Systematic Review and Meta-Analysis

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Vonoprazan vs proton pump inhibitors in treating post-endoscopic submucosal dissection ulcers and preventing bleeding

A meta-analysis of randomized controlled trials and observational studies

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Abstract

Background: Vonoprazan is a potassium-competitive acid blocker (P-CAB) that is frequently used in Japan for *Helicobacter pylori (H. pylori)* eradication, treatment of gastroesophageal reflux disease, and treatment of post endoscopic submucosal dissection (ESD) complications. We sought to determine if vonoprazan was superior to proton pump inhibitors (PPIs) for treating ESD-induced ulcers (as assessed by ulcer healing and shrinkage ratios) and preventing delayed bleeding over various treatment durations (2, 4, and 8 weeks).

Methods: We collected randomized controlled trials (RCTs) and observational studies that discussed the effectiveness of vonoprazan and PPIs on ESD-induced ulcers and bleeding from PubMed, Cochrane Library, ClinicalTrials.gov, and Google Scholar. Studies were selected according to pre-established eligibility criteria and data were extracted separately by 2 researchers with double-check. We used the Cochrane risk of bias tool to assess RCTs and the Newcastle–Ottawa Quality Assessment Scale to assess observational studies. Meta-analyses, based on the random-effects model, were conducted to compare differences in ulcer shrinkage ratios (%) and odds ratios (ORs) for ulcer healing and delayed bleeding. Publication bias was evaluated using funnel plots and Egger regression test. Heterogeneity was assessed using I^2 statistics. A sensitivity analysis was conducted to check the robustness of results. The evidential quality of the findings was assessed using the GRADE profiler.

Results: Thirteen studies were included in this meta-analysis. The OR effect sizes of vonoprazan relative to PPIs for ulcer healing were 1.33 ($P = .13$) with a 95% CI (0.33–3.21) at 4 weeks and 1.48 ($P = .09$) with a 95% CI (0.81–5.20) at 8 weeks. The overall effect size for the shrinkage ratio was 12.24% ($P = .16$) with a 95% CI (−4.96–29.44) at 2 weeks. The effect size of its subgroup of *H. pylori*-positive patients was 19.51% ($P < .001$) with a 95% CI (11.91–27.12). The overall OR for the occurrence of delayed bleeding was 0.66 ($P = .26$) with a 95% CI (0.32–1.35). After excluding combination drug studies, the overall ORs between vonoprazan and PPIs on ulcer healing and delayed bleeding were 1.44 and 0.76, respectively.

Conclusion: During the first 2 weeks of treatment, vonoprazan was more effective than PPIs for treating *H. pylori*-positive patients with ESD-induced gastric ulcers.

Abbreviations: EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, GRADE = Grading of Recommendations Assessment, Development and Evaluation, OR = odds ratio, P-CAB = Potassium-competitive acid blocker, PPI = proton pump inhibitors, PRISMA = Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized controlled trial.

Keywords: bleeding, meta-analysis, proton pump inhibitors, systematic review, ulcer, vonoprazan

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1. Introduction

Compared to gastrectomy, endoscopic submucosal dissection (ESD) and conventional endoscopic mucosal resection (EMR) are significantly less-invasive procedures for treating intraepithelial gastric neoplasms (gastric adenoma and early gastric cancer).[1,2] In Japan, ESD is considered superior to conventional EMR[3] owing to reducing the rate of local tumor recurrence more effectively[4,5] and allows for en bloc resection of large lesions.[1] Unfortunately, ESD tends to create larger iatrogenic ulcers and is associated with a higher risk of delayed bleeding complications.[1] Given the frequency with which these complications occur, PPIs are widely prescribed to treat ESD-induced ulcers.[6]

Vonoprazan (TAK-438), a novel potassium-competitive acid blocker (P-CAB) that inhibits gastric H^+/K^+-ATPase activity, was approved for clinical use in Japan in December 2014.[7] Unlike PPIs, P-CABs inhibit proton pump enzyme activity in a reversible and potassium-competitive manner.[8] Its treatment effects are more rapid, potent, and better inhibit gastric acid than PPIs.[9] Moreover, compared to PPI prodrugs,[10] P-CABs are unaffected by the timing of meals and by CYP2C19 polymorphisms.[11] Furthermore, vonoprazan is a preferred first-line therapy for *Helicobacter pylori* (*H. pylori*) eradication.[12–14]

Some studies have examined the effectiveness of vonoprazan compared with PPIs for treating ESD-induced ulcers at 2,[15,16] 4,[15,17–24] and 8 weeks.[15,17–19,22,25–27] However, the results of these studies are inconsistent and controversial. Typically, ESD-induced ulcers heal within 8 weeks regardless of their size, location,[28] presence or absence of *H. pylori* infection, and extent of gastric atrophy.[29] However, Otsuka et al reported that most ESD-induced ulcers were actually healed by 4 weeks, which implies that early-phase (by 2 weeks) evaluation is important for effective drug treatment. The previous meta-analyses[30–32] did not assess 2-week evaluation points and featured biased study selection and data extraction. Furthermore, several additional clinical trials[18,20,25] were published after these meta-analyses. Therefore, it is unknown if vonoprazan is superior to PPIs for healing ESD-induced ulcers and preventing post-ESD delayed bleeding, especially during the early post-ESD phase. In light of this, we critically evaluated the effectiveness of vonoprazan vs PPIs for treating ESD-induced ulcers during the first 2, 4, and 8 weeks post-ESD. We also compared vonoprazan and PPIs for the prevention of delayed bleeding after ESD.

2. Methods and analyses

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2015 checklist[33] (Appendix A, http://links.lww.com/MD/D880) and was designed in accordance with PRISMA guidelines.[34] The protocol of this systematic review and meta-analysis[35] was registered within the International Prospective Register of Systematic Reviews (PROSPERO) database with the identifier CRD42018116855.

2.1. Data sources and search strategies

We conducted an extensive search of PubMed, the Cochrane Library, ClinicalTrials.gov, and Google Scholar (from inception through 15 March 2019). The search strategy included the following keywords

"Vonoprazan," "TAK-438," and "ESD." (Appendix B, http://links.lww.com/MD/D881) If reported data were ambiguous, we subsequently initiated contact with the original authors. Study selection was conducted using a PRISMA-compliant flow chart.

