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Comparison of the Use of Vonoprazan and Proton Pump Inhibitors for the Treatment of Peptic Ulcers Resulting from Endoscopic Submucosal Dissection: A Systematic Review and Meta-Analysis

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Data Collection B
Statistical Analysis C
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Manuscript Preparation E
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Background: Currently, proton pump inhibitors (PPIs) are the first-line treatment for ulcers resulting from endoscopic submucosal dissection (ESD). Vonoprazan is a new oral potassium-competitive acid blocker (P-CAB). The aim of this systematic review and meta-analysis was to compare the efficacy, safety, and tolerance of vonoprazan with PPIs in the treatment of peptic ulcers resulting from ESD.





Material/Methods: Published results of randomized clinical trials (RCTs) comparing vonoprazan with PPIs in the treatment of ulcers resulting from ESD were identified up to March 2018. The main clinical endpoints evaluated were healing rate and adverse events. The meta-analysis included quality assessment of the studies, statistical analysis of endpoints, and sensitivity analysis using Revman version 5.3 meta-analysis software.

Results: Systematic literature review identified seven published studies that included 548 patients. Five studies were published as full-text manuscripts, and two studies were published as abstracts. Meta-analysis of the vonoprazan treatment, compared with PPI treatment, for ESD showed that the pooled relative risk (RR) of healing rate was 0.64 (95% CI, 0.33–1.22) for the 4-week study group and 0.98 (95% CI, 0.84–1.15) for the 8-week study group. The RR for adverse events was 0.65 (95% CI, 0.31–1.38) ($P > 0.05$). No statistical evidence of publication bias was found.

Conclusions: The findings of the systematic review and meta-analysis showed that the efficacy of vonoprazan was comparable with PPIs for the treatment of peptic ulcers following ESD. Further studies are required to support the safety and efficacy of vonoprazan compared with different types of PPIs.

MeSH Keywords: **Meta-Analysis • Peptic Ulcer • Proton Pump Inhibitors**

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Background

Endoscopic submucosal dissection (ESD) is a commonly used method for the treatment of gastrointestinal adenoma, precancerous lesions, or early-stage cancer without metastases, due to its clinical effectiveness and comparative safety. However, sometimes a large area of dissection results in post-ESD ulcers which can result in severe complications, including delayed bleeding and perforation, especially in the upper gastrointestinal tract, because of the effects of gastric acid on the ulcerated mucosa. The incidence of delayed bleeding from ruptured vessels and perforation following ESD has been reported to be approximately 3.5% [1]. Therefore, reducing gastric acid secretion following ESD of the upper gastrointestinal tract is required, and treatment with proton pump inhibitors (PPIs) have been commonly used. Uedo et al. [2] conducted a randomized controlled trial (RCT) that showed that PPI treatment was more effective than the use of histamine H₂-receptor antagonists in the prevention of bleeding from ulcers following ESD. Also, prophylactic coagulation of visible vessels is now recommended by many clinicians to prevent post-ESD bleeding [3].

Vonoprazan (Takecab®) (Takeda Pharmaceutical Co. Ltd., Tokyo, Japan) is a new oral potassium-competitive acid blocker (P-CAB), which received first approval in 2015 in Japan [4]. Vonoprazan competitively blocks the potassium-binding site of H⁺/K⁺-ATPase and the inhibitory action on gastric acid secretion of this novel drug is more stable than that of PPIs due to its higher pK_a value [5]. In preclinical research studies, vonoprazan has been shown to accumulate at high concentrations in cells of gastric glands and is slowly cleared, resulting in a more sustained and greater increase in gastric PH [6,7].

