antithrombotic medications were examined.

Statistical analysis

The required sample size was estimated from the results of a previous multicenter study conducted before the introduction of vonoprazan.[22] The type I error probability associated with this hypothesis was 0.05; an uncorrected chi-square test was used to evaluate this hypothesis. Prior data indicated that the rate of post-ESD bleeding in the PPI cohort was 15.6%.[22] If the rate of post-ESD bleeding for vonoprazan was considered as 7.8%, at least 265 patients were required in each group to reject the hypothesis that the proportion of post-ESD bleeding for vonoprazan and PPI subjects was equal with a probability (power) of 0.8. Therefore, more than 530 subjects were required for this study.

Eleven patient-related factors were selected before performing PSM, including age, sex, location of the gastric neoplasm, second endoscopic evaluation performance, low-dose aspirin, thienopyridine, other antiplatelet therapies, direct oral anticoagulants (DOACs), warfarin, nonsteroidal anti-inflammatory drugs (NSAIDs), hemodialysis, and Charlson Comorbidity Index (CCI) score ≥2.[23] The study population was divided into vonoprazan and PPI groups. A logistic regression model was used for the administration of vonoprazan as a function of patient characteristics to estimate the propensity score. The nearest neighbor method was used to perform a 1:1 PSM between the two groups, using a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Discrimination was assessed by calculating the C-statistic. After PSM, differences in the clinical outcomes were compared between the two groups. Wilcoxon rank-sum test and t-test were used to compare the means of continuous variables, whereas the chi-square test was used to compare the proportions of categorical variables between the groups. The log-rank test was used to compare the time interval between ESD and 30-day bleeding between the groups. The area under the receiver operating characteristic curve

(AUC) of the logistic regression model for propensity score was insufficient in the comparative analyses, which suggested the risk of losing a number of patients owing to PSM. Multivariate logistic and Cox hazard regression analyses were performed to determine the independent factors associated with primary outcomes. Additionally, a subgroup analysis was performed for patients who were on antithrombotic medications, which is a risk factor for post-ESD bleeding.[23-25] Statistical significance was defined by a two-tailed *P*-value <0.05. All analyses were performed using Stata version 16 (Stata Corp LP, College Station, TX, USA).

Results

Patient characteristics

A total of 1,715 patients who underwent ESD were included in this study; 1,059 (62%) were categorized into the vonoprazan group and 656 (38%) into the PPI group. The mean age of the patients in both groups was >70 years. More than 20% of the patients took any antithrombotic medication, and the same proportion of patients had comorbidities with a CCI score ≥2. Baseline characteristics of the study population are summarized in Table 1.

Vonoprazan vs. PPI

PSM yielded 627 pairs of patients who were administered vonoprazan and PPIs. The AUC of the logistic regression model for the propensity score was 0.62. The distribution of the propensity scores is shown in Supplemental Figure 1. The characteristics of each group are shown in Table 2. The overall post-ESD bleeding rate within 30 days was significantly lower in the vonoprazan group than in the PPI group (11.9% vs. 17.2%

respectively, *P*=0.008), with an absolute risk reduction of 5.3% (95% confidence interval [CI]: 1.4–9.2). Similarly, the post-ESD bleeding rate between days 2 and 30 was also significantly lower in the vonoprazan group (7.8% vs. 11.8%, P=0.015), with an absolute risk reduction of 4.0% (95% CI: 1.8–6.2). Although it did not reach statistical significance, the rates of readmission due to post-ESD bleeding (2.4% vs. 4.1%, *P*=0.081) was lower in the vonoprazan group. Blood transfusion (2.1% vs. 3.0%, P=0.15) and additional surgery due to delayed perforation (0.5% vs. 1.0%, *P*=0.32) were not significantly different between the two groups. No deaths were reported in either group (Table 3).

The cumulative incidence of post-ESD bleeding was significantly lower in the vonoprazan group than in the PPI group (log-rank, *P*=0.009) (Figure 1).

