

Efficacy of vonoprazan for the prevention of bleeding after gastric endoscopic submucosal dissection with continuous use of antiplatelet agents



Authors

Shunsuke Yoshii¹, Takuya Yamada^{2,3}, Shinjiro Yamaguchi⁴, Yoshito Hayashi¹, Masanori Nakahara⁵, Narihiro Shibukawa⁶, Masashi Yamamoto⁷, Ryu Ishihara⁸, Kazuo Kinoshita⁹, Satoshi Egawa¹⁰, Yoshiki Tsujii¹, Hideki Iijima¹, Tetsuo Takehara¹

Institutions

- 1 Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan
- 2 Department of Gastroenterology, Osaka Rosai Hospital, Osaka, Japan
- 3 Department of Gastroenterology, National Hospital Organization Osaka National Hospital, Osaka, Japan
- 4 Department of Gastroenterology, Kansai Rosai Hospital, Osaka, Japan
- 5 Department of Gastroenterology, Ikeda Municipal Hospital, Osaka, Japan
- 6 Department of Gastroenterology, NTT West Osaka Hospital, Osaka, Japan
- 7 Department of Gastroenterology, Toyonaka Municipal Hospital, Osaka, Japan
- 8 Department of Gastrointestinal Oncology, Osaka International Cancer Institute, Osaka, Japan
- 9 Department of Gastroenterology, Otemae Hospital, Osaka, Japan
- 10 Department of Gastroenterology, Osaka Police Hospital, Osaka, Japan

submitted 19.7.2019

accepted after revision 15.10.2019

Bibliography

DOI <https://doi.org/10.1055/a-1067-4380> |
Endoscopy International Open 2020; 08: E481–E487
© Georg Thieme Verlag KG Stuttgart · New York
eISSN 2196-9736

Corresponding author

Tetsuo Takehara, MD PhD, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita, Osaka, Japan
Fax: +81-6-68793629
takehara@gh.med.osaka-u.ac.jp

ABSTRACT

Background Post-procedural bleeding, after gastric endoscopic submucosal dissection (ESD) for high risk thromboembolic cases that require continuous antiplatelet therapy, is challenging. Its incidence rate is >20% among those using conventional antacids. We evaluated the efficacy of perioperative management with vonoprazan to prevent post-ESD bleeding.

Materials and methods This was a multicenter prospective interventional trial conducted at 10 Japanese referral centers. Patients who regularly used antiplatelet agents (aspirin or thienopyridine derivatives, etc.) and who required continuous antithrombotic medication due to high thromboembolic risk were enrolled. They underwent gastric ESD with continuous aspirin therapy. Oral administration of vonoprazan (20 mg daily) was started from the day of ESD and continued for 28 days. The primary end point was the incidence of post-ESD bleeding. The sample size was 50 patients, and vonoprazan was considered to be effective when the upper threshold of the 95% confidence interval (CI) for post-ESD bleeding did not exceed 20%.

Results Although 50 patients were enrolled, one patient withdrew consent. Therefore, 49 patients were included in the analysis. One patient who used aspirin and clopidogrel experienced bleeding 11 days after ESD. The overall post-ESD bleeding rate was 2.0% (1/49; 95%CI 0.4–10.7%). Thromboembolic events were not observed. One case of ESD-associated adverse events (perforation) and one case of drug-associated adverse events (drug eruption, possibly due to vonoprazan) were observed.

Conclusions Vonoprazan may be efficacious for preventing post-ESD bleeding in patients using continuous antiplatelet therapy, warranting further comparative study to definitively test the effectiveness of the drug.

UMIN-CTR

UMIN000020174

TRIAL REGISTRATION: multicenter, single-arm, prospective, interventional trial UMIN000020174 at umin.ac.jp

Introduction

Endoscopic submucosal dissection (ESD) has become a standard therapy for gastric epithelial neoplasia after the implementation of technical skills and instrumentation [1]. The minimal invasiveness and organ-preserving nature of this technique have allowed for broader applications in higher risk patients such as elderly patients and those with severe comorbidities [2–4]. An increase in the ageing population has been associated with a rise in the number of individuals on antithrombotic therapy. The Japan Gastrointestinal Endoscopy Society (JGES) guidelines have recommended either cessation or continuation of antiplatelet agents perioperatively for ESD, depending on the level of thromboembolic risk, and further advised continuous use or replacement of aspirin in high risk patients [5]. However, for patients requiring continuous antiplatelet therapy, even during gastric ESD, because of high thromboembolic risks, the post-ESD bleeding rate has been reported to be more than 20% [6–8]. This is strikingly high compared to the general rate of approximately 5% [1, 9–11].

