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ORIGINAL ARTICLE—ALIMENTARY TRACT

Prevention of delayed bleeding with vonoprazan in upper gastrointestinal endoscopic treatment

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Abstract

Background Delayed bleeding is the major adverse event in upper gastrointestinal endoscopic treatment (UGET). We aimed to investigate the efficacy of vonoprazan, which is the novel strong antisecretory agent, to reduce the risk for delayed bleeding in comparison with proton pump inhibitors (PPIs) in UGET.

Methods This retrospective population-based cohort study used the Diagnosis Procedure Combination database in Japan. We included patients on vonoprazan or PPI in UGET between 2014 and 2019. The primary outcome was delayed bleeding. We conducted propensity score matching to balance the comparison groups, and logistic regression analyses to compare the bleeding outcomes.

Results We enrolled 124,422 patients, in which 34,822 and 89,600 were prescribed with vonoprazan and PPI, respectively. After propensity score matching, the risk for delayed bleeding was lower in vonoprazan than in PPI (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.71–0.80), consistent with sensitivity analysis results. In the subgroup analyses of seven UGET procedures, vonoprazan was significantly advantageous in esophageal endoscopic submucosal dissection (E-ESD) (OR, 0.71; 95% CI, 0.54–0.94) and gastroduodenal endoscopic submucosal dissection (GD-ESD) (OR, 0.70; 95% CI, 0.65–0.75), although correction for multiple testing of the outcome data removed the significance in E-ESD. These results were also consistent with sensitivity analysis results. In the five other procedures, no significant advantage was found.

Conclusions This nationwide study found that, compared with PPI, vonoprazan can reduce delayed bleeding with approximately 30% in GD-ESD. Vonoprazan has the possibility to become a new treatment method for preventing delayed bleeding in this procedure.

Keywords Upper gastrointestinal endoscopic treatment · Vonoprazan · Delayed bleeding

Abbreviations

UGET	Upper gastrointestinal endoscopic treatment
E-ESD	Esophageal endoscopic submucosal dissection
ESD	Endoscopic submucosal dissection
EIS	Endoscopic injection sclerotherapy
EVL	Endoscopic variceal ligation
PPI	Proton pump inhibitor
H2RA	Histamine-2-receptor antagonist
EMR	Endoscopic mucosal resection
OR	Odds ratio
DPC	Diagnosis procedure combination

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ICD-10	International Classification of Diseases and Related Health Problems, 10th Revision
RECORD-PE	REporting of studies Conducted using Observational Routinely collected health Data statement for PharmacoEpidemiology
E-EMR	Esophageal endoscopic mucosal resection
GD-EMR	Gastroduodenal endoscopic mucosal resection/polypectomy
GD-ESD	Gastroduodenal endoscopic submucosal dissection
PEG	Percutaneous endoscopic gastrostomy
BMI	Body mass index
APAs	Antiplatelet agents
P2Y12RA	P2Y12 receptor antagonist
ACs	Anticoagulants
DOAC	Direct oral anticoagulant
NSAIDs	Non-steroidal anti-inflammatory drugs
PS	Propensity score
SDs	Standardized differences
AT	Antithrombotic
IPW	Inverse probability weighting
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
CCI	Charlson comorbidity index

Introduction

Endoscopic treatment has been widely applied because it is generally safe and less invasive. However, one of the major adverse events in upper gastrointestinal endoscopic treatment (UGET) is delayed bleeding, the incidence of which is 1.3–6.7% in esophageal endoscopic submucosal dissection (E-ESD) [1–7], 4.7–15.6% in gastric endoscopic submucosal dissection (ESD) [8–10], and 9.5–13.6% in endoscopic therapy for gastroesophageal varices such as endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL) [11].

Proton pump inhibitor (PPI) administration has been used for preventing delayed bleeding or healing post-treatment ulcers in UGET [11–14], but delayed bleeding cannot be completely prevented and this is still a clinically important issue to be addressed. Since the risk for delayed bleeding has been proven to be lower in PPI than in histamine-2-receptor antagonist (H2RA) in some UGET procedures such as gastric ESD or endoscopic mucosal resection (EMR) [15, 16], stronger acid suppression might contribute to reducing delayed bleeding in UGET.

Vonoprazan (Takeda Pharmaceutical Co., Tokyo, Japan) is a novel oral potassium-competitive acid blocker with strong and sustained acid-inhibitory activity [17], and compared with PPI, it has a superior effect in *Helicobacter pylori* eradication [18, 19] and a noninferior effect in acid-related diseases [20–22]. However, the effect of vonoprazan for preventing delayed bleeding in UGET remains unclear. Indeed, its effect was evaluated only in gastric ESD, with no significant difference between vonoprazan and PPI in randomized trials [23, 24] and meta-analysis [25]; however, the odds ratio (OR) in this meta-analysis was low (0.66) and these insignificant results may be due to low sample power.

Hence, this study primarily aimed to investigate whether vonoprazan can reduce the risk for delayed bleeding compared with PPI in UGET. The secondary aim was to examine the association of vonoprazan and PPI doses with delayed bleeding risk. This study specifically assessed outcomes stratified by UGET procedures.

Methods

Study design and data source

This retrospective population-based cohort study utilized the Diagnosis Procedure Combination (DPC) database. This database includes administrative claims as well as admission and discharge abstracts obtained from over 1000 acute-care hospitals throughout Japan, covering approximately 90% of all tertiary hospitals and 50% of all acute-care hospitalizations (7 million per year). The database includes the following data: patient demographics; diagnoses; comorbidities present at admission and complications during hospitalization coded with the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes [26], supplemented by text data in Japanese; procedures coded with the Medical Intervention Classification master code [27] (treatment code); medications, including drugs administered daily; and unique hospital identifier. This study conformed to the REporting of studies Conducted using Observational Routinely collected health Data statement for PharmacoEpidemiology (RECORD-PE) [28].