Cox regression analysis of the study population of all 1,715 cases of ESD demonstrated that vonoprazan significantly decreased the post-ESD bleeding risk when compared with PPIs (hazard ratio [HR] = 0.64, 95% CI: 0.47–0.85, *P*=0.002). Antral lesion location, low-dose aspirin use, DOAC use, and CCI ≥2 were identified as independent predictors of post-ESD bleeding (Table 4). Multivariate logistic regression analysis of the study population also revealed that vonoprazan was an independent factor associated with post-ESD bleeding (odds ratio [OR] = 0.64, 95% CI: 0.47–0.85, *P*=0.002 [Supplementary Table 2]).

Subgroup analysis based on the use of antithrombotic medications

The results of the subgroup analyses of the relationship between the type of gastric acid suppressant and post-ESD bleeding of patients on antithrombotic medications are shown in Figure 2. Patients who had been taking antithrombotic agents before undergoing ESD had a high incidence of post-ESD bleeding (22.1%). Although the post-ESD bleeding rate

was lower in the vonoprazan group than in the PPI group (20% vs. 24%, *P*=0.38 [Table 5]), this difference was not statistically significant.

Discussion

This large multicenter retrospective study using PSM compared the effectiveness between vonoprazan and PPIs in reducing the postoperative bleeding risk in patients who had undergone gastric ESD. Vonoprazan was associated with a significantly lower rate of post-ESD bleeding than PPIs (overall: *P*=0.008; between days 2 and 30: *P*=0.015).

Previous studies have reported that gastric acid-suppressing agents are beneficial for healing ESD-induced ulcers.[1,3,9-19] However, limited studies have compared the effectiveness between vonoprazan and PPIs in reducing post-ESD bleeding risk. Therefore, for more objective measures with less ascertainment bias, post-ESD bleeding was chosen as the primary outcome of this study. Vonoprazan has several advantages over PPIs, such as stability over a broad pH range, short time to maximal plasma concentration (1.5–2.0 hours after administration, increasing the gastric pH >4.0 within 4 hours), and long-lasting inhibition of gastric acid secretion (>24 hours after administration).[3-5] Additionally, the pharmacokinetics of vonoprazan are not affected by *CYP2C19* polymorphisms.[7]

In this study, the rate of post-ESD bleeding (overall bleeding and bleeding after day 2 of ESD) was lower in the vonoprazan group than in the PPI group (risk difference of 5.3% and 4.0%, respectively). This finding suggests that vonoprazan may be used as a standard treatment immediately after ESD, despite the fact that the cost of PPIs is five-eighths that of vonoprazan. The rate of overall post-ESD bleeding in this study was

higher (14.5%) than those reported in previous studies (5.6–11.2%).[20-21,25] This may be related to the high rate of antithrombotic administration (21.4%) as well as due to factors affecting ulcer healing such as old age, NSAID use, and comorbidities.[3] In addition, prophylactic coagulation during the second endoscopic evaluation on day 1 could be counted as a bleeding event. Therefore, we added the outcome of post-ESD bleeding after day 2 of ESD, which is not affected by the second endoscopic evaluation. Nonetheless, a comparison was made in a relatively large cohort with PSM, and the superiority of vonoprazan was observed.

Regarding other outcomes, the difference in the readmission rate due to post-ESD bleeding between the vonoprazan and PPI groups was marginally significant (2.4% vs. 4.1%; P=0.081). In addition, the rates of blood transfusion (2.1% vs. 3.0%) and additional surgery (0.5% vs. 1.0%) were also associated with improvements in the vonoprazan group compared with the PPI group, although statistical significance was not obtained. Several secondary outcomes related with post-ESD bleeding were associated with improvements in the vonoprazan group; therefore, we believe that vonoprazan use is superior compared to PPI use. We speculated that the relatively small number of events may have introduced non−statistical superiority; therefore, further large sample studies with various patient population settings are needed in the near future.

A multivariate analysis performed in our study revealed that antral lesion location, low-dose aspirin use, DOAC use, and CCI ≥2 were independent predictors of post-ESD bleeding. These findings are consistent with those reported by previous studies.[3,23,24-26] The lesions below the antrum have a higher incidence of post-ESD bleeding because of the influence of active peristalsis and bile juice reflux.[26] CCI ≥2 may have been related

to vascular predisposition due to comorbidities or systemic conditions related to ulcer healing.

