

## META-ANALYSIS

# A comparison of efficacy and safety of potassium-competitive acid blocker and proton pump inhibitor in gastric acid-related diseases: A systematic review and meta-analysis

Daniel Martin Simadibrata,\*  Ari Fahrial Syam<sup>†</sup> and Yeong Yeh Lee<sup>‡,§</sup> 

\*Faculty of Medicine Universitas Indonesia, <sup>†</sup>Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Ciptomangunkusumo General Hospital, Jakarta, Indonesia, <sup>‡</sup>School of Medical Sciences, Universiti Sains Malaysia, and <sup>§</sup>GI Function and Motility Unit, Hospital USM, Kota Bharu, Malaysia

**Key words**

gastric acid-related diseases, meta-analysis, potassium-competitive acid blocker, proton pump inhibitor, vonoprazan.

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**Correspondence**

Professor Ari Fahrial Syam, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Ciptomangunkusumo General Hospital, Jakarta, Indonesia.  
Email: [ari\\_syam@hotmail.com](mailto:ari_syam@hotmail.com)

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**Abstract**

**Background and Aim:** Potassium-competitive acid blocker (PCAB) is a recent alternative to proton pump inhibitor (PPI) for potent acid suppression. The current systematic review and meta-analysis aimed to compare the efficacy and safety of PCAB *versus* PPI in treating gastric acid-related diseases.

**Methods:** We searched up to June 5, 2022, for randomized controlled trials of gastric acid-related diseases that included erosive esophagitis, symptomatic gastroesophageal reflux disease (GERD), peptic ulcers, and *Helicobacter pylori* infection. The pooled risk ratio (RR) was evaluated for the efficacy outcome and treatment-emergent adverse events (TEAEs) as the safety outcome. Sensitivity analyses were performed to test the robustness of the study findings.

**Results:** Of the 710 screened studies, 19 studies including 7023 participants were analyzed. The RRs for the healing of erosive esophagitis with Vonoprazan *versus* PPI were 1.09 (95% confidence interval [CI] 1.03–1.14), 1.03 (95% CI 1.00–1.07), and 1.02 (95% CI 1.00–1.05) in Weeks 2, 4, and 8, respectively. There were no differences in the improvement of GERD symptoms and healing of gastric and duodenal ulcers between PCAB and PPI. The pooled eradication rates of *H. pylori* were significantly higher in Vonoprazan *versus* PPI first-line treatment (RR 1.13; 95% CI 1.04–1.22). The overall RR of TEAEs with Vonoprazan *versus* PPI was 1.08 (95% CI 0.89–1.31). Overall, the risk of bias was low to some concerns. Furthermore, sensitivity analyses confirmed the robustness of the study's conclusion.

**Conclusion:** Vonoprazan is superior to PPI in first-line *H. pylori* eradication and erosive esophagitis but non-inferior in other gastric acid-related diseases. Likewise, short-term safety is comparable in both treatment groups.

**Introduction**

The preferred treatment for many gastric diseases, especially gastric acid-related diseases, has been the proton pump inhibitor (PPI).<sup>1–3</sup> Such gastric acid-related conditions are not limited to symptomatic gastroesophageal reflux disease (GERD), erosive esophagitis, dyspepsia, chronic gastritis, gastric and duodenal

ulcers, and *Helicobacter pylori* infection.<sup>4,5</sup> However, despite being an effective acid suppression and only 1–3% of short-term adverse events, a recent umbrella review indicated more longer-term risks with PPI use, especially fractures and kidney disease in the elderly, and a more severe COVID-19 disease.<sup>6,7</sup> Furthermore, an estimated 10–40% of GERD patients have an

incomplete or no response to standard doses of PPI, otherwise termed refractory GERD.<sup>8</sup> Thus, the aforementioned limitations warrant an alternative acid-suppressive drug superior to or at least similar in efficacy to PPI.

Potassium-competitive acid blocker (PCAB) could be the potential alternative to PPI. PCABs are reversible, competitive antagonists of the H<sup>+</sup>/K<sup>+</sup> ATPase and have more potent, rapid-acting, and sustained acid suppression.<sup>9</sup> Vonoprazan, probably the best-known PCAB, received its first approval for use in Japan in 2015. Previous meta-analyses have confirmed the benefits of Vonoprazan alone (no other PCABs) and only in several disorders, including GERD, *H. pylori* eradication, and post-endoscopic submucosal dissection ulcers.<sup>10–12</sup> Furthermore, non-randomized studies were included in previous meta-analyses, prone to biases and heterogeneity, among other limitations. Therefore, the current systematic review and meta-analysis included only robust randomized controlled trials (RCTs) of all studied PCABs. The aims were to assess the efficacy (superiority or non-inferiority) and safety of PCAB compared with PPI in treating gastric acid-related diseases.