The Ethics Committee of Tohoku University Graduate School of Medicine approved this study (2020-1-325). Considering the anonymity of data, informed consent was waived.

Study population

Initially, we extracted the data of adult patients ($\geq$ 20 years) who underwent UGET once during hospitalization and were correspondingly prescribed with vonoprazan or PPI between April 2014 and March 2019. We selected this time window because vonoprazan has been

available since the fiscal year of 2014 (April 2014–March 2015). In this study, multiple entries of patients were permitted. UGET consisted of esophageal EMR (E-EMR), E-ESD, gastroduodenal EMR/polypectomy (GD-EMR), gastroduodenal ESD (GD-ESD), EIS, EVL, and percutaneous endoscopic gastrostomy (PEG). The exclusion criteria were patients (1) who were prescribed with both vonoprazan and PPI before the bleeding event; (2) who were prescribed with PPI or vonoprazan only after the bleeding event; (3) who were injected with PPI before the event; (4) who were prescribed or injected with H2RA before the event; and (5) missing data.

Vonoprazan and PPI doses

The standard daily dose of vonoprazan is 20 mg [29]: hence, vonoprazan dose was categorized into standard/high dose ($\geq$ 20 mg/day) and low dose ($<$ 20 mg/day). Regarding PPIs, the standard daily dose in Japan is 30, 10, 20 and 20 mg in lansoprazole, rabeprazole, esomeprazole, and omeprazole, respectively. In a study with 24 h pH monitoring, esomeprazole 20 mg, lansoprazole 30 mg and omeprazole 20 mg had similar pH values (median, 5.5–5.7) [30]. In another study, the acid suppression profiles for esomeprazole 20 mg and rabeprazole 10 mg were similar [17]. Hence, the PPI dose in this study was categorized into two groups: (1) standard/high-dose PPI, which included the standard or more dose of each PPI; (2) low dose, which included the dose under the standard dose of each PPI. Vonoprazan and PPI doses were determined according to the initial prescription dose regimen.

Data collection and variables

Data on age, sex, body mass index (BMI), comorbidities, concurrent medications, UGET type, annual hospital volume, and bleeding outcome were accessed. A complete list of codes is available in Table S1. The DPC database is highly specific and sensitive for the procedure records, whereas it is highly specific yet moderately sensitive in most diagnoses [31].

Comorbidities were assessed using the Charlson comorbidity index (Table S1) [32]. We also assessed hemodialysis because it reportedly has a high risk for delayed bleeding in gastric ESD [10]. Regarding concurrent medications, we evaluated drugs that had potential association with delayed bleeding. These drugs included 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. Annual hospital volume, which was investigated according to the number of UGET cases, was classified into quartiles: low (0–96 cases/year), intermediate (97–187 cases/year), high (188–325 cases/year), and very high ($\geq$ 326 cases/year).

Exposures

The primary exposure was oral vonoprazan or oral PPI, regardless of the dose, in UGET (Fig. 1). To reduce dose-selection bias for the outcome, the following groups were compared separately as the secondary exposures: (1) standard/high-dose vonoprazan or standard/high-dose PPI, (2) low-dose vonoprazan or standard/high-dose PPI, and (3) standard/high-dose or low-dose vonoprazan (Fig. 1).

Outcomes

The primary outcome of interest was delayed bleeding in UGET. Delayed bleeding was defined as overt bleeding that required endoscopic hemostasis and/or blood transfusion at $\geq$ 2 days after the treatment [33].

Statistical analysis

All statistical data were analyzed using SPSS version 25.0 for Windows software (IBM Corp., Armonk, NY, USA) and R software version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are expressed as frequency and proportion, and continuous variables as medians and 25th to 75th percentile (P25–P75).

The comparison groups were balanced using propensity score (PS) matching methods according to the estimated PS of each patient. The PSs were estimated by multivariate logistic regression with covariates including age, sex, BMI, comorbidities, concurrent medications, UGET procedure type, and annual hospital volume. For PS matching, we used the greedy nearest neighbor algorithm with a ratio of 1:1 and a caliper width of 0.2 of the pooled standard deviation of the PS logit. Model discrimination was assessed with *c*-statistic. Furthermore, we used standardized differences (SD) to evaluate the balance of the baseline characteristics between the two groups; an SD $\leq$ 0.1 denotes good balance of covariates [34]. After each PS matching, we compared the bleeding outcomes in each PS-matched cohort through logistic regression analysis. PS matching was performed separately for primary and secondary exposures. In addition, $P < 0.05$ was considered to be statistically significant. In the subgroup analysis of seven UGET procedures, the uncorrected P values are presented along with the effect of correction utilizing the method of Bonferroni, that is, $P < 0.0071$ was considered as statistically significant after the Bonferroni correction.