Given its strong inhibitory effect on gastric acid production, vonoprazan has been shown to be effective in the treatment of gastroesophageal reflux disease (GERD), peptic ulcers, and other gastric acid-related disorders [8–12]. Some recent comparative studies on the treatment of peptic ulcers following ESD have shown that vonoprazan had a stronger acid-inhibiting effect than PPIs [13,14]. However, these findings were not supported by two recent phase 3 RCTs [9]. There remains controversy regarding whether the use of vonoprazan is more effective than PPIs when used to heal iatrogenic peptic ulcers after ESD [14].

Therefore, this systematic review and meta-analysis aimed to compare the efficacy, safety, and tolerance of vonoprazan with PPIs in the treatment of peptic ulcers resulting from ESD.

Material and Methods

Search strategy

The systematic review of the literature and the meta-analysis were performed up to March 2018. Relevant publications were selected that compared vonoprazan with proton pump inhibitors (PPIs) for the treatment of ulcers resulting from endoscopic submucosal dissection (ESD). The following databases were searched: Web of Knowledge, PubMed, Embase, and the Cochrane Central Register of Controlled Trials. The following search terms were used: 'vonoprazan' or 'Takecab' or 'potassium-competitive' or 'acid blocker' or 'P-CAB,' and 'proton pump inhibitor' or 'PPI' or 'PPIs,' and 'endoscopic submucosal dissection' or 'ESD' or 'artificial ulcers' or 'post-ESD.' Also, all published studies in all forms of publication were identified, irrespective of outcomes, country, and language. The systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Inclusion and exclusion criteria

Irrelevant studies were initially excluded based on the content of their titles and abstracts. Potentially relevant published studies underwent a review of the entire published manuscript. The selection criteria for inclusion in the meta-analysis included: patients who has been diagnosed by upper gastrointestinal endoscopy; patients who underwent ESD for endoscopic mucosal lesions, adenoma, or early-stage gastric cancer; randomized controlled trials (RCTs) that compared the efficacy of vonoprazan 20 mg/day with standard-dose PPIs in the treatment of post-ESD peptic ulcers; patients who did not receive other medical treatments before the trials; study periods of at least 4 weeks; endoscopic assessment of the healing of the ulcers at 4 weeks or 8 weeks following ESD. There were no limitations on patient nationality or ethnicity. The decision to include or exclude the published studies was made separately by two researchers, and any differences in opinion were settled by consensus with the inclusion of a third study researcher.

Data extraction

Two reviewers independently extracted the following information, which was collected using an Excel spreadsheet: first author; year of publication; publication type; country of the study; publication language; therapeutic strategy; post-ESD follow-up period; clinical outcomes, including healing rate, shrinkage rate, and rate of adverse events. In this meta-analysis, the primary outcome measure was the comparison of the healing rates of post-ESD peptic ulcers between vonoprazan-based therapy and PPI-based therapy. The secondary outcome safety and tolerance events included delayed bleeding, perforation, and hepatic injury.

Quality of methodology

Quality assessment and risk of bias in the identified RCTs was performed using the Cochrane Risk of Bias Assessment Tool [16]. Two investigators individually assessed the methodological quality of each RCT.

Statistical analysis

Statistical analysis of data was performed using Review Manager (RevMan) version 5.3. Multiple comparisons were performed, and for each comparison, a 95% confidence interval (CI) of the pooled risk ratios (RRs) were calculated to analyze the variables. The Mantel-Haenszel method, or fixed-effects model, was used. However, when there was clear study heterogeneity, a random-effects model was chosen. Two methods were used to investigate study heterogeneity, the Cochrane's Q test considered the study to be heterogeneous if the P-value was <0.1 , and I^2 statistics values $\geq 25\%$, $\geq 50\%$, and $\geq 75\%$ indicated mild, moderate, and substantial study heterogeneity, respectively. All P-values were two-tailed, and the level of statistical significance was 0.05 in all tests. A funnel plot was performed to assess publication bias.