Antacid medications, mainly proton-pump inhibitors (PPIs), are administered after gastric ESD to prevent delayed bleeding [12]; however, conventional PPIs are inadequate for perioperative use in this instance as they require several days to exert maximum pharmacological effect, which means that the drugs are not at their peak activity during the immediate postoperative period of greatest risk for post-ESD bleeding [13]. Another limitation is that PPIs are influenced by gene polymorphism of the metabolic liver enzyme, cytochrome P450 (CYP) [14]. The frequency of occurrence of CYP2C19 mutant alleles was high among Asian patients, which led to corresponding, individual variation in response to PPIs [15]. Additionally, caution is necessary because of the potential for metabolic drug–drug interactions, especially for patients using antiplatelet agents. The drug efficacy of cilostazol was enhanced by concomitant administration of omeprazole because of the latter's competitive inhibitory effect on CYP2C19 [16]. Conversely, a PPI-mediated competitive inhibition of CYP2C19, which is also responsible for converting thienopyridine prodrugs into their active forms, could reduce the efficacy of an antiplatelet agent such as clopidogrel [17, 18].

Potassium-competitive acid blockers (P-CABs) exhibit rapid, long-lasting, and reversible inhibition of gastric hydrogen potassium ATPase, also known as the proton pump of the stomach [19]. Vonoprazan is a novel, orally active P-CAB which does not inhibit CYP2C19 [20, 21]. Therefore, it was hypothesized that vonoprazan may be more useful than conventional PPIs for perioperative use with gastric ESD, especially for patients who require continuous antiplatelet therapy. We sought to test this hypothesis in this prospective, multicenter study conducted in Japan, which aimed to evaluate the efficacy of perioperative administration of vonoprazan in patients who underwent gastric ESD, while undergoing continuous antiplatelet therapy.

Methods

Patients

This was a multicenter, prospective, interventional study conducted between December 2015 and June 2018, at 10 referral centers in Japan. This study was approved by the institutional review board of each participating institution. It was performed in accordance with the 2013 revision of the Helsinki Declaration. Written, informed consent was obtained from all patients before study registration. This study has been registered in the UMIN clinical trial registry (UMIN000020174).

Patients with a diagnosis of gastric adenoma or early gastric cancer according to the Japanese guideline criteria [22] who regularly used antiplatelet agents (aspirin, thienopyridine derivatives, etc.) and required continuous antithrombotic medication due to high thromboembolic risk were included in this study. Patients were required to consult the prescribing physician before trial registration, to assess their risk of thromboembolism according to the JGES guidelines. Patients with the following conditions were considered: coronary stenting within 2 months or coronary artery drug-eluting stent placement within 12 months; cerebral revascularization within 2 months; post-ischemic stroke or transient ischemic attack with >50% stenosis of major intracranial arteries; recent occurrence of ischemic stroke or transient ischemic attack; obstructive peripheral artery disease with Fontaine grade ≥ 3 ; and any similar conditions considered to be a high risk for thromboembolism. Enrolled patients underwent gastric ESD with continuous aspirin therapy based on the JGES guidelines.

Exclusion criteria were as follows: (i) patients who required only temporary antiplatelet therapy or for whom therapy could be interrupted during the perioperative period; (ii) participants aged <20 years; (iii) those scoring 3 or 4 as per the Eastern Cooperative Oncology Group [ECOG] system for evaluation of performance status; (iv) those with a history of gastrectomy, those scheduled to undergo concurrent endoscopic treatment for an upper gastrointestinal lesion, or those who had undergone the same within the last 28 days; (v) those who had received systemic (intravenous or oral) corticosteroids and/or anticoagulants; (vi) those diagnosed with any psychiatric illness, active bacterial or fungal infection, uncontrollable hypertension, or any severe comorbidities including hematological diseases (white blood cell count <3000/ μ L or >12000/ μ L, hemoglobin <9.0 g/dL, or platelets <100 000/ μ L), renal impairment (estimated glomerular filtration rate <30 mL/min), or liver disease (aspartate aminotransferase >150 IU/L, alanine aminotransferase >150 IU/L, or platelet international normalized ratio <70%).