2.2. Eligibility criteria

Eligible studies were selected in accordance with the following inclusion and exclusion criteria:

2.2.1. Study design. Randomized controlled trials (RCTs) and observational studies, such as cohort and case control studies, were included. Abstract articles, Case reports, review articles, preclinical studies, and other non-relevant studies were excluded.

2.2.2. Follow-up periods. In order to observe changes in the shrinkage ratios or scar stages of ESD-induced ulcers during the early post-ESD phase, we included only RCTs and observational studies with follow-up periods ≥2 weeks.

2.2.3. Participants. This meta-analysis included only RCTs and observational studies of patients with ESD-induced ulcers who were aged ≥18 years.

2.2.4. Interventions. This meta-analysis included only RCTs and observational studies of vonoprazan monotherapy or those that combined vonoprazan with a mucosal protective agent.

2.2.5. Comparators. This meta-analysis included only RCTs and observational studies that used a PPI monotherapy or those that combined a PPI with a mucosal protective agent therapy as comparator treatments.

2.2.6. Outcomes. This meta-analysis included RCTs and observational studies that measured ulcer healing, changes in shrinkage ratios, and instances of delayed bleeding post-ESD. We excluded studies that did not include one of these three outcomes. Percent ulcer healing included:

(1) S1 and S2 stage ulcers, in accordance with the Sakita-Miwa classification Scheme[36] or
(2) at least 90% shrinkage ratio at 4-week follow-up and 100% shrinkage ratio at 8-week follow-up.

The *shrinkage ratio* was defined as: (1–ulcer size at 2, 4, or 8 weeks after ESD/initial ulcer size) × 100. *Delayed bleeding* was defined as a reduction in hemoglobin level to ≥2 g/dL.

2.3. Study selection and data extraction

Two reviewers used the same eligibility evaluation form to evaluate RCTs and observational studies. Conflicting evaluations were discussed with a third investigator until the reviewers reached consensus.

Data were extracted by one reviewer and verified by another. In addition to the outcomes, we extracted the following information:

(1) authors and publication year,
(2) interventions (doses of vonoprazan, PPIs, and mucosal protective agents),
(3) participants' baseline characteristics,
(4) follow-up period duration,
(5) study design, and
(6) study findings.

2.4. Quality assessment

The Cochrane risk of bias tool[37] was used to assess the design, conduction, and outcomes of the included RCTs. The Newcastle–

Ottawa Quality Assessment Scale[38] was used to assess the selection, comparability, and outcomes of the observational studies. The quality of each study was assessed by one reviewer and verified by another. The quality of evidence was determined with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[39] The analysis was conducted using the GRADE profiler, where 5 down-grading and 3 up-grading criteria are adopted.

2.5. Data synthesis and analysis

This meta-analysis was based on the random-effects model and conducted using RevMan version 5.3.[40] Outcomes such as ulcer healing and delayed bleeding were presented as odds ratios with 95% CIs. We measured shrinkage ratio as the mean difference with 95% CIs. Funnel plots and Egger regression test were used to assess publication bias and were carried out using R 3.5.2 (https://www.r-project.org/). The I^2 statistic, which describes variations across trials rather than sampling errors, was calculated to assess heterogeneity. I^2 values of 25, 50, and 75% indicated low, medium, and high heterogeneity, respectively. Statistical significance was set at $P < .05$ for all analyses.

2.6. Sensitivity analysis

To evaluate the robustness of our results, we performed a sensitivity analysis by excluding trials that combined the target medication with a mucosal protective agent, trials that compared the efficacy of vonoprazan at a dose of other than 20 mg daily with standard-dose of PPIs, and trials that carried a high risk of bias (if any). A meta-analysis can be considered robust or reliable if the sensitivity analysis does not significantly differ from the results.

2.7. Ethical issues

This retrospective meta-analysis was an examination of literature only, and there was no direct contact with patients. Therefore, our study did not require ethics committee approval.

3. Results

3.1. Study selection

A total of 93 citations were retrieved during the first search, of which 68 were identified via bibliographical databases and 25 were identified using the Google Scholar supplementary search tool (Fig. 1). By screening the abstracts, we excluded 69 that did not meet the eligibility criteria and 19 duplicates. After a cursory review of the remaining 24 studies, we removed one protocol, seven reviews, 1 study with a different population, one on a different disease, and one with a different intervention. This left 13 studies which were then subjected to quantitative synthesis and meta-analysis.

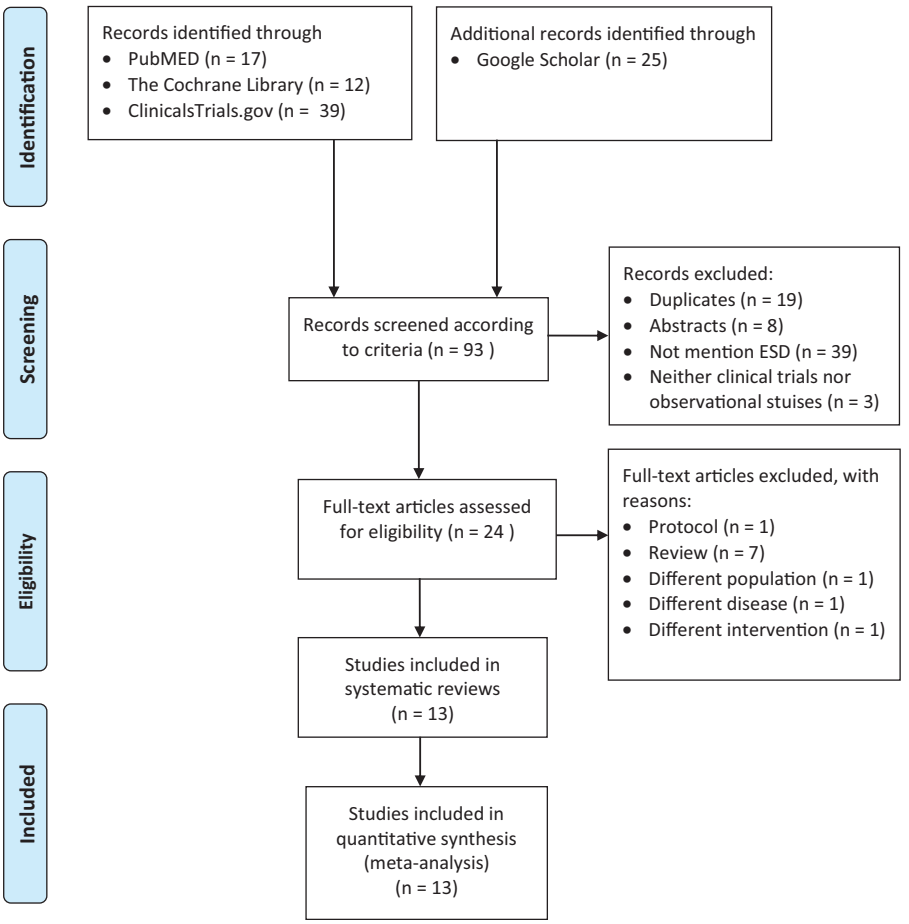

Figure 1. Flowchart of study inclusion in accordance with PRISMA guidelines.