## Methods

Before writing this systematic review and meta-analysis, a protocol was prospectively designed and registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42022307265).<sup>13</sup> We have followed the reporting guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA; Table S1).<sup>14</sup>

**Search strategy and selection criteria.** Only RCTs of gastric acid-related diseases randomized to either PCABs or PPIs were searched and selected if the inclusion criteria were satisfied. Gastric acid-related disorders included erosive esophagitis, *H. pylori* infection, gastric and duodenal ulcers, and symptomatic GERD. All studied PCABs were included, that is, Vonoprazan, Soraprazan, Revaprazan, Tegoprazan, Keverprazan, and Linaprazan. Meanwhile, any PPIs as the comparator were Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole, Pantoprazole, Dexlansoprazole, and Ilaprazole. For *H. pylori* studies, only RCTs that compared therapies (regardless of dual or triple, or quadruple therapies and their durations) with the exact dosages and drugs, aside from the PCAB or PPI, were included. Hence, studies that compared different numbers of regimens were excluded (i.e. dual *vs* triple or dual *vs* quadruple or triple *vs* quadruple). From inception to June 5, 2022, studies published in English were searched using the following electronic databases: Ovid MEDLINE, Ovid EMBASE, SCOPUS, and the Cochrane Library. The search terms are presented in Figure S1 and include the following keywords: gastric acid-related diseases, PCAB, PPI, and clinical trials. Additional studies were also identified through manual hand-searching, from relevant systematic reviews or meta-analyses and the reference lists of included studies.

**Data collection and risk of bias assessment.** All retrieved articles were imported into the Endnote 20 (Clarivate, Boston, USA) software, and duplicates were removed. Subsequently, two independent authors (D. M. S. and A. F. S.) screened the titles and abstracts, reviewed the full texts, performed data

extraction, and assessed the risk of bias. The following details were extracted: study identifier, publication date, recruitment period, study location, study design, baseline characteristics of the participants (number of participants, age, and gender), types of gastric acid-related disease, treatment regimen given, outcome measurement, and the treatment outcome. To rate the risk of bias, the Cochrane's Risk of Bias (RoB) tool 2.0 was used to assess the risk of bias in included studies.<sup>15</sup> The tool evaluated five major domains, which were (i) randomization process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome, and (v) the selection of the reported result. For any disagreement, the reviewers would reconcile until a mutual agreement was achieved.

**Outcomes.** The primary outcomes of interest for this review were the endoscopic healing rates of erosive esophagitis and gastrointestinal (GI) ulcers, the eradication rate of *H. pylori* (as assessed by urea breath test), and the improvement of any GI symptoms experienced by symptomatic GERD patients (as reported by patients). Only intention-to-treat (ITT) and full analysis set (FAS) outcome data were extracted and included in the analysis for efficacy outcomes. ITT outcomes were defined as data available for all randomization patients; however, many studies had minor variations concerning the definition of FAS outcome, which ultimately is, as described by the European Medicines Agency Guidance on Statistical Principles for Clinical Trials, as complete and close as possible to the ITT analysis of including all randomized subjects.<sup>16</sup> The ITT outcome data would be used for analysis where the study presented the ITT and FAS data. In addition, the pooled healing and eradication rates and the calculated risk ratio (RR) were determined from extracted data. The secondary outcome was the treatment-emergent adverse events (TEAEs), where we calculated the RRs from the available data. Only ITT and safety analysis set (SAS) outcome data were extracted and included in the analysis for safety outcomes. ITT data would be used if studies reported both datasets. SAS outcome data included all randomized patients with at least one safety assessment after randomization. Additionally, for studies that reported different doses of PCAB (such as Vonoprazan 20 mg, Linaprazan 75 mg, and/or Tegoprazan 50 mg), their inclusion in the meta-analysis would be based on clinical judgment. However, due to different efficacy and safety of individual PCAB, pooling of studies in a meta-analysis would be performed only if two or more studies had used the same type of PCAB.