Results

A qualitative summary of the systematic literature review

The literature search strategy initially identified 46 potentially relevant published studies, from which seven eligible published randomized controlled trials (RCTs) were selected, which included data from 548 patients (Figure 1) [17–23]. The seven identified studies compared vonoprazan with proton pump inhibitors (PPIs) for the treatment of ulcers resulting from endoscopic submucosal dissection (ESD), which fulfilled the inclusion criteria for the meta-analysis [17–23]. Five of the studies were published as full-text manuscripts [17,20–23], and the other two were meeting abstracts [18,19]. Table 1 shows the baseline characteristics of these seven studies, all of which were published in the English language between 2016 and 2018, which included patients who were recruited to studies between 2015 to 2017 in Japan. Table 2 summarizes the outcomes of these seven trials. The results of the quality assessment of the meta-analysis data are presented in Figure 2.

Meta-analysis findings on healing rates of post-ESD ulcers at 4 weeks and 8 weeks

An analysis was performed of the studies that provided 4-week or 8-week healing rates of post-ESD ulcers. As shown in Figure 3A and 3B, there was no difference between the healing rates of the vonoprazan-based therapy and PPI-based

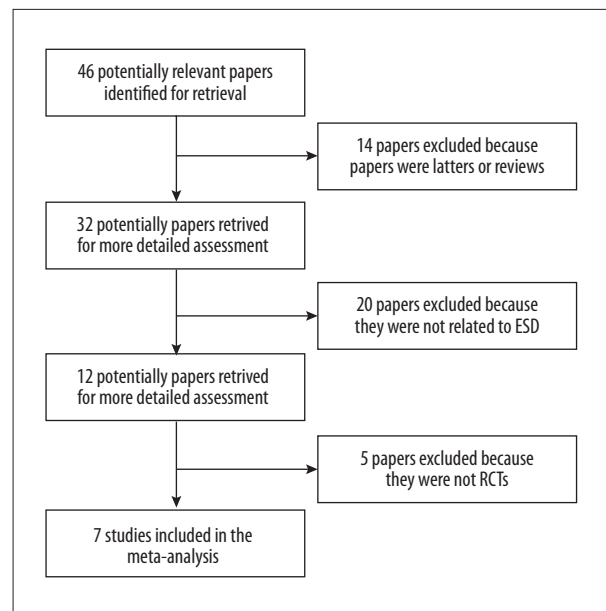


Figure 1. Flowchart of the study design and literature search performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

therapy. The pooled relative risk (RR) of healing rate was 0.64 (95% CI, 0.33–1.22) for the 4-week study group, and 0.98 (95% CI, 0.84–1.15) for the 8-week study group. Moderate heterogeneity was identified in the 8-week group using Cochrane's Q test ($df=4$; $P=0.04$; $I^2=60\%$).

In these five trials published as full texts, three used lansoprazole as control, and the other two used esomeprazole. To identify the reasons for the difference between relevant trials in the 8-week group, a subgroup analysis was performed for these studies. The random-effects model showed that the relative efficacy of the healing rates was different for the esomeprazole-treated group and the RR was 1.14 (95% CI, 0.99–1.32) and in the lansoprazole-treated group, the RR was 0.88 (95% CI, 0.72–1.06). Heterogeneity testing using Cochrane's Q test showed subgroup differences ($df=1$; $P=0.03$; $I^2=79.0\%$). The I^2 value of the lansoprazole-treated group decreased from 60% to 38%, and the I^2 value of the esomeprazole-treated group decreased to 7%.

Meta-analysis findings of adverse events

In the seven published RCTs, all of them provided information of delayed bleeding rate, but only two articles included the perforation rate and one article described the hepatic injury. As shown in Figure 4, the fixed-effects model showed no significant difference in adverse event rates between the vonoprazan-based therapy and PPI-based therapy. The pooled RR was 0.65 (95% CI, 0.31–1.38) and there is no significant heterogeneity

Table 1. Characteristics of the studies enrolled in the meta-analysis.