3.2. Study characteristics

The studies included 8 RCTs and 5 observational studies (Table 1). The interventions included 10 mg vonoprazan, 20 mg vonoprazan, and 20 mg vonoprazan combined with 300 mg rebamipide. Control arm (PPI) studies included 30 mg lansoprazole, 20 mg lansoprazole plus 300 mg rebamipide, 20 mg esomeprazole, 30 mg lansoprazole, 20 mg omeprazole, 10 mg rabeprazole, and 20 mg rabeprazole. All study participants were adults (> 18 years) and had undergone ESD. The effects of

Table 1

Basic characteristics of the included studies.

					Participants' characteristics						
					Age (mean ± SD/ median; years)		*H. pylori* (+/-)		Male/Female		
Study Year	Study design	Week	Intervention (control, experiment; mg)	N	VPZ	PPI	VPZ	PPI	VPZ	PPI	Findings
Ban 2017	RCT (letter)	8	VPZ 20 mg, LPZ 30 mg	95	65.3 ± 9.7 (*H. pylori* +); 71.3 ± 10.4 (*H. pylori* -)	73.2 ± 6.9 (*H. pylori* +); 68.7 ± 7.7 (*H. pylori* -)	20/25	13/37	33/12	41/9	The 2 weeks' reduction rate in the VPZ+, the VPZ-, and the LPZ- subgroups were significantly faster than in the LPZ+ group. The scar stage achievement at 4 and 8 weeks were not statistically different between the VPZ and LPZ groups
Hamada 2018	RCT	8	VPZ 20, LPZ 30	139	70.3 ± 6.8	70.1 ± 8.5	37/40/2 (+/-/NA)	29/41/0 (+/-/NA)	51/18	57/13	There were no significant groups difference in delayed bleeding rate and ulcer healing rate in the full analysis (p = 1.000)
Hirai 2018	RCT	8	VPZ 20, LPZ 30	149	73.16 ± 7.48	69.93 ± 11.0	51/23	60/15	62/12	55/20	The shrinkage ratio and delayed bleeding were not statistically different between the VPZ and LPZ groups
Horikawa 2018	Cohort study	2	VPZ 20, LPZ 30	115	69.5 (47-84)	73.0 (60.0–86.0)	48/3/11 (+/-/pEra.)	42/3/8 (+/-/pEra.)	44/18	34/19	VPZ group experienced a significant reduction in the ulcer size compared with the LPZ group (p < .0001)
Ichida 2018	RCT	8	VPZ 20 + R 300, LPZ 30 + R 300	82	72.4 (52–89)	73.9 (58–88)	21/22	21/18	31/12	34/5	The ulcer scar rates and reduction rates were not significantly different between the two groups
Ishii 2018	RCT	8	VPZ 20 + R 300, EPZ 20 + R 300	53	70 (65.3–75)	70 (66–75.3)	7/20	8/18	23/4	22/4	The ulcer scar stage and shrinkage rate were not significantly different between the VPZ and EPZ groups
Komori 2019	RCT	4	VPZ 20, RPZ 10	33	69 ± 9.3	70.9 ± 8.8	6/15	2/13	13/5	11/4	The shrinkage ratio was significant different in VPZ and RPZ groups
Maruoka 2017	Cohort study	2	VPZ 20, EPZ 20	70	70.9 ± 9.6	71.3 ± 9.6	20/17	25/8	25/12	19/14	There was no significant difference in the ulcer healing/scar stage between VPZ and EPZ groups
Otsuka 2018	Cohort study	8	VPZ 20, LPZ 30	132	71.0 ± 8.6		68/64		100/32		There was no significant difference in the ulcer reduction rate between VPZ and LPZ groups
Shimozato 2017	Case series	8	P-CAB (VPZ 10), PPI (EPZ 20, LPZ 30, OPZ 20, RPZ 10)	73	73 (66–77)		9/64		57/16		The rate of delayed ulcer healing was not statistically different between the two groups
Takahashi 2016	RCT	4	VPZ 20, LPZ 30	26	71.9 ± 7.9	74.8 ± 8.3	4/10	5/7	12/2	10/2	There were no significant differences in the shrinkage rate of ulcers between the two drug groups
Tsuchiya 2017	RCT	8	VPZ 20, EPZ 30	80	73 (67.5–80)	74 (71–80)	25/14	19/22	27/12	30/11	The scar stage rate was significantly higher in the VPZ group than in the EPZ group
Yamazaki 2018	Cohort study	4	VPZ 20, RPZ 20	167	71 (39–87)	70 (42–90)	48/29	50/40	54/23	66/24	There was no significant difference between VPZ and RPZ in scarring rate of all lesions

EPZ = esomeprazole, *H. pylori* = *Helicobacter pylori*, LPZ = lansoprazole, N = number of patients, NA = unknown, OPZ = omeprazole, P-CAB = potassium-competitive acid blocker, pEra. = post eradication, PPI = proton pump inhibitor, R = rebamipide, RCT = randomized controlled trial, RPZ = rabeprazole, VPZ = vonoprazan.