**Data analysis.** Data were presented in narrative form, and findings were summarized in tables. Due to the study's paucity and the heterogeneity of the improvement of GI symptoms in symptomatic GERD, we did not perform a meta-analysis for that particular outcome of interest. Quantitative synthesis and statistical analyses of the remaining outcomes were performed using the R program v.4.1.2 (Vienna, Austria).<sup>17</sup> To summarize the pooled effect size, the random-effects model was used. For data with dichotomized outcomes, we presented the data as proportion. We used the Mantel–Haenszel method to calculate the pooled RRs and 95% confidence interval (CI) of healing rates, eradication rates, and TEAEs. The heterogeneity of included studies was calculated using the Cochrane  $\chi^2$  and  $I^2$ . All statistical analyses were

two-tailed and considered significant with  $P < 0.05$ , except for the Cochrane  $\chi^2$  heterogeneity significance level, which was set to  $P < 0.10$ .

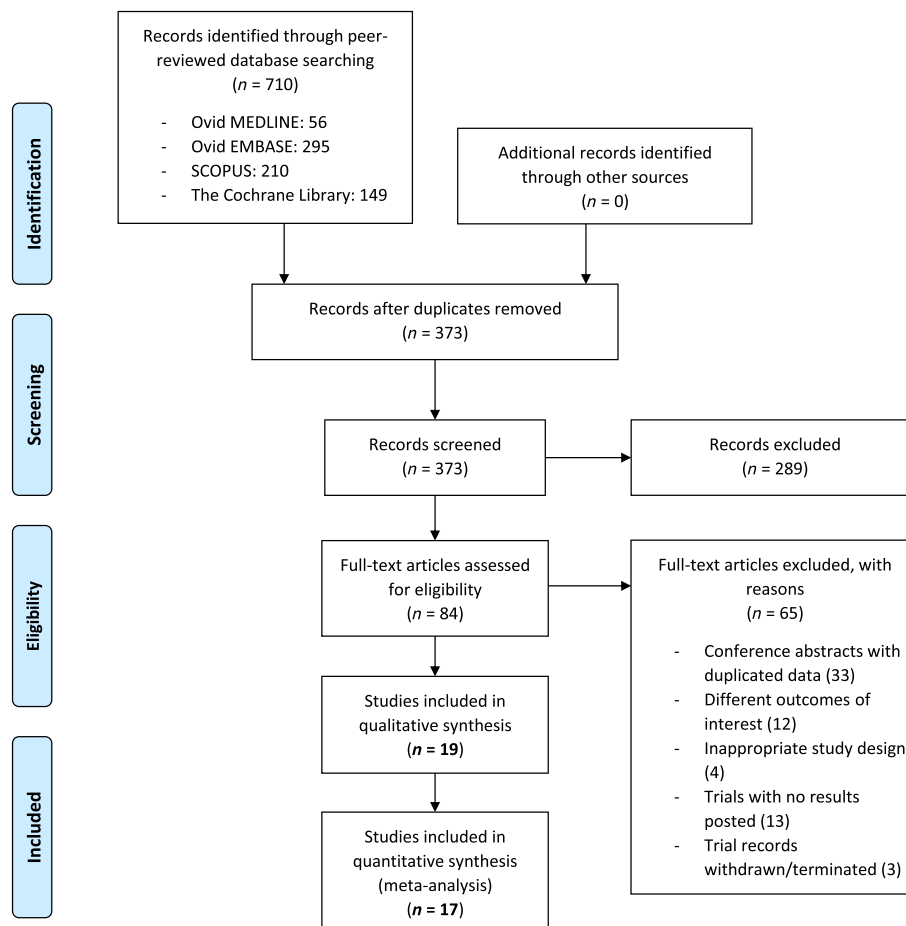
Due to study paucity ( $k < 10$ ), we did not perform a publication bias assessment qualitatively using the funnel plot or quantitatively using Egger's linear regression and Begg's rank tests. Sensitivity analysis using the leave-one-out analysis was used to assess the robustness of the results. Furthermore, subgroup analyses (if  $k \geq 2$  in both subgroups) were performed to analyze the effect estimate based on the study location, the publication type, the study's risk of bias, and the specific intervention-comparator combination or type of PCAB as the comparator. Differences in subgroup analyses were considered significant if the interaction was  $P < 0.10$ .