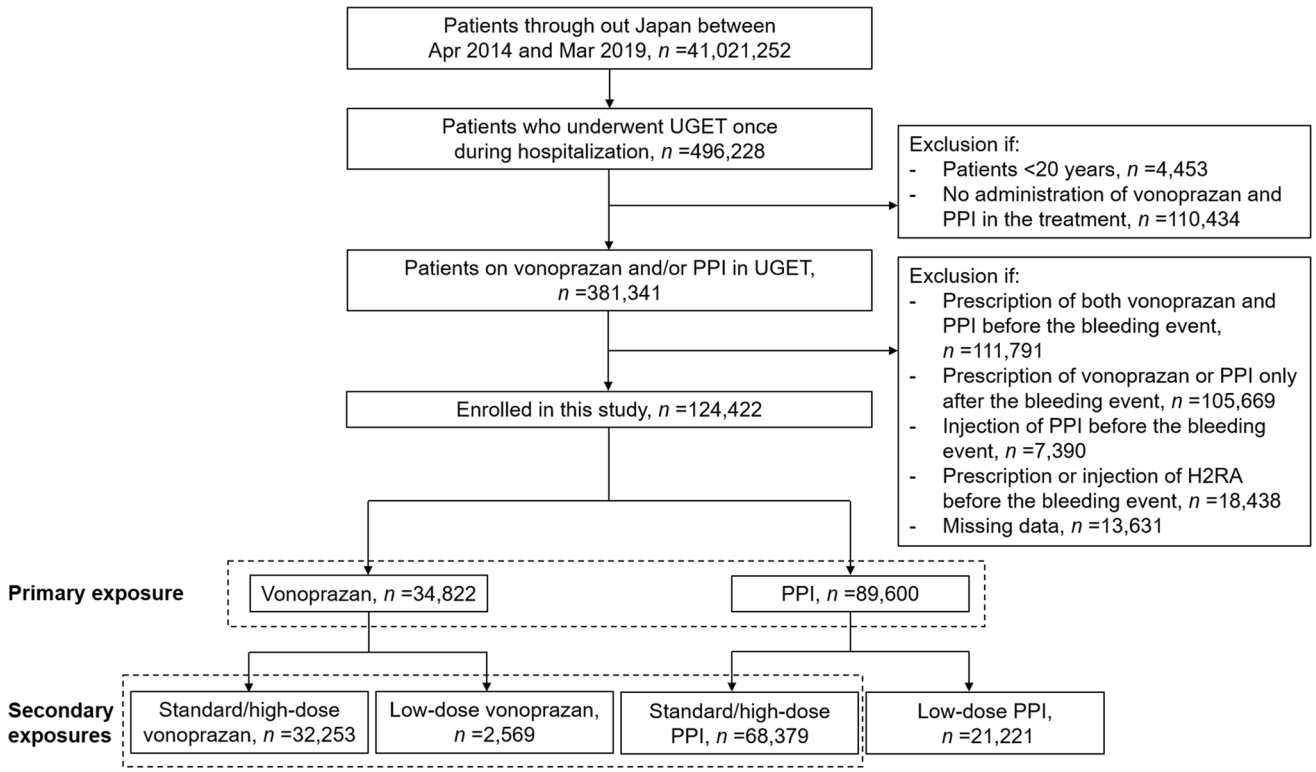


Fig. 1 Study population enrolment flow. A total of 124,422 patients were enrolled in this study. The primary exposure was vonoprazan or PPI, regardless of the dose, and the secondary exposures were standard/high-dose vonoprazan, low-dose vonoprazan, or standard/high-dose PPI. *PPI* proton pump inhibitor, *UGET* upper gastrointestinal endoscopic treatment, *H2RA* histamine-2-receptor antagonist

Sensitivity analysis

We evaluated the robustness of our results by conducting several sensitivity analyses for primary and secondary exposures. First, we conducted stratified analyses based on age, sex, hemodialysis, and antithrombotic (AT) agent status, which was then subdivided into none, APAs, ACs, and APAs and ACs. Whether the ORs were consistent across the stratified groups was examined by the significance of an interaction term between the two comparison groups. Second, instead of PS matching, inverse probability weighting (IPW) [35] was performed using the same variables to confirm the robustness of the PS matching results. Furthermore, as post hoc sensitivity analyses, additional PS matching and IPW were conducted in each exposure for patients who underwent E-ESD, GD-EMR, and GD-ESD separately to confirm the robustness of the subgroup analysis results.

To assess unmeasured confounders after PS matching, we further performed two analyses, namely, falsification endpoints analysis [36] and E-value analysis [37, 38]. First, we assessed three prespecified falsification endpoints that were unlikely to occur as a result of vonoprazan or PPI administration but might be associated with unmeasured frailty or sickness; fracture, subarachnoid hemorrhage, and chronic obstructive pulmonary disease (COPD). This analysis provided some insights on whether substantial unmeasured confounders appeared after PS matching [36]. Second, we computed an E value to evaluate the extent of unmeasured confounders that would be needed to negate the observed significant association [37, 38].

Results

Patient characteristics

Among 381,341 patients who received vonoprazan or PPI in UGET, 124,422 patients were enrolled in this study, with 34,822 patients on vonoprazan and 89,600 patients on PPI (Fig. 1). As a primary exposure, 34,767 pairs of the vonoprazan and PPI users were analyzed after PS matching. The *c*-statistic of this PS model was 0.69. Table 1 summarizes the baseline characteristics before and after PS matching. For the secondary exposure, the comparison groups in each exposure were balanced after PS matching (Tables S2–S4), and their *c*-statistics were 0.64–0.87.