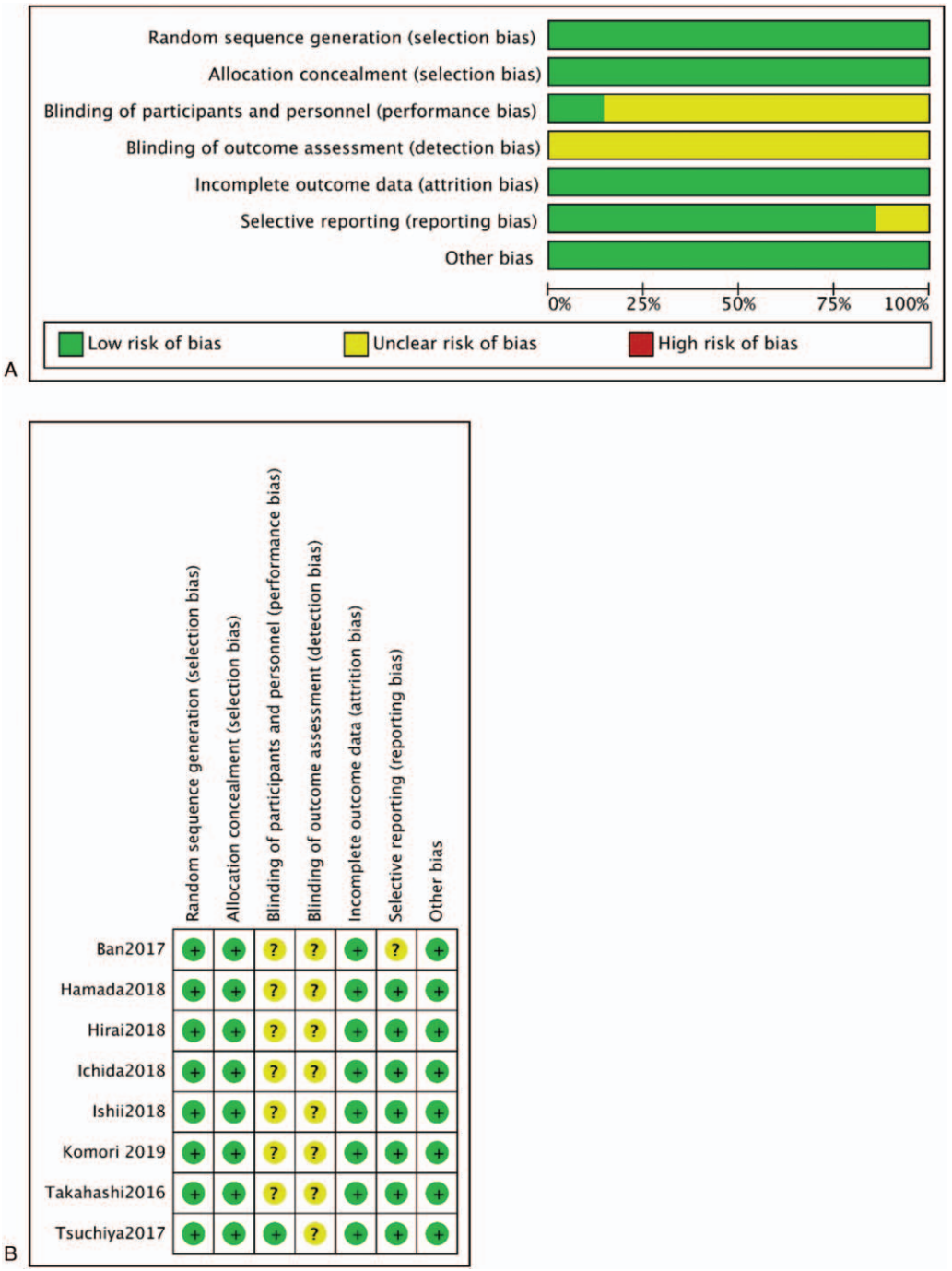

Figure 2. Cochrane risk of bias of (A) graph and (B) summary.

Table 2

Quality assessment with Newcastle-Ottawa Quality Assessment Scale.

	Horikawa 2018	Maruoka 2017	Otsuka 2018	Yamasaki 2018	Shimozato 2017
Selection					
Representativeness of the exposed cohort	★	★	★	★	★
Selection of the non-exposed cohort	★	★	★	★	★
Ascertainment of exposure	★	★	★	★	★
Demonstration that outcome of interest was not present at start of study	★	★	★	★	★
Comparability					
Comparability of cohorts on the basis of the design or analysis	★★	★★	★★	★★	★
Outcome					
Assessment of outcome	★	★	★	★	★
Was follow-up long enough for out comes to occur	★	★	★	★	★
Adequacy of follow up of cohorts	★	★	★	★	★

Table 3

GRADE assessment of the outcomes (ulcer healing, shrinkage ratio, and delayed bleeding).

Question A: Vonoprazan compared to PPIs for ESD for ulcer healing

Certainty assessment[a]							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vonoprazan	PPIs	Relative (95% CI)	Absolute (95% CI)		
Ulcer healing (follow up: 4 weeks; assessed with: OR)												
6	randomised trials	not serious	not serious	not serious	serious[b]	none	133/350 (38.0%)	158/414 (38.2%)	**OR 1.33** (0.92 to 1.93)	**7 more per 100** (from 2 fewer to 16 more)	⊕⊕⊕○ MODERATE	CRITICAL
3	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed					⊕⊕⊕⊕ HIGH	CRITICAL
Ulcer healing (follow up: 8 weeks; assessed with: OR)												
6	randomised trials	not serious	not serious	not serious	serious[c]	none	289/326 (88.7%)	351/420 (83.6%)	**OR 1.48** (0.94 to 2.32)	**5 more per 100** (from 1 fewer to 9 more)	⊕⊕⊕○ MODERATE	CRITICAL
2	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed					⊕⊕⊕⊕ HIGH	CRITICAL

Question B: Vonoprazan compared to PPIs for shrinkage ratio

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vonoprazan	PPIs	Relative (95% CI)	Absolute (95% CI)		
Shrinkage ratio - Week 2 *(H. pylori* +) (follow up: 2 weeks; assessed with: MD)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	48	41	-	MD **19.51 higher** (11.91 higher to 27.12 higher)	⊕⊕⊕○ MODERATE	CRITICAL
1	observational studies	not serious	not serious	not serious	not serious	very strong association all plausible residual confounding would suggest spurious effect, while no effect was observed					⊕⊕⊕⊕ HIGH	CRITICAL
Shrinkage ratio - Week 2 (*H. pylori* -) (follow up: 2 weeks; assessed with: MD)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	29	41	-	MD **2.02 higher** (5.66 lower to 9.71 higher)	⊕⊕⊕○ MODERATE	CRITICAL
1	observational studies	not serious	not serious	not serious	not serious	very strong association all plausible residual confounding would suggest spurious effect, while no effect was observed					⊕⊕⊕⊕ HIGH	CRITICAL