Our study patients who had been taking antithrombotic agents before undergoing ESD had a higher incidence of post-ESD bleeding (22.1%) than those not taking such medications (12.2%); this finding was similar to those reported by previous studies.[3,27-28] The subgroup analysis confirmed that the incidence of post-ESD bleeding between vonoprazan and PPI groups on antithrombotic therapy was not statistically significant (20% vs. 24%, *P*=0.38). We hypothesize that vascular disruption caused by antithrombotic agents contributes to post-ESD bleeding rather than the ulcer healing effect. In patients on antithrombotic therapy, it may be better to seek other methods for prevention. Although a prior prospective study revealed that vonoprazan contributed to a reduction in post-ESD bleeding risk in patients taking antiplatelet medications,[29] further comparative studies are required to establish the effectiveness of vonoprazan with concomitant antithrombotic use. Moreover, owing to the increasing number of aging individuals, the incidence of cerebrovascular and ischemic heart disease has also increased. Therefore, endoscopic procedures are more frequently performed on patients taking antithrombotic agents, and our study provides new evidence for the prevention of post-ESD bleeding in these patients.

This study has some limitations due to its retrospective design. Some unmeasured confounders might have been included in the PSM. The database analyzed did not include any information on the endoscopists and the size or morphology of the gastric neoplasms. The C-statistic of PSM was not high (0.62). However, the patient characteristics were well-balanced in both the groups, and the absolute values of the standardized differences were <0.1 for all confounders. Lastly, the postprocedural care

protocols in this study, including the hospitalization of all patients after ESD, the administration of fasting and intravenous PPI, and a second endoscopic evaluation (in 50% of patients), may not be fully generalizable to all practices, especially those in Western countries. Despite these limitations, this study has a relatively large sample that satisfied the calculated sample size to analyze the effects of vonoprazan on post-ESD bleeding.

In conclusion, our data suggested that vonoprazan use was associated with reduced post-ESD bleeding rates. Vonoprazan may be used as a standard treatment after ESD for gastric cancer. However, further randomized prospective studies are required to confirm the validity of these results.

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Table 1. Characteristics of the study population categorized by the gastric acid suppressant used

	Vonoprazan (n=1,059)	PPI (n=656)	*P*	ASD
Demographic characteristics				
Mean age yr	72.0 ± 9.2	73.8 ± 8.6	<0.001	0.210
Age ≥65 yr	853 (81)	544 (83)	0.22	0.062
Sex, male	769 (73)	483 (74)	0.65	0.023
Location of the lesion				
Upper	101 (10)	103 (16)	<0.001	
Middle	659 (62)	372 (57)	0.023	0.110
Lower	299 (28)	181 (28)	0.78	
Second look	503 (48)	331 (51)	0.21	0.080
Medications use				
Antithrombotic agents	212 (20)	155 (24)	0.034	0.110
Antiplatelets	148 (14)	119 (18)	0.021	0.114
LDA	114 (11)	98 (15)	0.01	0.125
Thienopyridine	57 (5)	53 (8)	0.027	0.108
Other antiplatelets	30 (3)	24 (4)	0.34	0.047
Anticoagulants	79 (8)	61 (9)	0.176	0.066
Warfarin	30 (3)	34 (5)	0.013	0.120
DOAC	59 (6)	33 (5)	0.63	0.024
NSAIDs	48 (5)	40 (6)	0.153	0.070
Medical history				
Cerebrovascular disease	64 (6)	57 (9)	0.038	0.101
Arterial thrombosis	9 (1)	9 (1)	0.3	0.050
Pulmonary disease	46 (4)	40 (6)	0.106	0.101
Chronic heart failure	69 (7)	59 (9)	0.058	0.093
Ischemic heart disease	11 (1)	17 (3)	0.014	0.116
Gastrointestinal ulcer	413 (39)	214 (33)	<0.001	0.332
Liver disease	57 (6)	46 (7)	0.167	0.068
Chronic kidney disease	24 (2)	22 (3)	0.176	0.066
Hemodialysis	11 (1)	6 (1)	0.81	0.013
Deep vein clot	13 (1)	4 (1)	0.21	0.065
Malignant tumor†	185 (17)	113 (17)	0.89	0.006
Hypertension	286 (27)	190 (29)	0.42	0.104
Diabetes	236 (22)	178 (27)	0.023	0.113
CCI ≥2	210 (20)	135 (21)	0.71	0.019

NOTE. Values presented with a ± symbol show the mean ± standard deviation. Values presented n (%) show the number of values and percentages.