Table 1 Baseline characteristics before and after PS matching in the entire cohort

	Before PS matching			After PS matching		
	Vonoprazan (n = 34,822)	PPI (n = 89,600)	SD (%)	Vonoprazan (n = 34,767)	PPI (n = 34,767)	SD (%)
Age (y), median (P25–P75)	73 (67–79)	74 (66–80)	5.6	73 (67–79)	73 (66–79)	0.2
Sex, n (%)						
Male	25,375 (72.9)	60,928 (68.0)	8.7	25,325 (72.8)	25,242 (72.6)	0.4
Female	9,447 (27.1)	28,672 (32.0)	8.7	9,442 (27.2)	9,525 (27.4)	0.4
BMI (kg/m^2), median (P25–P75)	22.9 (20.7–25.2)	22.0 (19.4–24.5)	20.6	22.9 (20.7–25.1)	22.8 (20.5–25.0)	3.2
CCI, median (P25–P75)	1 (0–1)	1 (0–2)	15.2	1 (0–1)	1 (0–1)	0.8
Hemodialysis, n (%)	569 (1.6)	1,645 (1.8)	1.3	569 (1.6)	545 (1.6)	0.0
Hospital volume, n (%)						
Low (0–96)	6,757 (19.4)	26,147 (29.2)	18.4	6,753 (19.4)	6,852 (19.7)	0.6
Intermediate (97–187)	8,793 (25.2)	22,411 (25.0)	0.6	8,775 (25.2)	8,776 (25.2)	0.0
High (188–325)	9,915 (28.5)	20,952 (23.4)	9.6	9,888 (28.4)	9,631 (27.7)	1.3
Very high (≥ 326)	9,357 (26.9)	20,090 (22.4)	8.6	9,351 (26.9)	9,508 (27.3)	0.7
Drug use, n (%)						
Aspirin	2,716 (7.8)	7,293 (8.1)	0.9	2,691 (7.7)	2,571 (7.4)	0.9
Cilostazol	743 (2.1)	2,937 (3.3)	5.8	738 (2.1)	693 (2.0)	0.6
P2Y12RA	1,199 (3.4)	4,401 (4.9)	6.0	1,192 (3.4)	1,172 (3.4)	0.0
Other antiplatelet drugs	635 (1.8)	1,387 (1.5)	2.0	624 (1.8)	583 (1.7)	0.6
Warfarin	695 (2.0)	3,752 (4.2)	9.8	695 (2.0)	674 (1.9)	0.6
DOAC	1,440 (4.1)	4254 (4.7)	2.4	1,390 (4.0)	1,322 (3.8)	0.8
Heparin	1,623 (4.7)	7,734 (8.6)	12.3	1,619 (4.7)	1,691 (4.9)	0.8
Other anticoagulants	75 (0.2)	601 (0.7)	5.6	75 (0.2)	69 (0.2)	0.0
NSAIDs	2,345 (6.7)	12,414 (13.9)	18.5	2,343 (6.7)	2,388 (6.9)	0.6
Mucosal protective agents	23,280 (66.9)	47,924 (53.5)	22.3	23,234 (66.8)	23,105 (66.5)	0.5
Corticosteroids	2,380 (6.8)	10,077 (11.2)	12.2	2,373 (6.8)	2,380 (6.8)	0.0
UGIT procedure, n (%)						
E-EMR	223 (0.6)	693 (0.8)	1.9	223 (0.6)	195 (0.6)	0.0
E-ESD	2,298 (6.6)	4,974 (5.6)	3.5	2,297 (6.6)	2,297 (6.6)	0.0
GD-EMR	4,700 (13.5)	9,528 (10.6)	7.4	4,699 (13.5)	4,678 (13.5)	0.0
GD-ESD	24,042 (69.0)	37,862 (42.3)	45.1	23,989 (69.0)	24,040 (69.1)	0.2
EIS	445 (1.3)	2,739 (3.1)	9.4	445 (1.3)	380 (1.1)	1.5
EVL	1,145 (3.3)	8,387 (9.4)	19.2	1,145 (3.3)	1,111 (3.2)	0.5
PEG	1,969 (5.7)	25,417 (28.4)	47.3	1,969 (5.7)	2,066 (5.9)	0.7

PS propensity score, *PPI* proton pump inhibitor, *SD* standardized difference, *BMI* body mass index, *CCI* Charlson comorbidity index, *CKD* chronic kidney disease, *P2Y12RA* P2Y12 receptor antagonist, *DOAC* direct oral anticoagulant, *NSAIDs* non-steroidal anti-inflammatory drugs, *UGET* upper gastrointestinal endoscopic treatment, *E-EMR* esophageal endoscopic mucosal resection, *E-ESD* esophageal endoscopic submucosal dissection, *GD-EMR* gastroduodenal endoscopic mucosal resection/polypectomy, *GD-ESD* gastroduodenal endoscopic submucosal dissection, *EIS* endoscopic sclerotherapy, *EVL* endoscopic variceal ligation, *PEG* percutaneous endoscopic gastroscopy

Delayed bleeding risk for primary exposure

In all-dose analysis, delayed bleeding occurred in 5.3% and 6.9% of vonoprazan and PPI users, respectively (Fig. 2). The OR (95% CI) of all-dose vonoprazan for delayed bleeding, with a reference to all-dose PPI, was 0.75 (0.71–0.80) (Fig. 3). In the subgroup analysis of each UGET procedure, E-ESD (OR, 0.71; 95% CI, 0.54–0.94) and GD-ESD (OR, 0.70; 95% CI, 0.65–0.75) had a significantly lower risk for delayed bleeding under vonoprazan administration (Fig. 4); however, correction for multiple testing of the outcome data removed the significance in E-ESD. Other procedures revealed no statistically significant differences.