Perioperative management and ESD procedures

Oral administration of 20 mg vonoprazan was initiated from the day of ESD and continued for 28 days. No other antacids or gastroprotective agents were administered during this period.

Perioperative administration of antiplatelet agents was carried out in accordance with the JGES guidelines, meaning that aspirin monotherapy was continued, and other antiplatelet agents were switched to aspirin monotherapy during the periendoscopic period. Thienopyridine derivatives (e.g. clopido-

grel, ticlopidine, prasugrel) and other antiplatelet agents (e.g. cilostazol) were withdrawn 5–7 days and 1 day before ESD, respectively. After gastric ESD, switched or withdrawn antiplatelets were resumed as soon as possible, generally 1 day after ESD, at the discretion of medical professionals. In summation, as a part of the study protocol, all enrolled patients underwent gastric ESD while on continuous treatment with aspirin, and their pre-surgical, regular antiplatelet therapy (if different from aspirin) was resumed 1 day after the procedure.

ESD was performed in a standard manner, and patients were monitored while under anesthetic sedation. N-butyl-scopolammonium bromide or glucagon was administered as needed to counter peristalsis. Electrosurgical knives, hemostatic forceps, and electrosurgical generators were not specified, and each endoscopic professional used their preferred devices. Any visible vessels in the resected portion were coagulated immediately after the ESD to prevent delayed bleeding [9]. No other prophylactic procedures to prevent post-procedural bleeding, such as clip closure [23] or shield application using a polyglycolic acid sheet [24] (for a post-ESD ulcer), were performed during this study. Although a second-look endoscopy was not a part of the study protocol, a follow-up endoscopy could be allowed, and preventive coagulation of the visible vessels at the post-ESD ulcer could be performed according to the endoscopist's decision, even in the absence of clinical signs of bleeding.

Study end points

The primary end point was the incidence of post-ESD bleeding within 28 days after gastric ESD. Post-ESD bleeding was defined as bleeding with symptoms of hematemesis, melena, or a decrease in hemoglobin of >2.0 g/dL. This was endoscopically confirmed as active bleeding caused by a post-ESD ulcer or blood retention in the stomach. A visible vessel or a small amount of coagulated blood at the post-ESD ulcer site, fortuitously detected during follow-up endoscopy, without presenting symptoms of hematemesis, melena, or hemoglobin decrease of >2.0 g/dL, were not defined as post-ESD bleeding.

The secondary end points included: (i) prevalence of massive intraoperative bleeding that necessitated blood transfusion, surgical intervention, or interventional radiology during ESD; (ii) prevalence of cardiovascular, cerebral, and systemic thromboembolic events within 28 days after gastric ESD, which were identified via physical examinations conducted by attending doctors; (iii) bleeding severity in cases of post-ESD bleeding; and (iv) ESD-associated or any other adverse events.

Estimation of sample size and statistical analysis

The post-ESD bleeding rate in patients using continuous antiplatelet therapy was previously reported as 21.1–31.8% [6–8]; however, at the time this study was conducted, there were no data available on the effects of vonoprazan on post-ESD bleeding. The expected incidence rate of post-procedural bleeding was set as 10%, i.e. at approximately half the incidence rate observed with administration of conventional PPIs. When setting the sample size, we considered that perioperative management with vonoprazan could be effective for patients using continuous antiplatelet therapy, relative to previous reports, if the up-

per threshold of the 95% confidence interval (CI) of post-ESD bleeding did not exceed 20%. Therefore, the sample size was set at 50 (5/50; 95%CI 1.7–18.3%). Performance of an interim analysis to assess safety was prescribed when the number of participants reached 30.

Statistical analyses were conducted using Fisher's exact test. An alpha value of $P<0.05$ was considered to be statistically significant. All statistical analyses were conducted with JMP 13 (SAS Institute Japan, Tokyo, Japan) software.