## Results

**Study selection and baseline characteristics.** From a total of 686 potential studies screened, 19 studies with 7023 patients were included in the final analysis (Fig. 1). Of the gastric acid-related diseases, six were erosive esophagitis,<sup>18–23</sup> two were symptomatic GERD,<sup>24,25</sup> nine were *H. pylori* infection,<sup>26–34</sup> three were gastric ulcers,<sup>34–36</sup> and the remaining two were duodenal

ulcers<sup>33,35</sup> (Table 1). All studies were peer-reviewed published clinical trials except for two unpublished clinical trials.<sup>25,34</sup> Nine of the 19 studies were from Japan,<sup>19,20,24,26–30,35</sup> eight were from other parts of Asia,<sup>21–23,31–34,36</sup> and only two were from the Western countries<sup>18,25</sup> (European countries and the USA). The most common drug–drug comparison was Vonoprazan 20 mg–Lansoprazole 30 mg (8/19 studies; 42.1%). Overall, the risk of bias was generally low-to-some concerns; 10 studies (52.6%) had low risks of bias. We did not identify any studies with a high risk of bias. The overall risk of bias and the individual study's risk of bias are presented in Figure S2. Of the 7023 patients, 4271 (60.8%) received PCAB therapy, and 2752 (39.2%) received PPI therapy. The duration of treatment for PCAB and PPI ranged from 7 days (in *H. pylori* eradication) to 8 weeks (in erosive esophagitis and peptic ulcers). Study participants' baseline characteristics (age and gender) did not differ between the two treatment groups (Table 1).

**Erosive esophagitis.** Overall, six studies investigated the use of PCAB *versus* PPI for healing of erosive esophagitis; three of which used Vonoprazan, while the remaining three used Linaprazan (AZD0865), Keverprazan, and Tegoprazan. The six studies reported three different endpoints (healing rates at Weeks



**Figure 1** Summary of study search and study selection process (flow chart).

**Table 1** Characteristics of included studies investigating the efficacy and safety of PCAB and PPI in gastric acid-related diseases

Gastric acid-related disease	Study identifier	Country	Treatment (PCAB/PPI)	Duration	N	Age (in years); mean $\pm$ SD/ (range)	Male; N (%)	RoB2
Erosive esophagitis	Kahrilas (2007)	188 centers in the USA, Canada, France, Germany, Norway, the UK, Finland, Italy, Sweden, and Denmark	AZD0865 75 mg	8 weeks	375	45.8 $\pm$ 13.1	236 (63)	?
			AZD0865 50 mg	8 weeks	377	47.4 $\pm$ 12.2	245 (65)	
			AZD0865 25 mg	8 weeks	386	47.3 $\pm$ 12.1	233 (60)	
			ESO 40 mg	8 weeks	376	46.5 $\pm$ 13.2	243 (65)	
	Ashida (2015)	Japan	VPZ 40 mg	8 weeks	146	57.6 $\pm$ 12.8	114 (78)	?
			VPZ 20 mg	8 weeks	154	58.3 $\pm$ 13.9	115 (75)	
			VPZ 10 mg	8 weeks	145	57.3 $\pm$ 13.0	113 (78)	
			VPZ 5 mg	8 weeks	148	57.9 $\pm$ 13.0	110 (74)	
	Ashida (2016)	Japan	LPZ 30 mg	8 weeks	140	55.8 $\pm$ 13.9	99 (71)	
			VPZ 20 mg	8 weeks	207	58.3 $\pm$ 13.8	137 (66)	-
			LPZ 30 mg	8 weeks	202	57.4 $\pm$ 13.2	154 (76)	
			TPZ 100 mg	8 weeks	102	52.8 (20–74)	66 (65)	-
	Lee (2019)	South Korea	TPZ 50 mg	8 weeks	99	52.7 (21–74)	62 (63)	
			ESO 40 mg	8 weeks	99	50.4 (21–75)	53 (54)	
GERD	Xiao (2020)	56 centers in China, South Korea, Taiwan, and Malaysia	VPZ 20 mg	8 weeks	244	54.1 $\pm$ 13.2	176 (72)	?
			LPZ 30 mg	8 weeks	237	53.8 $\pm$ 12.5	179 (76)	
	Chen (2022)	44 sites in China	KPZ 20 mg	8 weeks	119	49.7 $\pm$ 12.1	99 (83)	-
			LPZ 30 mg	8 weeks	119	48.8 $\pm$ 12.3	91 (76)	
	Sakurai (2019)	Japan	VPZ 20 mg	4 weeks	22	58.0 $\pm$ 13.8	6 (27)	?
			ESO 20 mg	4 weeks	25	54.7 $\pm$ 13.2	10 (40)	
	NCT02743949	33 centers in Belgium, Bulgaria, Czech Republic, Estonia, Poland, and the UK	VPZ 40 mg	4 weeks	85	52.0 $\pm$ 14.7	32 (38)	-
			VPZ 20 mg	4 weeks	85	51.8 $\pm$ 14.1	34 (40)	
	Murakami (2016)	Japan	ESO 40 mg	4 weeks	86	53.9 $\pm$ 13.9	38 (44)	
			VPZ 20 mg	7 days	329	55.2 $\pm$ 12.3	196 (60)	-
	Maruyama (2017)	Japan	LPZ 30 mg	7 days	321	53.9 $\pm$ 12.9	194 (60)	
			VPZ 20 mg	7 days	72	58 (32–80)	41 (57)	?
	Sue (2018)	Japan	RPZ 20 mg or LPZ 30 mg	7 days	69	60 (36–77)	40 (58)	
			VPZ 20 mg	7 days	55	64.3 $\pm$ 12.3	37 (68)	-
<i>Helicobacter pylori</i>	Sue (2019)	Japan	LPZ 30 mg or RPZ 10 mg or ESO 20 mg	7 days	51	61.9 $\pm$ 13.3	35 (69)	
			VPZ 20 mg	7 days	33	62.4 $\pm$ 14.1	18 (55)	-
	Hojo (2020)	Japan	LPZ 30 mg or RPZ 10 mg or ESO 20 mg	7 days	30	64.0 $\pm$ 12.3	15 (50)	
			VPZ 20 mg	7 days	23	56.0 $\pm$ 10.9	12 (52)	?
	Bunchohtavakul (2021)	Thailand	RPZ 10 mg	7 days	23	57.2 $\pm$ 14.4	14 (61)	
			VPZ 20 mg	7 days	61	54.2 $\pm$ 12.3	26 (43)	?
	Huh (2021)	Korea	OMZ 20 mg	14 days	61	56.8 $\pm$ 13.3	31 (51)	
			VPZ 20 mg	14 days	15	32.8 $\pm$ 6.9	14 (93)	-
			LPZ 30 mg	14 days	15	33.3 $\pm$ 8.6	14 (93)	