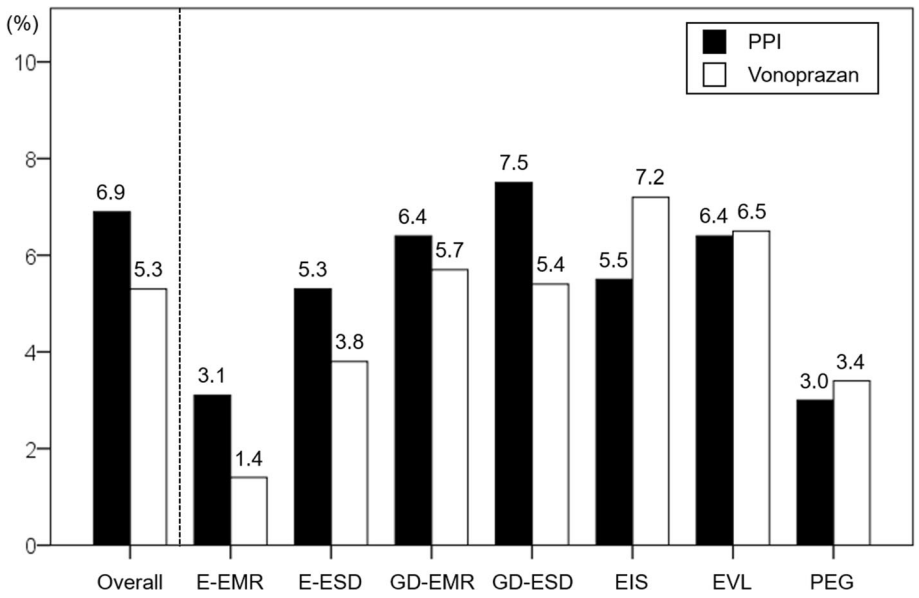
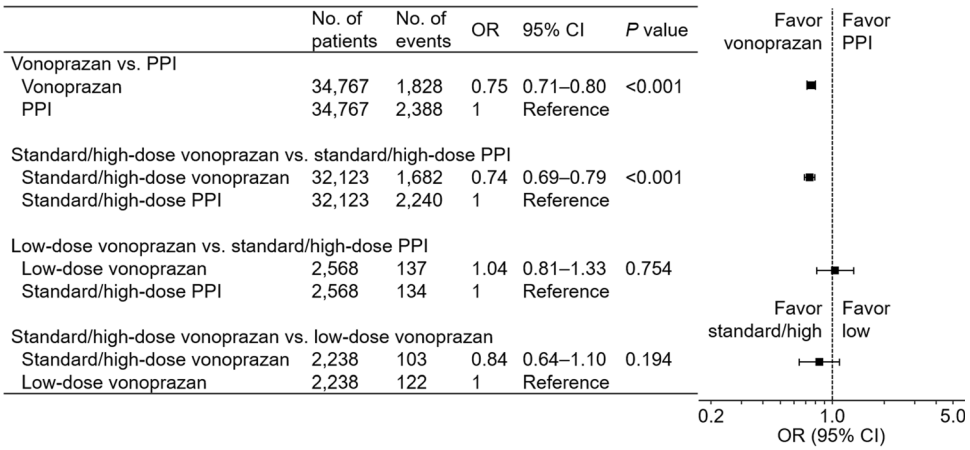


Fig. 2 The delayed bleeding rates of vonoprazan and PPI in overall and each UGET procedure. *PPI* proton pump inhibitor, *UGET* upper gastrointestinal endoscopic treatment, *E-EMR* esophageal endoscopic mucosal resection, *E-ESD* esophageal endoscopic submucosal dissection, *GD-EMR* gastroduodenal endoscopic mucosal resection/polypectomy, *GD-ESD* gastroduodenal endoscopic submucosal dissection, *EIS* endoscopic sclerotherapy, *EVL* endoscopic variceal ligation, *PEG* percutaneous endoscopic gastroscopy



	No. of patients	No. of events	OR	95% CI	*P* value
Vonoprazan vs. PPI					
Vonoprazan	34,767	1,828	0.75	0.71–0.80	<0.001
PPI	34,767	2,388	1	Reference	
Standard/high-dose vonoprazan vs. standard/high-dose PPI					
Standard/high-dose vonoprazan	32,123	1,682	0.74	0.69–0.79	<0.001
Standard/high-dose PPI	32,123	2,240	1	Reference	
Low-dose vonoprazan vs. standard/high-dose PPI					
Low-dose vonoprazan	2,568	137	1.04	0.81–1.33	0.754
Standard/high-dose PPI	2,568	134	1	Reference	
Standard/high-dose vonoprazan vs. low-dose vonoprazan					
Standard/high-dose vonoprazan	2,238	103	0.84	0.64–1.10	0.194
Low-dose vonoprazan	2,238	122	1	Reference	

Fig. 3 Delayed bleeding risk of the comparison groups for primary and secondary exposures. In all-dose and standard/high-dose comparison, vonoprazan had a significantly lower risk of delayed bleeding than PPI in UEGT. *PPI* proton pump inhibitor, *UGET* upper gastrointestinal endoscopic treatment, *OR* odds ratio, *CI* confidence interval, *E-EMR* esophageal endoscopic mucosal resection, *E-ESD* esophageal endoscopic submucosal dissection, *GD-EMR* gastroduodenal endoscopic mucosal resection/polypectomy, *GD-ESD* gastroduodenal endoscopic submucosal dissection, *EIS* endoscopic sclerotherapy, *EVL* endoscopic variceal ligation, *PEG* percutaneous endoscopic gastroscopy

Delayed bleeding risk for secondary exposures

When vonoprazan and PPI were restricted to the standard/high dose, most results in vonoprazan vs. PPI were similar to those in all-dose classification (Figs. 3, 4, 5). In GD-EMR, standard/high-dose vonoprazan had a nominal significance for reducing risk of delayed bleeding compared with standard/high-dose PPI (OR, 0.82; 95% CI, 0.69–0.97); however, Bonferroni correction removed the significance (Fig. 5).

Conversely, no significant difference was found between low-dose vonoprazan and standard/high-dose PPI for delayed bleeding risk in overall and each UGET procedure (Fig. 3, Fig. S1). Likewise, comparison between standard/high-dose and low-dose vonoprazan yielded no significant results, except in GD-ESD (OR, 0.47; 95% CI, 0.29–0.76) (Fig. 3, Fig. S2).