First author	Publication date	Year of patients recruitment	Country	Publication type	Patients Enrolled (n)	Therapy strategy	No. of weeks of follow-up
Ai et al. [17]	2018	2015–2017	Japan	Full-text	149/127	O: 20 mg iv bid for first 2 days + po. V: 20 mg qd or L: 30 mg qd.	8
Koizumi et al. [18]	2016	2015–2016	Japan	Abstract	37/35	V: 20 mg po qd or L: 30mg qd.	8
Komori et al. [19]	2016	2015–2016	Japan	Abstract	40/33	V: 20 mg po qd or R: 10 mg qd.	4
Tsuchiya et al. [20]	2017	2015–2016	Japan	Full-text	92/80	O: 20 mg iv bid for first 2 days + po. V: 20 mg qd or E: 20 mg qd.	8
Hamada et al. [21]	2018	Not stated	Japan	Full-text	140/139	V: 20 mg po qd or L: 30 mg qd.	8
Takahashi et al. [22]	2016	2015–2016	Japan	Full-text	30/26	O: 20 mg iv bid for first 2 days + po. V: 20 mg qd or L: 30 mg qd.	4
Ishii et al. [23]	2018	2015–2017	Japan	Full-text	60/53	O: 20 mg iv bid for first 2 days + po. V: 20 mg qd or E: 20 mg qd.	8

RCT – randomized controlled trial; V – vonoprazan; L – lansoprazole; E – esomeprazole; R – rabeprazole.

Table 2. Results of the enrolled randomized controlled trials (RCTs).

RCTs	Regimen	Healing rate	Delayed bleeding	Shrinkage rate	Perforation
Ai et al., 2018 [17]	V	86.89% (53/61)	6.56% (4/61)	Not stated	1.64% (1/61)
	L	90.90% (60/66)	6.06% (4/66)		3.03% (2/66)
Koizumi et al., 2016 [18]	V	57.90%	5.56% (1/18)	99.60%	Not stated
	L	87.50%	5.89% (1/17)		
Komori et al., 2016 [19]	V	Not stated	5.56% (1/18)	93.3%	Not stated
	R		0 (0/15)		
Tsuchiya et al., 2017 [20]	V	94.87% (37/39)	0 (0/39)	Not stated	0 (0/39)
	E	78.05% (32/41)	7.32% (3/41)		2.44% (1/41)
Hamada et al., 2018 [21]	V	Not stated	4.35% (3/69)	Not stated	Not stated
	L		5.71% (4/70)		
Takahashi et al., 2016 [22]	V	78.57% (11/14)	0 (0/14)	95.3%	Not stated
	L	91.67% (11/12)	0 (0/12)		
Ishii et al., 2018 [23]	V	88.9% (24/27)	0 (0/27)	100%	Not stated
	E	84.6% (22/26)	0 (0/26)		

RCT – randomized controlled trial; V – vonoprazan; L – lansoprazole; E – esomeprazole; R – rabeprazole.