† Malignancy included solid tumors and malignant lymphomas.

Abbreviations: ASD, absolute standardized difference; CCI, Charlson comorbidity index; DOAC, direct oral anticoagulants; LDA, Low-dose aspirin; NSAIDs, Nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitors

Table 2. Confounders of patients who had undergone gastric ESD in the matched cohort

	Matched cohort (n=1,254)			
	Vonoprazan (n=627)	PPI (n=627)	*P*	ASD
Confounders				
Mean age yr	74.4 ± 8.3	73.6 ± 8.6	0.20	0.090
Sex, male	459 (73)	457 (73)	0.89	0.007
Location, Upper, Middle, Low	96, 363, 168	81, 369, 177	0.46	0.061
Second look	307 (49)	313 (50)	0.32	0.075
LDA	101 (16)	89 (14)	0.35	0.053
Thienopyridine	54 (9)	49 (8)	0.61	0.029
Other antiplatelets therapy	25 (4)	22 (4)	0.66	0.025
DOAC	28 (5)	31 (5)	0.69	0.023
Warfarin	30 (5)	27 (4)	0.68	0.023
NSAIDs	30 (5)	29 (5)	0.72	0.020
Hemodialysis	9 (1)	7 (1)	0.38	0.044
CCI ≥2	133 (21)	130 (20)	0.84	0.046

NOTE. Values presented with a ± symbol show the mean ± standard deviation.
Values presented n (%) show the number of values and percentages.

Abbreviations: ASD, absolute standardized difference; CCI, Charlson comorbidity index; DOAC, direct oral anticoagulants; LDA, Low-dose aspirin; NSAIDs, Nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitors

Table 3. Comparison of the clinical outcomes between the vonoprazan and PPI groups in the matched cohort

Outcomes	Matched cohort (n=1,254)			
	Vonoprazan (n=627)	PPI (n=627)	*P*	Absolute risk reduction and 95%CI (%)
Overall Post-ESD bleeding	75 (11.9)	108 (17.2)	0.008	5.3 (2.2, 8.4)
Post-ESD bleeding after day 2	49 (7.8)	76 (11.8)	0.015	4.0 (1.8, 6.2)
Readmission due to bleeding	15 (2.4)	26 (4.1)	0.081	1.7 (-0.7, 2.9)
Blood transfusion within 30 days	13 (2.1)	19 (3.0)	0.15	0.9 (-0.6, 2.4)
Additional surgery due to delayed perforation	3 (0.5)	6 (1.0)	0.32	0.5 (-2.5, 3.5)
Death within 30 days	0	0	NA	0

NOTE. Values presented n (%) show the number of values and percentages.

Abbreviations: NA, not applicable; PPI, proton-pump inhibitors

Table 4. Cox regression analysis of the association between the gastric acid suppressant and post-ESD bleeding in the study population