Sensitivity analysis

The results in stratified analyses are consistent with the main results (Fig. 6, Fig. S3). For instance, delayed bleeding in all-dose vonoprazan or PPI had no significant interaction across the groups stratified by age, sex, hemodialysis, and AT agent status in overall procedure. Meanwhile, the ORs (95% CIs) in IPW were similar to

	No. of patients	No. of events	OR	95% CI	*P* value
E-EMR					
Vonoprazan	223	8	1.17	0.40–3.44	0.772
PPI	195	6	1	Reference	
E-ESD					
Vonoprazan	2,297	88	0.71	0.54–0.94	0.017†
PPI	2,297	122	1	Reference	
GD-EMR					
Vonoprazan	4,699	270	0.90	0.76–1.06	0.205
PPI	4,678	298	1	Reference	
GD-ESD					
Vonoprazan	23,989	1,290	0.70	0.65–0.75	<0.001
PPI	24,040	1,808	1	Reference	
EIS					
Vonoprazan	445	32	1.33	0.75–2.34	0.332
PPI	380	21	1	Reference	
EVL					
Vonoprazan	1,145	74	1.01	0.72–1.42	0.944
PPI	1,111	71	1	Reference	
PEG					
Vonoprazan	1,969	66	1.12	0.79–1.59	0.525
PPI	2,066	62	1	Reference	

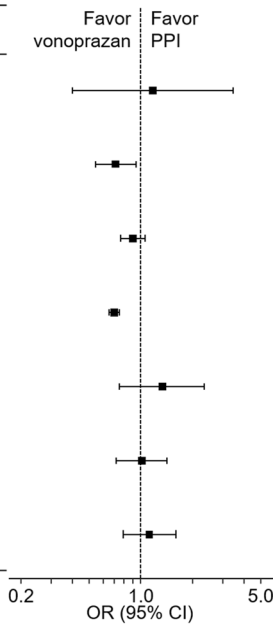


Fig. 4 Delayed bleeding risk for vonoprazan vs. PPI in each UGET procedure. Vonoprazan had a significant reduced effect on delayed bleeding with approximately 30% compared with PPI in GD-ESD. † Nominal significance for this *P* value in a logistic regression; however, correction for multiple testing of the outcome data removes this significance. *PPI* proton pump inhibitor, *UGET* upper gastrointestinal endoscopic treatment, *E-ESD* esophageal endoscopic submucosal dissection, *GD-ESD* gastroduodenal endoscopic submucosal dissection, *OR* odds ratio, *CI* confidence interval, *E-EMR* esophageal endoscopic mucosal resection, *GD-EMR* gastroduodenal endoscopic mucosal resection/polypectomy, *EIS* endoscopic sclerotherapy, *EVL* endoscopic variceal ligation, *PEG* percutaneous endoscopic gastroscopy

	No. of patients	No. of events	OR	95% CI	*P* value
E-EMR					
Standard/high-dose vonoprazan	200	8	0.91	0.34–2.48	0.856
Standard/high-dose PPI	183	8	1	Reference	
E-ESD					
Standard/high-dose vonoprazan	2,180	81	0.74	0.55–0.99	0.043†
Standard/high-dose PPI	2,153	107	1	Reference	
GD-EMR					
Standard/high-dose vonoprazan	4,450	254	0.82	0.69–0.97	0.021†
Standard/high-dose PPI	4,387	303	1	Reference	
GD-ESD					
Standard/high-dose vonoprazan	23,406	1,235	0.70	0.65–0.76	<0.001
Standard/high-dose PPI	23,507	1,725	1	Reference	
EIS					
Standard/high-dose vonoprazan	307	24	1.31	0.66–2.60	0.432
Standard/high-dose PPI	231	14	1	Reference	
EVL					
Standard/high-dose vonoprazan	761	54	0.92	0.63–1.35	0.656
Standard/high-dose PPI	767	59	1	Reference	
PEG					
Standard/high-dose vonoprazan	819	26	1.19	0.68–2.09	0.545
Standard/high-dose PPI	895	24	1	Reference	

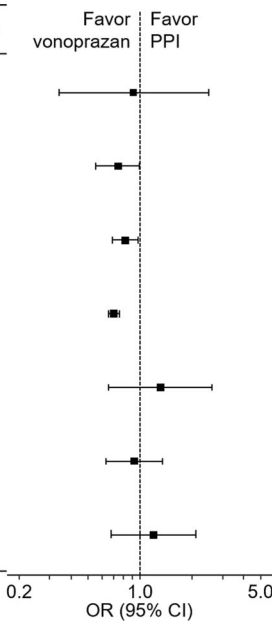


Fig. 5 Delayed bleeding risk for standard/high-dose vonoprazan vs. standard/high-dose PPI in each UGET procedure. Standard/high-dose vonoprazan had a significantly lower risk for delayed bleeding than standard/high-dose PPI in GD-ESD. †Nominal significance for this *P* value in a logistic regression; however, correction for multiple testing of the outcome data removes this significance. *PPI* proton pump inhibitor, *UGET* upper gastrointestinal endoscopic treatment, *E-ESD* esophageal endoscopic submucosal dissection, *GD-EMR* gastroduodenal endoscopic mucosal resection/polypectomy, *GD-ESD* gastroduodenal endoscopic submucosal dissection, *OR* odds ratio, *CI* confidence interval, *E-EMR* esophageal endoscopic mucosal resection, *EIS* endoscopic sclerotherapy, *EVL* endoscopic variceal ligation, *PEG* percutaneous endoscopic gastroscopy