Results

Characteristics of patients and lesions

In total, 2231 patients underwent gastric ESDs in all participating institutions, irrespective of their antiplatelet treatment status, during the study period, and 108 patients were found to meet the inclusion criteria of this study. Of these, 50 patients were enrolled non-consecutively in this study; however, one patient withdrew consent after enrollment, and finally, 49 patients were analyzed. The characteristics of all included patients are summarized in ► **Table 1**. The median age of the study group was 77 years, and 47 patients (95.9%) were male. The most common comorbidities requiring continuation of antiplatelet therapy were ischemic heart disease (69.4%) and cerebral infarction (24.5%). Thirteen patients (26.5%) were administered multiple antiplatelet drugs, while 18 patients (36.7%) received thienopyridine derivatives. The characteristics of the treated gastric lesions are also recorded in ► **Table 1**. The median lesion diameter was 15.0 mm, and two lesions were endoscopically diagnosed with ulceration. The presence of atrophic gastritis was confirmed endoscopically in the background mucosa of all patients. Nineteen patients had undergone successful *Helicobacter pylori* eradication in the past, and 16 of the remaining 30 patients tested positive for an ongoing infection with the organism, as indicated by their levels of serum anti-H. pylori IgG antibody, stool antigen, or according to the results of the urea breath test.

Outcomes of ESD procedures

The outcomes of all ESD procedures are summarized in ► **Table 2**. The ESD procedures were performed using a Flush knife (FUJIFILM Medical, Tokyo, Japan) or insulated tipped (IT) knife-2 (Olympus Medical Systems, Co. Ltd., Tokyo, Japan) with an electrosurgical generator (VIO300D, VIO3, or ICC200; Erbe Co., Tübingen, Germany). A Coagrasper, Coagrasper G (Olympus Medical Systems, Co. Ltd.), or hot biopsy forceps (Radial Jaw 4; Boston Scientific Japan, Co. Ltd., Tokyo, Japan) was used as the hemostatic forceps. All lesions were successfully resected. The median diameter of the resected specimens was 35.0 mm, and the median procedure time was 75 minutes. The median time for the coagulation procedure for visible vessels in the resection area immediately after ESD for the prevention of delayed bleeding was 9 minutes.

A second-look endoscopy was routinely performed in three of the 10 participating institutions, regardless of concurrent administration of antiplatelet agents, and 22 patients (44.9%) underwent this step in this study. Of these, the proportions of

► **Table 1** Characteristics of the patients and lesions.

Variable	
Age, median (range), years	77 [55–88]
Sex, male/female	47/2
Performance Status (ECOG), 0/1/2	38/9/2
Habitual drinking	16 (32.7%)
Habitual smoking	14 (28.6%)
Comorbidities	
▪ Ischemic heart disease	34 (61.2%)
▪ Cerebral infarction	12 (24.5%)
▪ Internal carotid artery stenosis	3 (6.1%)
▪ Obstructive peripheral artery disease	2 (4.1%)
Antiplatelet drugs	
▪ Aspirin and thienopyridine derivatives	11 (22.4%)
▪ Thienopyridine derivatives and cilostazol	1 (2.0%)
▪ Aspirin and cilostazol	1 (2.0%)
▪ Aspirin monotherapy	30 (61.2%)
▪ Thienopyridine derivatives monotherapy	6 (12.2%)
Tumor location, upper third/middle third/lower third	5/22/22
Tumor location, anterior/posterior/greater curvature/lesser curvature	7/9/15/18
Endoscopic tumor size, mm	15 [4–50]
Endoscopic ulceration or fold conversion	2 (4.1%)

Data are presented as median [range] or n (%).
ECOG, Eastern Cooperative Oncology Group.

the patients taking either thienopyridine derivatives or multiple antiplatelet drugs were 6.1% (3/22) each. Conversely, of the 27 patients who did not undergo a second-look endoscopy, 55.6% (15/27) and 37.0% (10/27) patients received thienopyridine agents and multiple antiplatelet drugs, respectively. Thus, the ratio of patients with thienopyridine derivatives or multiple antiplatelet drugs was not high among those who underwent the second-look endoscopy. No active bleeding was detected during the second-look endoscopy, and preventive coagulation for post-ESD ulcers was performed for seven of the 22 patients (31.8%). En bloc resection was achieved in 46 patients (93.9%). Histological analysis revealed the presence of submucosal invasion in three patients, including one with submucosal invasion deeper than 500 μ m from the muscularis mucosae with lymphatic invasion.