Question C: Vonoprazan compared to PPIs for delayed bleeding

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vonoprazan	PPIs	Relative (95% CI)	Absolute (95% CI)		
Delayed bleeding (assessed with: OR)												
5	randomised trials	not serious	not serious	not serious	serious[e]	none	13/347 (3.7%)	23/376 (6.1%)	**OR 0.66** (0.32 to 1.35)	**20 fewer per 1,000** (from 41 fewer to 20 more)	⊕⊕⊕◯ MODERATE	CRITICAL
2	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed					⊕⊕⊕⊕ HIGH	CRITICAL

CI = confidence interval, MD = mean difference, OR = odds ratio.

a. Certainty assessment was split into assessments of randomized trials and observational studies; for randomized trials, we evaluated the first four criteria and publication bias; for observational studies, we evaluated (1) large effect, (2) plausible confounding, and (3) dose response gradient.

b. The RCT of Komori 2019 was suspected to be imprecise due to the outcome of 0 event in both arms.

c. The RCT of Tsuchiya 2017 was suspected to be imprecise due to the large 95% CI.

d. Only one RCT, Ban 2017 was involved in the synthesis of result.

e. The RCTs of Komori 2019 and Tsuchiya 2017 were suspected to be imprecise due to the 0 event in the vonoprazan arm.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

vonoprazan were assessed according to reported shrinkage ratios, scar stages, and instances of delayed bleeding.

The data extracted for meta-analysis were the number of patients demonstrating each scar stage or with delayed bleeding. We also examined changes in the shrinkage ratio from the initial ulcer size, such as mean and SD. We obtained complete outcomes from three studies by personally contacting the authors.[15,16,26]

3.3. Risk of bias within studies

According to the Cochrane Risk of Bias Tool (Fig. 2), one RCT[15] had more than 2 items where there was an unclear risk of bias. The common bias was a detection bias due to a lack of blinding of the outcome assessment. The Newcastle–Ottawa Quality Assessment Scale indicated acceptable quality of selection, comparability, and outcomes for the five cohort studies[16,21,22,24,26] (Table 2).

GRADE evaluation results indicated that the average study quality was acceptable (Table 3). Furthermore, high certainty of evidence was observed for all three outcomes.

3.4. Synthesis of results from individual studies

3.4.1. Ulcer healing. A total of 13 studies, including 1,510 participants, reported instances of ulcer healing and/or measurement of shrinkage ratios of ESD-induced ulcers following the administration of vonoprazan and PPI (lansoprazole, esomeprazole, omeprazole, and rabeprazole) treatments. There were 676 participants in the intervention groups (10 mg vonoprazan, 20 mg vonoprazan, and 20 mg vonoprazan plus 300 mg rebamipide) and 834 participants in the PPI group (30 mg lansoprazole, 30 mg lansoprazole plus 300 mg rebamipide, 20 mg esomeprazole, 20 mg omeprazole, and 10 mg rabeprazole). The follow-up durations were 4 and 8 weeks. As depicted in the ulcer healing forest plot (Fig. 3), the ORs between vonoprazan and PPIs ranged from 0.33 to 5.20. The overall OR for ulcer healing between vonoprazan and PPIs was 1.39 ($Z = 2.23$, $P = .03$) with a 95% CI (1.04–1.85). At 4 weeks, the mean effect size of the ORs was 1.33 ($Z = 1.50$, $P = .13$), and individual effect sizes ranged from 0.33 to 3.21. At 8 weeks, the mean effect size of ORs was 1.48 ($Z = 1.69$, $P = .09$), and individual effect sizes ranged from 0.81 to 5.20. As depicted by the funnel plot (Fig. 4), we detected no publication bias and Egger's regression test produced non-significant asymmetry ($Z = 0.005$, $P = .878$).

3.4.2. Shrinkage ratio. Two studies with 159 participants were included in the meta-analysis of effects of vonoprazan on shrinkage ratios after ESD ulcer. There were 77 patients in the intervention group (20 mg vonoprazan) and 82 in the PPI group (30 mg lansoprazole). The follow-up period was 2 weeks. A forest plot of the shrinkage ratios is shown in Figure 3.

The mean differences on shrinkage ratios between vonoprazan and lansoprazole ranged from 3.44% to 20.99%. The shrinkage ratio became greater after vonoprazan administration. The overall mean difference was 12.24% ($Z = 1.40$, $P = .16$) with 95% CI (−4.96–29.44). The studies featured high heterogeneity with an $I^2 = 92\%$ ($P < .001$).

Subgroup meta-analysis were conducted by stratifying patients who were *H. pylori*-positive and *H. pylori*-negative. The effect sizes were 19.51% ($Z = 5.03$, $P < .00001$) with 95% CI (11.91–27.12) for the *H. pylori*-positive subgroup and 2.02% ($Z = 0.52$, $P = .61$) with 95% CI (−5.66–9.71) for the *H. pylori*-negative subgroup at the 2 week follow-up. A funnel plot analysis showed no publication bias (Fig. 4) and Egger regression test was non-significant indicating symmetry in the funnel plot ($Z = -0.134$, $P = .893$).