Confounders	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Vonoprazan	0.62 (0.46-0.84)	0.001	0.64 (0.47-0.85)	0.002
PPI	1		1	
Age ≥65 yr	1.50 (0.97-2.25)	0.062	1.21 (0.82-1.83)	0.35
Sex, male	1.45 (1.02-2.24)	0.032	1.24 (0.90-1.70)	0.21
Location (Upper)	1		1	
Location (Middle)	1.13 (0.70-1.84)	0.61	1.40 (0.86-2.29)	0.18
Location (Low)	1.68 (1.00-2.79)	0.048	2.03 (1.21-3.47)	0.009
Second look	1.18 (0.77-1.68)	0.31	1.32 (0.86-1.88)	0.27
LDA	2.52 (1.78-3.57)	<0.001	1.92 (1.25-2.96)	0.004
Thienopyridine	2.42 (1.52-3.79)	<0.001	1.07 (0.47-2.35)	0.77
Other antiplatelets therapy	0.77 (0.33-1.83)	0.56	0.52 (0.34-1.09)	0.08
DOAC	2.99 (1.90-4.82)	<0.001	1.89 (1.22-2.43)	0.001
Warfarin	3.02 (1.74-5.41)	<0.001	1.66 (0.90-3.03)	0.12
NSAIDs	1.58 (0.92-2.89)	0.092	1.18 (0.66-2.11)	0.47
Hemodialysis	1.32 (0.48-4.62)	0.55	1.29 (0.83-2.02)	0.42
Charlson comorbidity index ≥2	2.51 (1.92-3.50)	<0.001	1.96 (1.51-2.89)	<0.001

Age, sex, and factors with potential confounders that used in propensity score matching analysis (vonoprazan, proton pump inhibitor, location, aspirin, thienopyridine, other antiplatelets therapy, direct oral activating anticoagulants, warfarin, nonsteroidal anti-inflammatory drugs, hemodialysis, and Charlson comorbidity index) were included in the multivariate logistic regression model.

Abbreviations: CCI, Charlson comorbidity index; DOAC, direct oral anticoagulants; HR, hazard ratio; LDA, Low-dose aspirin; NSAIDs, Nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitors

Table 5. Subgroup analysis: Comparison of outcomes between the vonoprazan and proton pump inhibitor groups taking antithrombotic agents

Outcomes	Anti-thrombotic therapy (+) Vonoprazan	PPI	*P*	Absolute risk reduction and 95%CI (%)
Overall Post-ESD bleeding	32 (20)	34 (24)	0.38	4.0 (-1.9, 9.9)
Post-ESD bleeding after day 2	23 (14.3)	24 (16.9)	0.44	2.6 (-2.0, 7.2)
Readmission due to bleeding	8 (5.0)	11 (7.4)	0.32	2.4 (-1.0, 5.4)
	Anti-thrombotic therapy (-)			
	Vonoprazan	PPI	*P*	Absolute risk reduction and 95%CI (%)
Overall Post-ESD bleeding	43 (8.5)	74 (15)	0.001	6.5 (1.6, 11.4)
Post-ESD bleeding after day 2	26 (5.1)	52 (10.5)	0.004	5.4 (1.2, 9.6)
Readmission due to bleeding	7 (1.5)	15 (2.9)	0.18	1.4 (-0.4, 3.1)

NOTE. Values presented n (%) show the number of values and percentages.
Abbreviations: PPI, proton-pump inhibitors

Supplemental Table 1. ICD-10 and diagnosis procedure combination codes

Comorbidity	ICD-10 codes
Atrial fibrillation	I480–I489
AIDS	B200–B229, B24
Arterial thrombosis	I740–I749
Carotid disease	I652, I720
Cerebrovascular disease	G450-G469, H340, I600–639, I64, I650–I699
Chronic heart failure	I099, I110, I130, I132, I255, I420, I425–I439, I500–I509, P290
Chronic kidney disease < stage 5	I120, I131, N032–N037, N052–N057, N180–N189, N19, N250, Z490–Z492, Z940, Z992
Chronic kidney disease stage 5	N185
Dementia	F000–F029, F03, F051, G300–G309, G311
DM without complication	E100, E101, E106, E108–E111, E116, E118–E121, E126, E128–E131, E136, E138–E141, E146, E148, E149
DM with complications	E102–E105, E107, E112–E117, E122–E125, E132–E135, E137, E142–E145, E147
Deep vein thrombosis	I800–I809, I820–I829
Gastroesophageal reflux disease	K210
Hemiplegia	G041, G114, G801, G802, G810–G834, G839
Hypertension	I10, I110–I159
Hyperlipidemia	E780–E785
Ischemic heart disease	I210–I229, I252
Liver disorder (mild)	B180–B189, K700–K703, K709, K713–K715, K717, K730–K749, K760, K762–K764, K768–K769, Z944
Liver disorder (severe)	I850, I859, I864, I982, K704, K711, K721, K729, K765–K767
Malignancy without metastasis	C000–C009, C01, C020–C69, C07, C080–C119, C12, C130–C189, C19, C20, C210–C229, C23, C240–C329, C33, C340–C349, C37, C380–C519, C52, C530–C549, C55,C56, C570–C570, C58, C600–C609, C61, C620–C639, C64, C65, C66, C670–C729, C73, C740–C769, C810–C969, C97
Malignancy with metastasis	C770–C809
Peripheral vascular disease	I700–I719, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
Pulmonary disease	I278, I279, J40, J410–J419, J42, J430–J459, J46, J47, J60, J61, J620–J639, J64, J65, J660–J679, J684, J701, J703
Rheumatic disease	M050–M069, M315, M320–M349, M351, M353, M360
Transient ischemic attack	G459
Peptic ulcer disease	K250–K289
Unstable angina	I200–I209
Valvular disease	I340–I379