Study end points

Only one patient experienced post-ESD bleeding in this study. The overall post-ESD bleeding rate was 2.0% (1/49; 95%CI 0.4–10.7%) (► **Table 3**). We conducted subgroup analysis according to the antiplatelet drugs administered. The post-ESD

► **Table 2** Outcomes of endoscopic submucosal dissection (ESD).

Variable	
Electrosurgical knives	
▪ Flush knife	26 (53.1%)
▪ IT knife 2	23 (46.9%)
Hemostatic forceps	
▪ Coagrasper	21 (42.9%)
▪ Coagrasper G	15 (30.6%)
▪ Hot biopsy forceps	13 (26.5%)
Electrosurgical generator	
▪ VIO300D	40 (81.6%)
▪ VIO3	7 (14.3%)
▪ ICC200	2 (4.1%)
Resected specimen size, mm	35 [12–70]
Procedure time, min	75 [12–210]
En bloc resection	46 (93.9%)
Histology, adenoma/adenocarcinoma	6/43
Invasion depth of cancer, M/SM1/SM2	40/2/1
Histological ulceration (fibrosis)	2 (4.1%)

Data are presented as median [range] or n (%).
ESD, endoscopic submucosal dissection; IT, insulated tipped; M, mucosal; SM1, submucosal invasion <500 μ m from the muscularis mucosae; SM2, submucosal invasion >500 μ m from the muscularis mucosae.

bleeding rate for patients using multiple antiplatelet drugs was 7.7% (1/13), relative to 0% (0/36) for patients using single antiplatelet drugs. Patients using thienopyridine derivatives demonstrated a post-ESD bleeding rate of 5.6% (1/18), in contrast to the 0% (0/31) rate found among those not using thienopyridine derivatives.

Of the 49 patients, one experienced intraoperative perforation, and the administration of vonoprazan was discontinued on the day after ESD. Drug-eruption, possibly due to vonoprazan, occurred in one patient 5 days after ESD, and the administration of vonoprazan was discontinued 7 days after the procedure. Therefore, of the 49 patients, 47 completed the study protocol. The incidence rate of post-ESD bleeding among the 47 patients who completed the study protocol was 2.1% (1/47; 95%CI 0.4–11.1%).

Post-ESD bleeding occurred in a male patient in his 70s at 11 days after ESD. The lesion was an early gastric cancer, 10 mm in diameter, located on the greater curvature of the lower gastric body. This patient had a medical history of cardiac infarction with coronary artery drug-eluting stent placement 6 months before the ESD, and was taking aspirin and clopidogrel regularly. Hemorrhage from a post-ESD ulcer was successfully treated using emergent endoscopy, and no other subsequent adverse event such as recurrent bleeding, was observed.

► **Table 3** Incidence rate of post-endoscopic submucosal dissection (ESD) bleeding.

	Post-ESD bleeding	95 % CI	P value
Total	2.0 % (1/49)	0.4–10.7 %	
Antiplatelet drug number			
▪ Single drug	0.0 % (0/36)	0–9.6 %	0.27
▪ Multiple drugs	7.7 % (1/13)	1.4–33.3 %	
Thienopyridine derivatives			
▪ Presence	5.6 % (1/18)	1.0–25.8 %	0.37
▪ Absence	0.0 % (0/31)	0–11.0 %	

ESD, endoscopic submucosal dissection; CI, confidence interval.

No massive intraoperative bleeding or any thromboembolic events, including cardiovascular, cerebral, and/or systemic thromboembolic events, were observed in this study. Both ESD-associated and drug-associated adverse events showed an incidence of 2.0 % (one case each of intraoperative perforation and drug eruption), as described. The patient who experienced intraoperative perforation, recovered with conservative management. Drug eruption was treated with administration of an antihistaminic drug and the application of a corticosteroid ointment, after switching the antacids to lansoprazole.

Discussion

To the best of our knowledge, this is the first prospective study to report the efficacy of perioperative management using vonoprazan for patients requiring continuous use of antiplatelet agents. The post-ESD bleeding rate was 2.0 % (1/49) in this study. The upper threshold of the 95 % CI of the post-ESD bleeding rate did not exceed the predetermined threshold, and perioperative management using vonoprazan could be considered effective. No thromboembolic events were observed during the study.