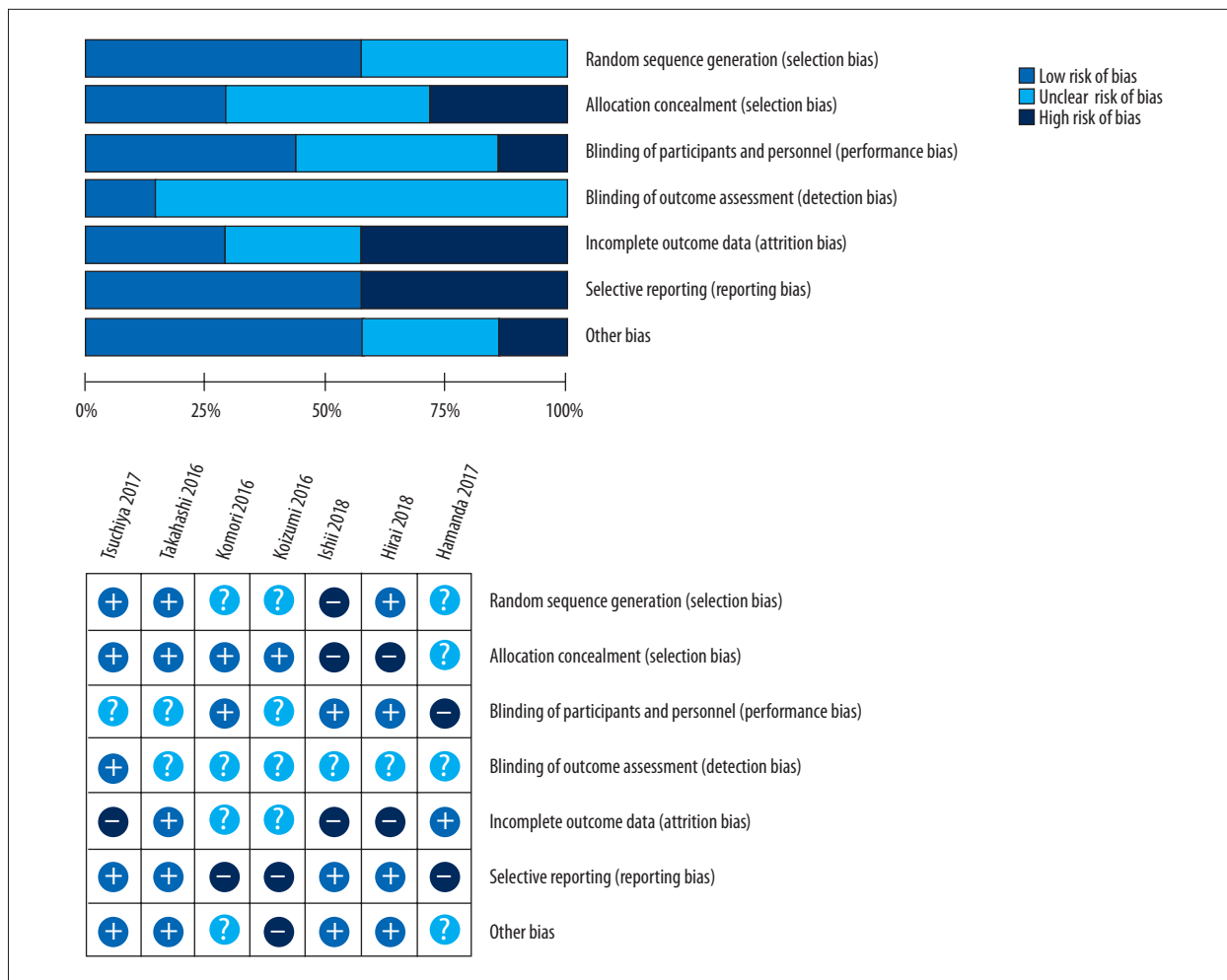


Figure 2. The results of the quality assessment of the enrolled studies.

among these studies, as determined by Cochrane's Q test (df=4; P=0.77; I²=0%).

Sensitivity analysis

The funnel plot for the rate of adverse events showed some asymmetry, indicating the occurrence of publication bias (Figure 5). Accordingly, a sensitivity analysis was conducted to evaluate the reliability of this meta-analysis. In five trials, the duration of therapy was 8 weeks, and the duration of the remaining two trials was 4 weeks. A sensitivity analysis was undertaken that included the 8-week treatment trials, which did not show significant differences (Table 3). A further sensitivity analysis was performed that only included trials using lansoprazole treatment, and the sensitivity analysis did not show any significant differences (Table 3).