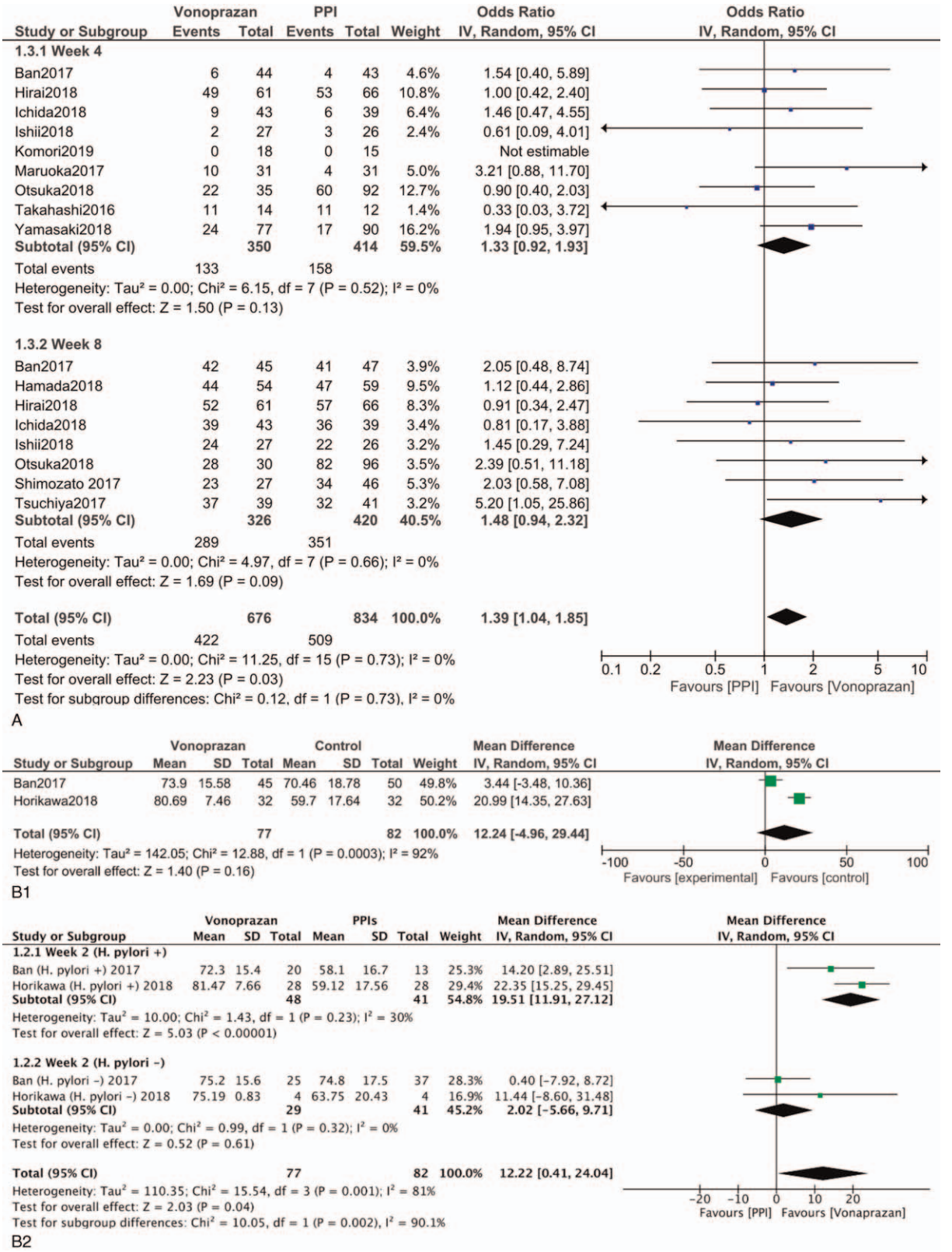

Figure 3. Forest plots of ulcer healing, shrinkage ratio, the occurrence of delayed bleeding on ESD-induced ulcers; (A) ulcer healing at 4 weeks and 8 weeks; (B-1) shrinkage ratio at 2 weeks; (B-2) shrinkage ratio in *H. pylori*-positive and *H. pylori*-negative groups at 2 weeks; (C) the occurrence of delayed bleeding.

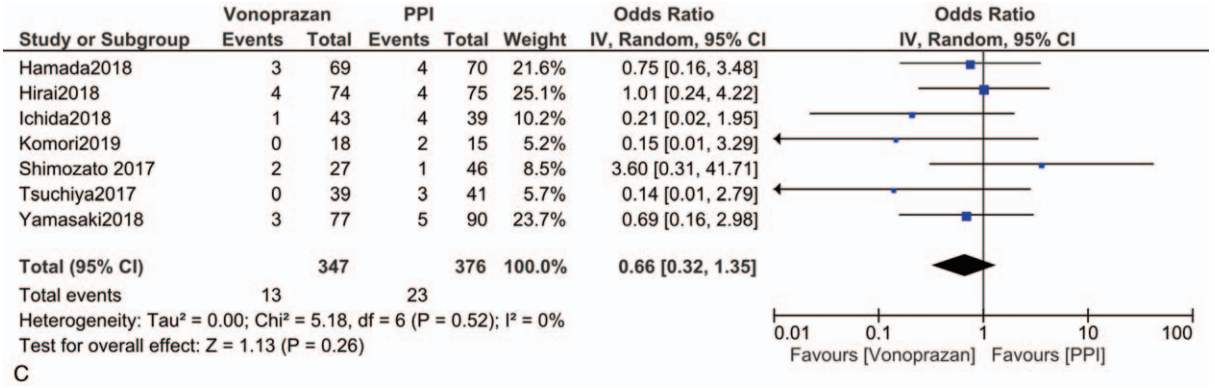

Figure 3. (Continued)

3.4.3. Delayed bleeding. Seven studies that included 723 participants examined delayed bleeding complications in patients who underwent treatment with vonoprazan and PPIs. A total of 347 participants were included in the intervention group (10 mg vonoprazan, 20 mg vonoprazan, and 20 mg vonoprazan plus 300 mg rebamipide) and 376 participants were included in the control group (30 mg lansoprazole, 30 mg lansoprazole plus 300 mg rebamipide, 20 mg esomeprazole, 20 mg omeprazole, and 10 mg rabeprazole). The ORs for delayed bleeding after vonoprazan ranged from 0.14 to 3.60. The overall mean OR for delayed bleeding following the administration of vonoprazan was 0.66 ($Z=1.13$, $P=.26$) with a 95% CI (0.32–1.35). A funnel plot analysis showed no publication bias (Fig. 4) and Egger's regression test was non-significant indicating symmetry in the funnel plot ($Z=-0.654$, $P=.513$).

3.5. Risk of bias across studies

We checked the possibility of publication bias using funnel plots for shrinkage ratio, scar stage, and delayed bleeding (Fig. 4). The results of the Egger regression test were negative for publication bias.

3.6. Sensitivity analysis

The Cochrane Risk of Bias (Fig. 2) and Newcastle-Ottawa Quality Assessment scales (Table 2) indicated that the included studies were of acceptable quality. After excluding the two published studies that combined the target medication with a mucosal protective agent,[18,19] we re-examined the robustness of our findings. The overall ORs came to 1.41 for ulcer healing and 0.64 for delayed bleeding (Fig. 5), indicating that the elimination of these studies did not significantly affect the robustness of our results.