The incidence of post-procedural bleeding after gastric ESD in patients undergoing antithrombotic therapy has frequently been reported. In some recent studies, patients receiving aspirin preoperatively showed a similar incidence of post-ESD bleeding, regardless of whether aspirin monotherapy was continued or withdrawn [25–28]. Conversely, there are also reports of high post-ESD bleeding rates in patients requiring uninterrupted, antiplatelet therapy, especially in those who used multiple antiplatelet agents (including thienopyridine derivatives) preoperatively, despite institution of a temporal, perioperative switch to aspirin monotherapy [6–8]. Thus, the type of antiplatelet therapy (thienopyridine derivatives or multiple antiplatelet drugs) was also considered to influence the risk of bleeding. Therefore, stratification of the post-ESD bleeding risk in study patients by aspirin monotherapy/multiple antiplatelet drugs or with/without thienopyridine derivatives, is necessary. A previous multicenter, prospective, observational study performed in Japan by Ono et al. indicated post-ESD bleeding rates of 50 % and 42.9 % among patients who received thienopyridine deriva-

tives and multiple agents, respectively, compared to a 0 % post-procedural rate of bleeding in patients maintained only on low-dose aspirin monotherapy [6]. In the present study, we found no cases of post-ESD bleeding with low-dose aspirin monotherapy with vonoprazan and a relatively low incidence of post-ESD bleeding, even for patients using thienopyridine derivatives (5.6 % with 25.8 % of upper 95 % CI) or multiple antiplatelet drugs (7.7 % with 33.3 % of upper 95 % CI) with vonoprazan.

Platelet function depends on the pH conditions; a pH level of <6.0 can lead to lysis of blood clots, leading to hemorrhage from post-endoscopic treatment ulcers [29]. Therefore, antacid medications (usually PPIs) are commonly administered perioperatively for gastric ESD [12]. Considering the rapid and strong antacid action of vonoprazan, we expected the drug to be a more promising alternative for the prevention of post-ESD bleeding. A few studies have been conducted to examine the prevention and effects of post-ESD bleeding after gastric ESD. Kagawa et al. reported that vonoprazan could reduce post-ESD bleeding, compared to conventional PPIs [30]. Hamada et al. also reported that vonoprazan significantly reduced delayed bleeding, relative to the predetermined threshold bleeding rate [31]; however, these previous reports included a small number of patients (or no patients) who used antithrombotic agents. This is the first report to describe the perioperative use of vonoprazan for gastric ESD with continuous antiplatelet therapy.

In addition to superior bleeding control effects, several studies have reported that vonoprazan can improve healing relative to conventional PPIs. Horikawa et al. reported that the ulcer reduction rate was significantly higher and the coverage ratio of the ulcer base by granulation tissue was significantly accelerated in the vonoprazan group compared to the lansoprazole group at 2 weeks after gastric ESD [32]. Although several reports have supported the conclusion that vonoprazan promotes more effective postoperative healing [33–35], some found no difference in its ulcer-healing ability, 4 or 8 weeks following gastric ESD [36, 37]. A systematic review and meta-analysis of these reports showed that patients treated with vonoprazan demonstrated a significantly higher rate of completely healed ulcers, compared to that observed in those managed with PPIs [38]. Although controversy remains regarding the

better ability of vonoprazan to accelerate ulcer healing after gastric ESD compared to conventional PPIs, a plausible mechanism would be its greater antacid effect which means a significantly higher pH 4-holding time ratio of vonoprazan relative to that of conventional PPIs, from day-1 of administration, which explains the stronger antacid activity of the former drug [19].