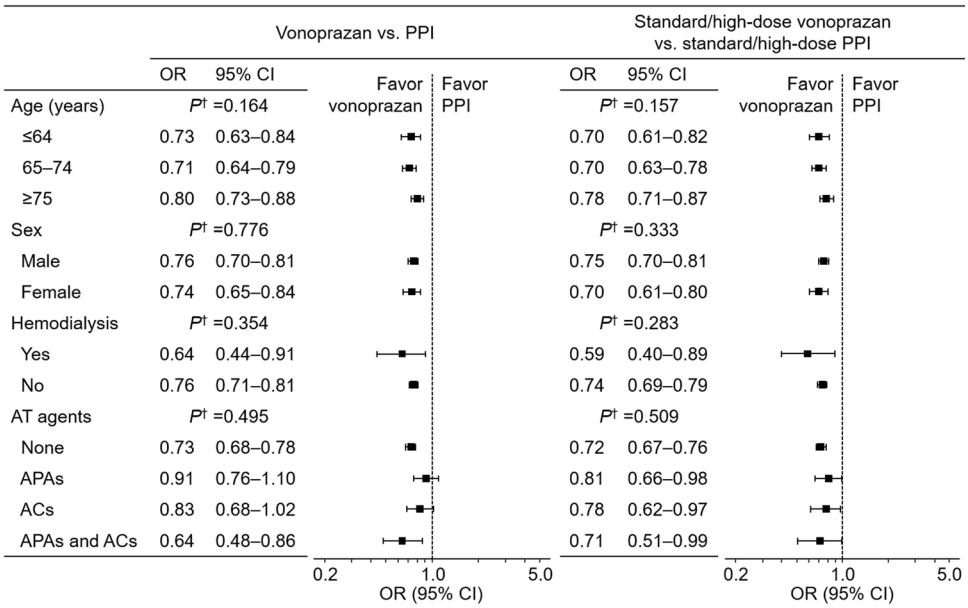


Fig. 6 Stratified analyses for vonoprazan vs. PPI and standard/high-dose vonoprazan vs. standard/high-dose PPI according to age, sex, hemodialysis, and AT agent status. Delayed bleeding in all-dose and standard/high-dose vonoprazan or PPI had no significant interaction across the stratified groups. †*P* for interaction. *PPI* proton pump inhibitor, *AT* antithrombotic, *OR* odds ratio, *CI* confidence interval, *APAs* antiplatelet agents, *ACs* anticoagulants

those in PS matching in most analyses (Table S5). Moreover, the ORs in additional PS matching and IPW in patients with E-ESD, GD-EMR, and GD-ESD were similar to those from original subgroup analyses, especially in all-dose and standard/high-dose vonoprazan vs. PPI (Table S6).

Regarding unmeasured confounders, we revealed no significant association of exposures with fracture, subarachnoid hemorrhage, and COPD in falsification endpoints analyses (Table S7). The E values for the ORs of vonoprazan vs. PPI in all-dose and standard/high-dose classification were 2.00 and 2.04, respectively (Fig. S4).

Delayed bleeding risk for primary exposure according to the location in E-ESD and GD-ESD

To reveal the difference in the potential reduced effect of vonoprazan on delayed bleeding risk among the tumor locations in E-ESD, we performed additional PS matching and IPW for all-dose vonoprazan and PPI, divided into the tumors located on the upper, middle, and lower parts of the esophagus. In the results, vonoprazan had low ORs (0.60–0.65) in tumors located on the middle and lower parts of the esophagus, whereas ORs in tumors located on the upper part were 0.91–1.10 (Table S8).

The reduced effect of vonoprazan on delayed bleeding in GD-ESD was also evaluated in each of gastric and duodenal tumors by additional PS matching and IPW. In GD-ESD for gastric tumors, vonoprazan had a significantly reduced effect on delayed bleeding with similar ORs (0.70–0.71) to those in GD-ESD for all tumors (Table S9). Meanwhile, ORs (0.07–0.14) in GD-ESD for duodenal tumors were much low, although the number of cases was rather small (Table S9).

Discussion

Vonoprazan is a new, potent antisecretory agent that has a more rapid and more sustained acid-inhibitory effect than PPIs [17]. However, much less clarity exists about whether vonoprazan is beneficial for reducing delayed bleeding risk in UGET and, if it is beneficial, which procedures are most likely to benefit from the new agent. The current study revealed that vonoprazan was associated with a lower risk for delayed bleeding than PPI in UGET; however, the effect of vonoprazan varied across the UGET procedures. In GD-ESD, vonoprazan had a 30% lower risk for delayed bleeding than PPI. Furthermore, delayed bleeding risk was lower in standard/high-dose vonoprazan than in standard/high-dose PPI or low-dose vonoprazan. Therefore, standard/high-dose vonoprazan would be optimal for preventing delayed bleeding in GD-ESD. In particular, patients taking AT agents are at high risk for delayed bleeding [10] and our study found a reduced effect of standard/high-dose vonoprazan on delayed bleeding regardless of the status of AT agents. Thus, this antisecretory agent would be optimal also in patients at high risk. In GD-EMR, vonoprazan tended to have a lower risk for delayed bleeding than PPI when restricted to standard/high dose. Although the effect of vonoprazan in reducing the risk for delayed bleeding in GD-EMR is still inconclusive, such reducing effect in GD-EMR might be lesser than that in GD-ESD.