4. Discussion

Acid blockers, whether vonoprazan or PPIs, are widely prescribed for the treatment of ESD-induced ulcers and delayed bleeding. Some studies concluded that vonoprazan was as effective as PPIs for treating ESD-induced ulcers.[17–20,23,26] On the other hand, some studies suggested that vonoprazan was superior to PPIs for healing ESD-induced ulcers.[15,16,21,24,27] These controversial results were based on observed differences in shrinkage ratios and ulcer healing. Takahashi et al. declared that shrinkage ratios < 90% at 4 weeks should be considered *delayed ulcer healing*.[23] Meanwhile, Maruoka et al defined ulcer healing as a 100% contraction (shrinkage) rate at 4 weeks.[21] For 8 weeks, Otsuka et al. reported that the scar formation group demonstrated a 100% reduction (shrinkage) rate.[22] In this meta-analysis, we clarified the definition of ulcer healing using shrinkage ratios and scar stages (see section 2.2.6).

We searched for relevant publications and double-checked the accuracy of extracted data. The results showed that the healing rate of vonoprazan was not superior to PPIs for treatment of ESD-induced ulcers at 4 and 8 weeks, with low heterogeneity. However, in the shrinkage ratio at 2 weeks, we detected high heterogeneity and therefore divided the patients into *H. pylori*-positive and *H. pylori*-negative groups for further analysis. We discovered that vonoprazan was far more effective than PPIs for treating patients who were *H. pylori*-positive. Vonoprazan was comparable to PPIs for the prevention of delayed bleeding after ESD, as observed differences between the two classes of drugs were non-significant. Egger regression tests indicated no publication biases for any of the three outcomes.

To date, four meta-analyses of vonoprazan have generated divergent results. One reported that vonoprazan was superior to PPIs for ulcer healing at 8 weeks post-ESD,[31] and another concluded that vonoprazan was associated with a significantly faster rate of healing at 4 and 8 weeks post-ESD.[30] On the contrary, the recent published meta-analysis by Kang et al[41] concluded that vonoprazan was inferior to PPIs at 8 weeks post-ESD but was superior at 4 weeks post-ESD. In contrast, we found that the ulcer healing was not significantly different between vonoprazan and PPIs at 4 and 8 weeks. One potential reason for this difference might be that the previous meta-analyses did not specifically define ulcer healing, thereby altering study selection and data extraction. In contrast to Kang et al's review,[41] we did not include abstract articles and Kagawa et al's study[42] due to different length of treatment. In addition, Kang et al's review[41] reported Tsuchiya et al's data[27] as post-ESD healing rate both at 4 weeks (RR 1.216 [1.017–1.452]) and 8 weeks (RR 0.951 [0.822–1.101]), while Tsuchiya et al[27] only evaluated 8-week cure rate with RR 1.22 [1.02–1.45] based on our calculation.

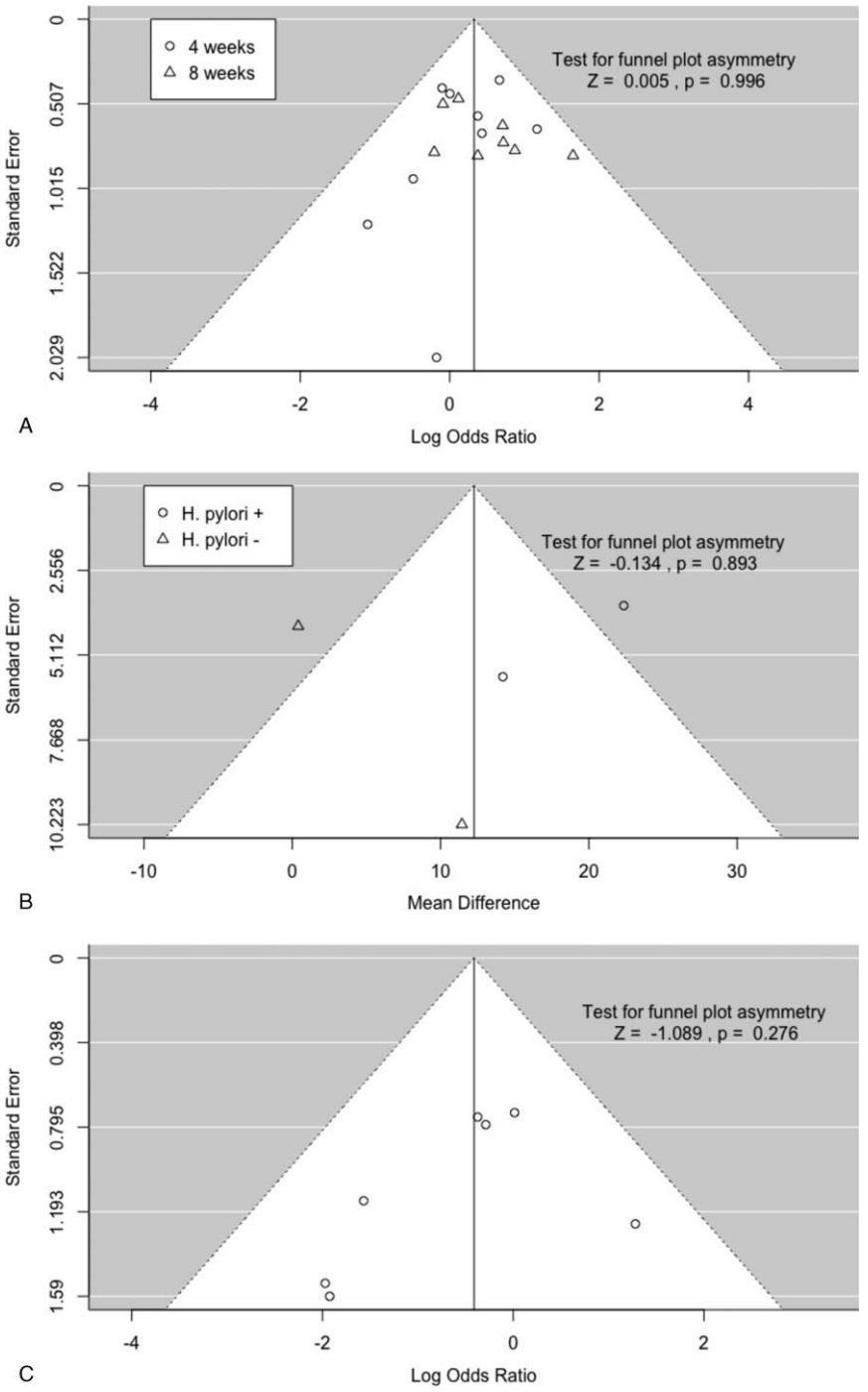

Figure 4. Funnel plots of (A) ulcer healing, (B) shrinkage ratio, and (C) delayed bleeding.