There were several limitations to this study such as the relatively small sample size and the use of a single-arm study without two-stage design. We determined the sample size using a bleeding rate of more than 20% based on the previous reports of continuous aspirin users with varying perioperative usage of antacids including those who transiently interrupted multiple antiplatelet agents or thienopyridine derivatives [6–8]; however, some other reports did not show an increased risk of bleeding in patients on aspirin monotherapy [27,28], and more than 60% of the patients in our study took aspirin monotherapy. Thus, our predetermined bleeding rate might be relatively high, and the sample size may be too small to draw robust conclusions. In addition, non-consecutive enrollment of patients in the study, and the lack of a comparative control group, may imply the existence of a latent selection bias. The median size of lesions was relatively small, and there were only two lesions with ulceration. Therefore, when associated with the lesion-related risk factors of post-ESD bleeding, the included lesions might have had a relatively low risk of bleeding. In addition, although the utility of a second-look endoscopy is uncertain [39], second-look endoscopy was performed in 44.9% of the included patients and might have affected the incidence of post-ESD bleeding observed in this study. Despite these limitations, satisfactory results were demonstrated regarding the post-ESD bleeding rate and the present study suggested that vonoprazan can contribute towards a reduction of post-procedural bleeding after gastric ESD for patients using continuous antiplatelet therapy. Larger studies, ideally randomized controlled trials with high risk patients on antiplatelet agents, such as those taking thienopyridine derivatives and multiple antiplatelet agents, are needed to clarify the utility of this new antacid medication compared with conventional PPIs.

Competing interests

Tetsuo Takehara received a research grant from the Takeda Pharmaceutical Company. All other authors have no conflict of interest to declare.

References

- [1] Akasaka T, Nishida T, Tsutsui S et al. Short-term outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasm: multicenter survey by Osaka University ESD study group. *Dig Endosc* 2011; 23: 73–77
- [2] Kato M, Nishida T, Hamasaki T et al. Outcomes of ESD for patients with early gastric cancer and comorbid liver cirrhosis: a propensity score analysis. *Surg Endosc* 2015; 29: 1560–1566
- [3] Yoshioka T, Nishida T, Tsujii M et al. Renal dysfunction is an independent risk factor for bleeding after gastric ESD. *Endosc Int Open* 2015; 3: E39–E45
- [4] Nishida T, Kato M, Yoshio T et al. Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions. *World J Gastrointest Endosc* 2015; 7: 524–531
- [5] Fujimoto K, Fujishiro M, Kato M et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig Endosc* 2014; 26: 1–14
- [6] Ono S, Fujishiro M, Yoshida N et al. Thienopyridine derivatives as risk factors for bleeding following high risk endoscopic treatments: Safe Treatment on Antiplatelets (STRAP) study. *Endoscopy* 2015; 47: 632–637
- [7] Cho SJ, Choi IJ, Kim CG et al. Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms. *Endoscopy* 2012; 44: 114–121
- [8] Tounou S, Morita Y. Gastric and duodenal endoscopic submucosal dissection in patients on aspirin therapy has increased risk of hemorrhage but is feasible. *Gastroenterol Endosc* 2011; 53: 3326–3335
- [9] Takizawa K, Oda I, Gotoda T et al. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection—an analysis of risk factors. *Endoscopy* 2008; 40: 179–183
- [10] Okada K, Yamamoto Y, Kasuga A et al. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; 25: 98–107
- [11] Suzuki H, Takizawa K, Hirasawa T et al. Short-term outcomes of multicenter prospective cohort study of gastric endoscopic resection: ‘Real-world evidence’ in Japan. *Dig Endosc* 2019; 31: 30–39
- [12] Uedo N, Takeuchi Y, Yamada T et al. Effect of a proton pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: a prospective randomized controlled trial. *Am J Gastroenterol* 2007; 102: 1610–1616
- [13] Hershcovici T, Fass R. Management of gastroesophageal reflux disease that does not respond well to proton pump inhibitors. *Curr Opin Gastroenterol* 2010; 26: 367–378
- [14] Li XQ, Andersson TB, Ahlstrom M et al. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab Dispos* 2004; 32: 821–827
- [15] Katsuki H, Nakamura C, Arimori K et al. Genetic polymorphism of CYP2C19 and lansoprazole pharmacokinetics in Japanese subjects. *Eur J Clin Pharmacol* 1997; 52: 391–396
- [16] Suri A, Bramer SL. Effect of omeprazole on the metabolism of cilostazol. *Clin Pharmacokinet* 1999; 37: (Suppl. 02): 53–59
- [17] Malhotra K, Katsanos AH, Bilal M et al. Cerebrovascular outcomes with proton pump inhibitors and thienopyridines: A systematic review and meta-analysis. *Stroke* 2018; 49: 312–318
- [18] Ho PM, Maddox TM, Wang L et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; 301: 937–944
- [19] Sakurai Y, Mori Y, Okamoto H et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects – a randomised open-label crossover study. *Aliment Pharmacol Ther* 2015; 42: 719–730
- [20] Jenkins H, Sakurai Y, Nishimura A et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment Pharmacol Ther* 2015; 41: 636–648
- [21] Echizen H. The first-in-class potassium-competitive acid blocker, vonoprazan fumarate: Pharmacokinetic and pharmacodynamic considerations. *Clin Pharmacokinet* 2016; 55: 409–418