This large-scale study provided an unexpected result, that is, vonoprazan tended to reduce the risk of vonoprazan

for delayed bleeding in E-ESD. Compared with standard/high-dose PPI, standard/high-dose vonoprazan tended to have a reduced effect on delayed bleeding (OR, 0.74), but not in low-dose vonoprazan (OR, 1.36). Furthermore, this trend was shown in tumors located on the middle or lower part of the esophagus. Although the results in E-ESD have the limitation of a higher rate of delayed bleeding (5.3%) compared with those in most previous studies from Japan (1.3–4.3%) [1–4], vonoprazan may have the potential to prevent delayed bleeding after E-ESD in the middle or lower part of the esophagus, possibly due to the lower clearance of refluxate by esophageal motility impairment after E-ESD [39] and the necessity of strict acid suppression for controlling bleeding (pH $>$ 6 is required in upper gastrointestinal bleeding [40]). However, further studies are required for confirming the advantage of vonoprazan to prevent delayed bleeding in E-ESD, and if its advantage is demonstrated, the cost-effectiveness of this agent should be also evaluated.

Paradoxically, delayed bleeding risk did not significantly differ between vonoprazan and PPI in the four other procedures, namely, E-EMR, EIS, EVL, and PEG. A possible explanation for the different effect of vonoprazan between these procedures and E-ESD/GD-ESD may be the variation in ulcer size after the treatment. In gastric ESD, the difference in the acid-inhibitory effect between vonoprazan and PPI tended to be clearer in larger tumors (and subsequent larger ulcers) [24]. Although the ulcer size was not investigated in the DPC database, the ulcer after E-ESD/GD-ESD is generally larger than that after the other procedures; this finding possibly explains the difference in the results. In terms of cost–benefit, PPI might be more appropriate than vonoprazan in the four procedures ($1.85 and $0.82–$1.11 in standard daily dose in Japan, respectively). Furthermore, the effect of antisecretory agents themselves for preventing delayed bleeding after PEG or E-EMR has not been clarified; thus, further studies are required in these procedures.

The present study has several strengths. First, this research is the first nationwide population-based study to evaluate the effect of vonoprazan in reducing delayed bleeding in UGET. This study enrolled a considerably larger cohort than the previous studies, including the largest meta-analysis in gastric ESD (n = 1189) [41]; thus, we could clarify the significant benefit of vonoprazan in GD-ESD. This large sample size also allowed us to evaluate the benefit of vonoprazan in the other procedures for the first time. Second, our strict eligibility criteria precluded patients who were administered with antisecretory agents except vonoprazan and oral PPI, warranting the appropriate comparison between the effect of vonoprazan and that of PPI. Moreover, the detailed analyses considering the doses of these drugs removed dose-selection bias for the outcome. Third, the study design was rigid, in accordance with the RECORD-PE guidelines [28]. Furthermore, numerous sensitivity analyses including IPW found what results are robust and rigorous.

Limitations

This study has several limitations. First, majority of the study cohort were Japanese; thus, our study findings have an uncertain external generalizability, particularly to the Western population. Second, antisecretory agents were not randomly assigned. Although PS matching was used and balanced well between the comparison groups, unmeasured confounders might be residual. Indeed, some previously reported risk factors for delayed bleeding, i.e., tumor location, tumor size, multiple tumors [10], were not investigated in this study. However, in the analyses of all-dose and standard/high-dose vonoprazan vs. PPI, the E value indicated that an unmeasured variable would need an OR of at least 2.00 or 2.04 with both delayed bleeding and use of vonoprazan to explain away the observed associations, and the E values were higher than the ORs of the unmeasured risk factors for delayed bleeding after gastric ESD in the largest study to date [10]. In addition, the falsification endpoints yielded no statistical significant results, thereby providing us some reassurance that these PS-matched analyses may have no evidence for substantial unmeasured confounding. Nevertheless, a randomized trial demonstrating benefit of vonoprazan is required before widely advocating this practice. Third, the DPC database does not include the data about intervention to prevent delayed bleeding after GD-ESD, such as polyglycolic acid sheet with fibrin glue and mucosal defect closure, although these methods were proven not to prevent delayed bleeding [42, 43]. This leads to a selection bias in this study. Fourth, the results in the analyses including low-dose vonoprazan are not robust because of the small sample power. Thus, although our results may suggest that low-dose vonoprazan is not recommended in any type of UGET procedures due to its lack of effect on delayed bleeding and higher cost compared with PPI, the findings about low-dose vonoprazan need to be confirmed by future studies. Fifth, we used the initially prescribed dose of vonoprazan or PPI for the analysis. We did not consider the change of the dose after the initial prescription. In addition, adherence of drugs could not be confirmed. Lastly, the present study has potential inaccuracy of coding, although a previous validation study demonstrated that the reliability of this database was relatively high in general [31].

Conclusion

This nationwide population-based study first found that compared with PPI, vonoprazan can reduce delayed bleeding with approximately 30% in GD-ESD. Vonoprazan, in particular standard/high dose, has the possibility to become a new treatment method for preventing delayed bleeding in this procedure.

Author contributions Conception and design: WH; collecting data: HA, WH, and KT; interpreting data: HA and WH; statistical analysis: HA, WH, and YO; drafting of the manuscript: HA and WH; critical revision of the manuscript: TK, MS, XJ, KN, TK, KU, NA, AI, SH, TN, NN, KT, KF, KF, and AM; study supervision: KF and AM. All authors listed have contributed substantially to the design, data collection and analysis, and editing of the manuscript.

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Declarations

Competing interests Atsushi Masamune declared that he received lecture honoraria from EA Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo, Inc., and Mylan.co.jp and he received commercial research funding from Otsuka Pharmaceutical Co., Ltd., EA Pharma Co., Ltd., Gilead Sciences, Inc., Asahi Kasei Pharma Corp., Eisai Co., Ltd., AbbVie GK, Takeda Pharmaceutical Co., Ltd., and Daiichi Sankyo, Inc. outside the submitted work.

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