Another meta-analysis reported, like us, that vonoprazan was comparable to PPIs for treating post-ESD gastric ulcers; though they examined both full-text studies and abstracts.[32] In contrast, our meta-analysis was PRISMA-compliant, included an investigation of 2 weeks' treatment, and analyzed the sensitivity and publication biases of past examinations of the efficacy of vonoprazan for treating ESD-induced ulcers.

Our new finding was that vonoprazan was superior than PPIs for treating patients who were *H. pylori*-positive at 2 weeks, therefore implying that, in the presence of *H. pylori*, vonoprazan had faster and better short-term efficacy than PPIs. This observed superiority at 2 weeks was also in line with the superiority of vonoprazan over PPIs in *H. pylori* eradication therapy that last from 7 to 14 days.[12–14] One theoretical explanation is that vonoprazan neutralizes intragastric pH levels more potently than PPIs,[9] thereby promoting post-ESD ulcers healing to a greater extent in the early phase.

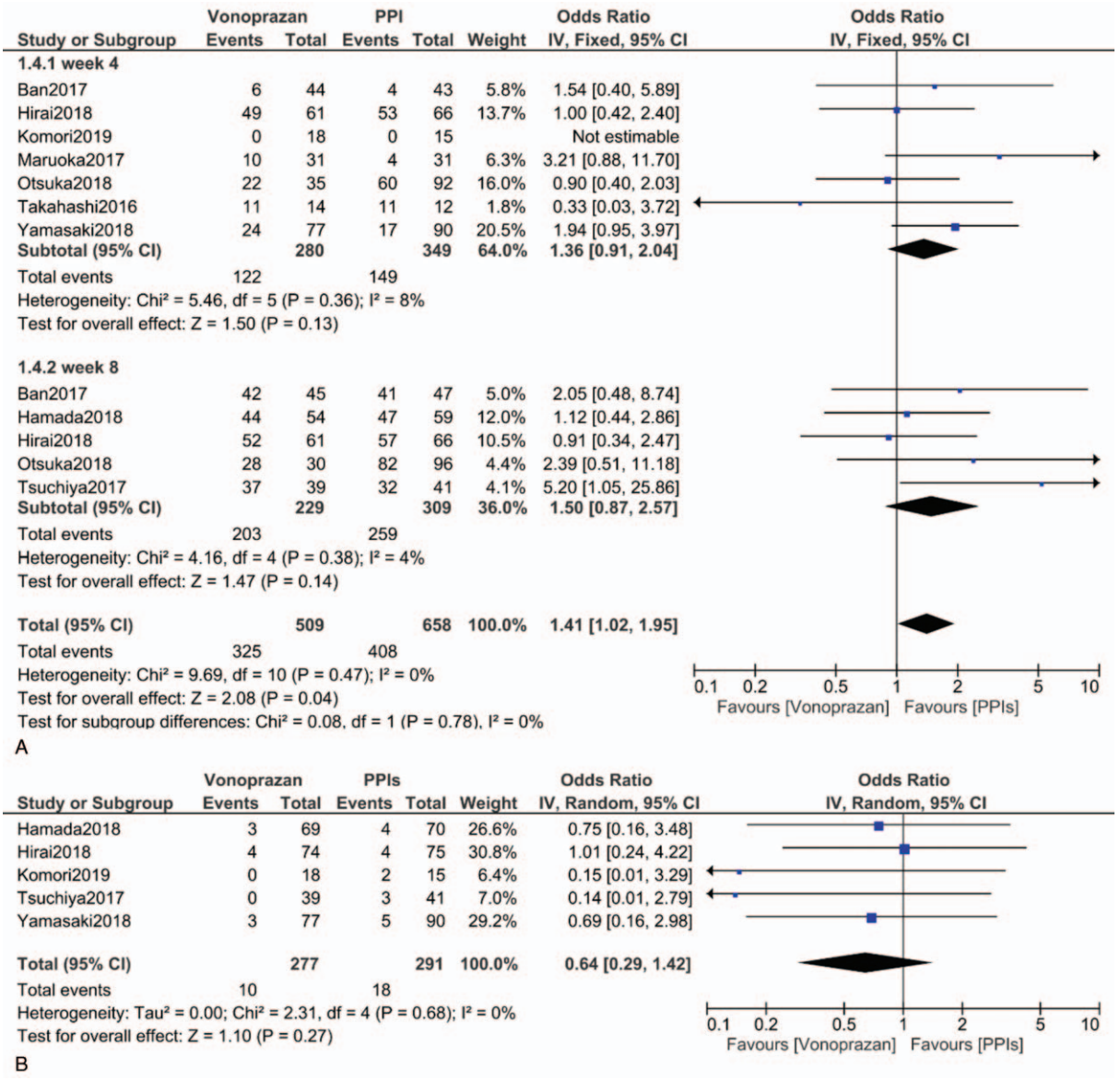

Figure 5. Sensitivity analyses of (A) ulcer healing and (B) delayed bleeding.

There were limitations to this meta-analysis that should be considered when designing future studies. Only 2 studies reported 2-week results from patients who were *H. pylori*-positive and *H. pylori*-negative. Also, the small number of included studies might have led us to overestimate the effects of vonoprazan. More RCTs on the efficacy of vonoprazan and PPIs at 2 weeks are expected. As these are published, we expect to update this meta-analysis with additional RCTs with proper registration and fewer potential biases.

5. Conclusion

Compared to PPIs, vonoprazan was associated with a higher rate of healing at the 2-week treatment mark in patients with ESD-induced gastric ulcers who were positive for *H. pylori*. Hence, doctors who treat these patients should consider administering vonoprazan for the first 2 weeks, before then switching to a PPI to carry out cost effective treatment.

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