- [22] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017; 20: 1–19
- [23] Maekawa S, Nomura R, Murase T et al. Complete closure of artificial gastric ulcer after endoscopic submucosal dissection by combined use of a single over-the-scope clip and through-the-scope clips (with videos). *Surg Endosc* 2015; 29: 500–504
- [24] Tsuji Y, Fujishiro M, Kodashima S et al. Polyglycolic acid sheets and fibrin glue decrease the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms (with video). *Gastrointest Endosc* 2015; 81: 906–912
- [25] Tounou S, Morita Y, Hosono T. Continuous aspirin use does not increase post-endoscopic dissection bleeding risk for gastric neoplasms in patients on antiplatelet therapy. *Endosc Int Open* 2015; 3: E31–E38
- [26] Lim JH, Kim SG, Kim JW et al. Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms? *Gastrointest Endosc* 2012; 75: 719–727
- [27] Sanomura Y, Oka S, Tanaka S et al. Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic submucosal dissection for early gastric cancer. *Gastric Cancer* 2014; 17: 489–496
- [28] Kataoka Y, Tsuji Y, Hirasawa K et al. Endoscopic tissue shielding to prevent bleeding after endoscopic submucosal dissection: a prospective multicenter randomized controlled trial. *Endoscopy* 2019; 51: 619–627
- [29] Green FW Jr., Kaplan MM, Curtis LE et al. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology* 1978; 74: 38–43
- [30] Kagawa T, Iwamuro M, Ishikawa S et al. Vonoprazan prevents bleeding from endoscopic submucosal dissection-induced gastric ulcers. *Aliment Pharmacol Ther* 2016; 44: 583–591
- [31] Hamada K, Uedo N, Tonai Y et al. Efficacy of vonoprazan in prevention of bleeding from endoscopic submucosal dissection-induced gastric ulcers: A prospective randomized phase II study. *J Gastroenterol* 2019; 54: 122–130
- [32] Horikawa Y, Mizutamari H, Mimori N et al. Short-term efficacy of potassium-competitive acid blocker following gastric endoscopic submucosal dissection: a propensity score analysis. *Scand J Gastroenterol* 2018; 53: 243–251
- [33] Tsuchiya I, Kato Y, Tanida E et al. Effect of vonoprazan on the treatment of artificial gastric ulcers after endoscopic submucosal dissection: Prospective randomized controlled trial. *Dig Endosc* 2017; 29: 576–583
- [34] Maruoka D, Arai M, Kasamatsu S et al. Vonoprazan is superior to proton pump inhibitors in healing artificial ulcers of the stomach post-endoscopic submucosal dissection: A propensity score-matching analysis. *Dig Endosc* 2017; 29: 57–64
- [35] Yamasaki A, Yoshio T, Muramatsu Y et al. Vonoprazan is superior to rabeprazole for healing endoscopic submucosal dissection: Induced ulcers. *Digestion* 2018; 97: 170–176
- [36] Hirai A, Takeuchi T, Takahashi Y et al. Comparison of the effects of vonoprazan and lansoprazole for treating endoscopic submucosal dissection-induced artificial ulcers. *Dig Dis Sci* 2018; 63: 974–981
- [37] Ishii Y, Yamada H, Sato T et al. Effects of vonoprazan compared with esomeprazole on the healing of artificial postendoscopic submucosal dissection ulcers: A prospective, multicenter, two-arm, randomized controlled trial. *Gastroenterol Res Pract* 2018; 2018: 1615092
- [38] Jaruvongvanich V, Poonsombudlert K, Ungprasert P. Vonoprazan versus proton-pump inhibitors for gastric endoscopic submucosal dissection-induced ulcers: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2018; 30: 1416–1421
- [39] Mochizuki S, Uedo N, Oda I et al. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. *Gut* 2015; 64: 397–405