Discussion

Proton pump inhibitors (PPIs) are commonly used in the management of conditions associated with increased acid production and ulceration of the upper gastrointestinal tract, including gastroesophageal reflux disease (GERD), Barrett's esophagus, and *Helicobacter pylori*-associated peptic ulcer. Since the development of first-generation PPIs, similar drugs have been developed and shown to be effective. The long-term use of PPIs can be associated with adverse effects including bone fracture, myocardial infarction, and infections, although the risk of these complications is quite low [24]. Although changing the type of PPI or adding other medications have been proposed, there is currently a lack of evidence to provide the basis for guidelines for combination therapy [25].

Vonoprazan (Takecab®) (Takeda Pharmaceutical Co. Ltd., Tokyo, Japan) is a new potassium-competitive acid blocker (P-CAB) and is a novel treatment for peptic ulcer disease that inhibits gastric acid production that first received approval in Japan in 2015.

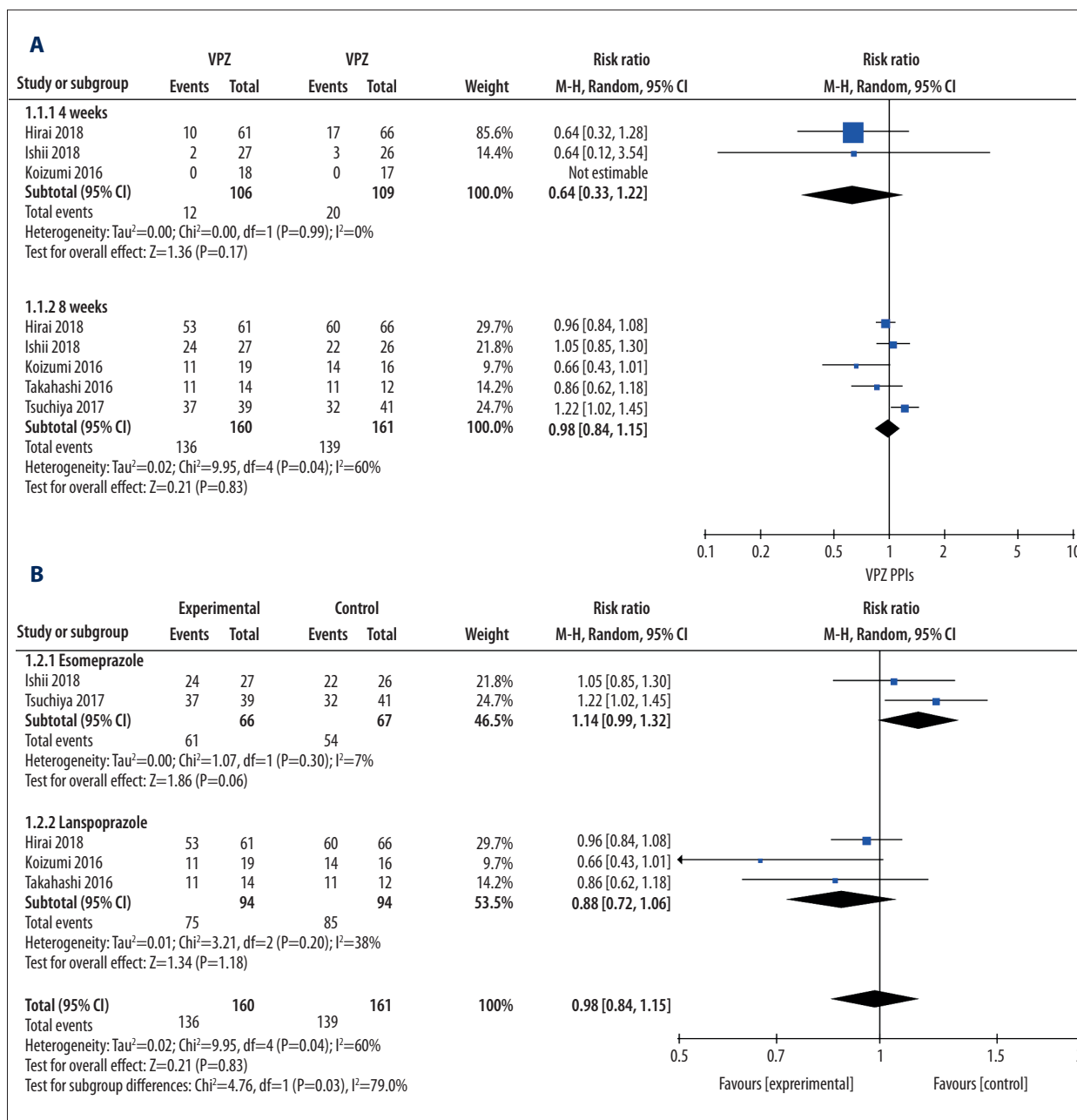


Figure 3. Meta-analysis of the healing rate and subgroup analysis. (A) Meta-analysis of the healing rate and subgroup analysis in terms of esomeprazole and lansoprazole treatment of patients with ulcers resulting from endoscopic submucosal dissection (ESD). (B) Subgroup analysis at 8 weeks and 4 weeks. VPZ – vonoprazan; PPIs – proton pump inhibitors; ESD – endoscopic submucosal dissection.

Therefore, the majority of randomized controlled trials (RCTs) on vonoprazan have been conducted in Japanese hospitals or research centers. Clinically, the safety and efficacy of vonoprazan remain to be established [24]. Therefore, this study aimed to compare the effects of vonoprazan and PPIs for the treatment of ulcers resulting from endoscopic submucosal dissection (ESD) by performing a systematic review and meta-analysis.

In this meta-analysis, pooled data were analyzed from seven published studies that included 548 patients. The results of this meta-analysis showed no apparent difference between 20 mg/day of vonoprazan and standard doses of PPIs in term of treating post-ESD peptic ulcers. The healing rate of PPI-based therapy had a marginally, but not significantly improved efficacy when compared with vonoprazan-based therapy. In term of safety, the meta-analysis showed that adverse effects,