Abbreviations: AIDS, acquired immunodeficiency syndrome; DM, diabetes mellitus.

Supplemental Table 2. Multivariate analysis of the association between gastric acid suppressant and post-ESD bleeding in the study population

Confounders	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Vonoprazan	0.62 (0.47-0.82)	0.001	0.64 (0.47-0.85)	0.002
PPI	1		1	
Age ≥65 yr	1.48 (1.00-2.18)	0.050	1.20 (0.80-1.80)	0.37
Sex, male	1.45 (1.04-2.02)	0.028	1.29 (0.91-1.81)	0.15
Location (Upper)	1		1	
Location (Middle)	1.13 (0.70-1.82)	0.60	1.40 (0.86-2.29)	0.18
Location (Low)	1.70 (1.02-2.73)	0.042	2.06 (1.23-3.44)	0.006
Second look	1.24 (0.82-1.88)	0.28	1.38 (0.88-1.83)	0.20
LDA	2.54 (1.80-3.59)	<0.001	1.93 (1.27-2.93)	0.002
Thienopyridine	2.40 (1.53-3.77)	<0.001	1.17 (0.67-2.05)	0.57
Other antiplatelets therapy	0.77 (0.33-1.83)	0.56	0.56 (0.34-1.12)	0.10
DOAC	2.96 (1.86-4.72)	<0.001	2.27 (1.38-3.75)	0.001
Warfarin	3.00 (1.73-5.19)	<0.001	1.71 (0.94-3.13)	0.08
NSAIDs	1.53 (0.89-2.65)	0.127	1.16 (0.65-2.09)	0.50
Hemodialysis	1.34 (0.38-4.70)	0.65	1.58 (1.15-2.23)	0.04
Charlson comorbidity index ≥2	2.61 (1.95-3.53)	<0.001	2.22 (1.61-3.07)	<0.001

Age, sex, and factors with potential confounders that used in propensity score matching analysis (vonoprazan, proton pump inhibitor, location, aspirin, thienopyridine, other antiplatelets therapy, direct oral activating anticoagulants, warfarin, nonsteroidal anti-inflammatory drugs, hemodialysis, and Charlson comorbidity index) were included in the multivariate logistic regression model.

Abbreviations: CCI, Charlson comorbidity index; DOAC, direct oral anticoagulants; LDA, Low-dose aspirin; NSAIDs, Nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPI, proton-pump inhibitors

Figure legends

Figure 1. Kaplan-Meier curve of the cumulative probability of post-endoscopic submucosal dissection bleeding by gastric acid suppressant

Figure 2. Comparison of the distribution of post-endoscopic submucosal dissection bleeding days between the vonoprazan and proton pump inhibitor groups

Histogram showing the number of patients with post-ESD bleeding and the days since ESD.

Yellow column: post-endoscopic submucosal dissection (ESD) bleeding in patients not receiving any antithrombotic agents.

Blue column: post-ESD bleeding in patients receiving antiplatelet agents

Green column: post-ESD bleeding in patients receiving anticoagulants

Red column: post-ESD bleeding in patients receiving both antiplatelet agents and anticoagulants

Supplemental Figure 1. Propensity score distribution