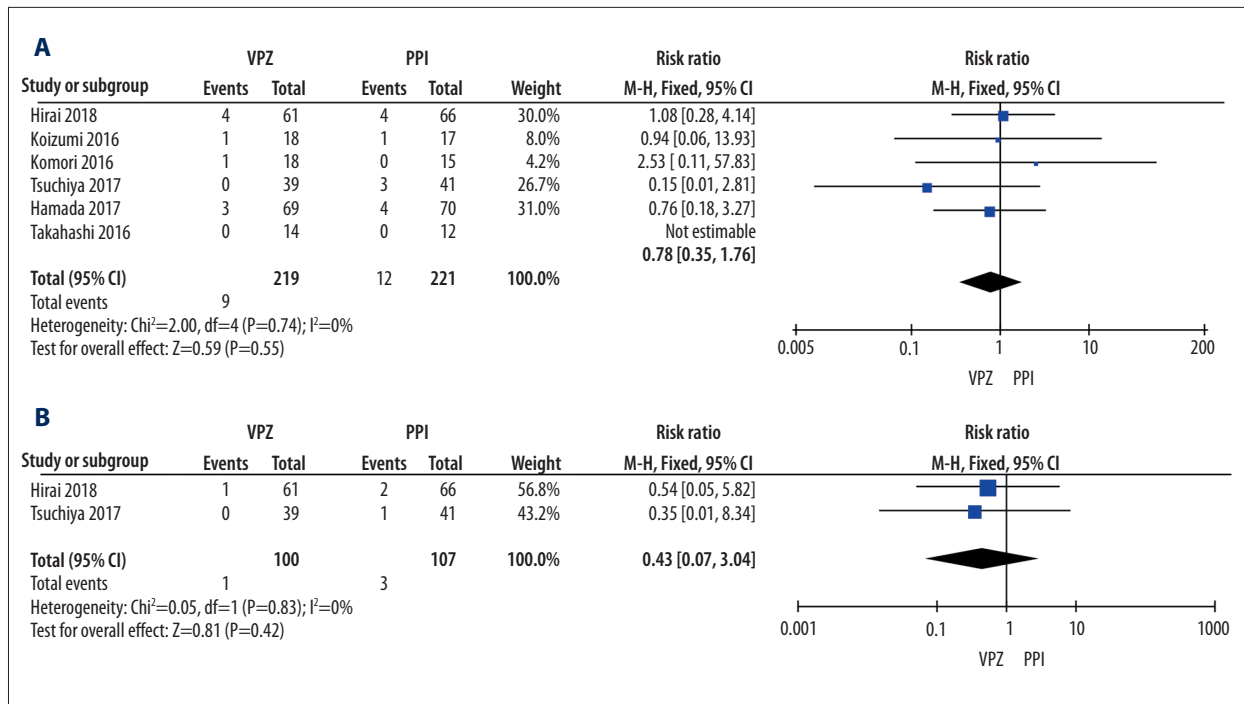


Figure 4. Meta-analysis of the bleeding rate and perforation rate. **(A)** Meta-analysis of the delayed bleeding rate following treatment with vonoprazan (VPZ) and proton pump inhibitors (PPIs) in patients with ulcers resulting from endoscopic submucosal dissection (ESD). **(B)** Meta-analysis of the perforation rate following treatment with vonoprazan (VPZ) and PPIs in patients with ulcers resulting from ESD. VPZ – vonoprazan; PPIs – proton pump inhibitors; ESD – endoscopic submucosal dissection.

including delayed bleeding and perforation, showed fewer adverse effects in the vonoprazan-treated group, which did not reach statistical significance. These findings not only add to current evidence obtained from clinical trials but also call for more high-quality controlled clinical studies.

This meta-analysis study had several limitations. Two clinical trials were published in abstract form only, which might have resulted in the acquisition of limited data for meta-analysis. Also, vonoprazan was first approved for clinical use in Japan, and the majority of published clinical trials were undertaken in Japan, and the results of further trials are still needed from multiple countries. The observation periods of the enrolled studies were limited, and so chronic adverse events, such as bone fracture, myocardial infarction, and infection, could not be evaluated. In view of the moderate heterogeneity identified by meta-analysis on the healing rate (Figure 3A), it appeared that combining lansoprazole and esomeprazole with

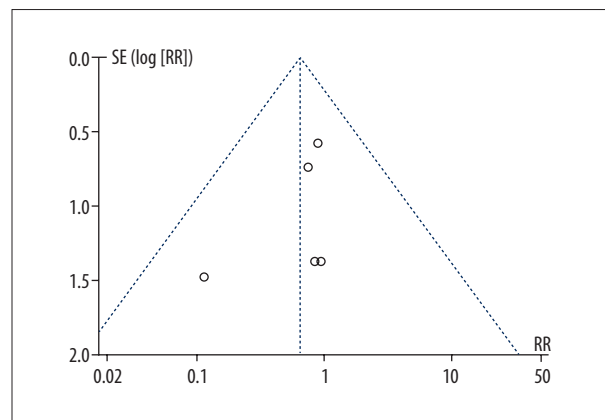


Figure 5. Funnel plot of the findings of the enrolled trials based on healing rate and delayed bleeding rate.

Table 3. Sensitivity of the meta-analysis of the enrolled trials.

Analysis	Trials (n)	Z-value	RR (95% CI)	P-value
Treatment lasting 8 weeks	4	0.80	0.71 (0.30–1.65)	0.42
Trials using lansoprazole as a control	4	0.17	0.92 (0.37–2.32)	0.86

RR – risk ratio; CI – confidence interval.

vonoprazan had a different outcome and so further meta-analysis is needed to compare lansoprazole and esomeprazole with vonoprazan separately.

Conclusions

Systematic review and meta-analysis compared the efficacy, safety, and tolerance of vonoprazan with proton pump inhibitors

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