(Continues)

**Table 1** (Continued)

Gastric acid-related disease	Study identifier	Country	Treatment (PCAB/PPI)	Duration	N	Age (in years); mean $\pm$ SD/ (range)	Male; N (%)	RoB2
LPZ 30 mg	Hou (2022) <sup>†</sup>	52 hospitals in China, South Korea, and Taiwan	VPZ 20 mg	6 weeks	226	NR	NR	-
	NCT03050307	60 centers in China, Korea, and Taiwan	LPZ 30 mg	6 weeks	229	NR	NR	NR
				VPZ 20 mg		8 weeks	115	NR
Gastric ulcer	8 weeks		NR	-				
			NR		NR			
	Miwa (2017) <sup>†</sup>	119 Japan						
Duodenal ulcer	Cho (2020)	South Korea	VPZ 20 mg	8 weeks	244	58.2 $\pm$ 13.2	163 (67)	?
			LPZ 30 mg	8 weeks	238	58.6 $\pm$ 13.5	170 (71)	?
			TPZ 100 mg	8 weeks	93	54.11	61 (66)	?
			TPZ 50 mg	8 weeks	88	53.39	58 (66)	
			LPZ 30 mg	8 weeks	85	54.22	47 (55)	
	NCT03050307	60 centers in China, Korea, and Taiwan	VPZ 20 mg	8 weeks	115	54.0 $\pm$ 13.7	86 (75)	-
	Miwa (2017) <sup>†</sup>	Japan	LPZ 30 mg	8 weeks	119	53.5 $\pm$ 13.4	92 (77)	?
			VPZ 20 mg	6 weeks	184	49.9 $\pm$ 14.6	125 (68)	
			LPZ 30 mg	6 weeks	188	50.2 $\pm$ 14.8	120 (64)	
	Hou (2022) <sup>†</sup>	52 hospitals in China, South Korea, and Taiwan	VPZ 20 mg	6 weeks	265	42.0 $\pm$ 12.2	166 (63)	-
			LPZ 30 mg	6 weeks	268	41.4 $\pm$ 12.9	176 (66)	

<sup>†</sup>Same study.

- indicates low risk of bias; ? indicates some risk of bias. ESO, Esomeprazole; GERD, gastroesophageal reflux disease; KPZ, Keprazan; LPZ, Lansoprazole; NR, not reported; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; RoB2, Cochrane's Risk of Bias 2 tool; RPZ, Rabepazole; TPZ, Tegoprazan; VPZ, Vonoprazan.

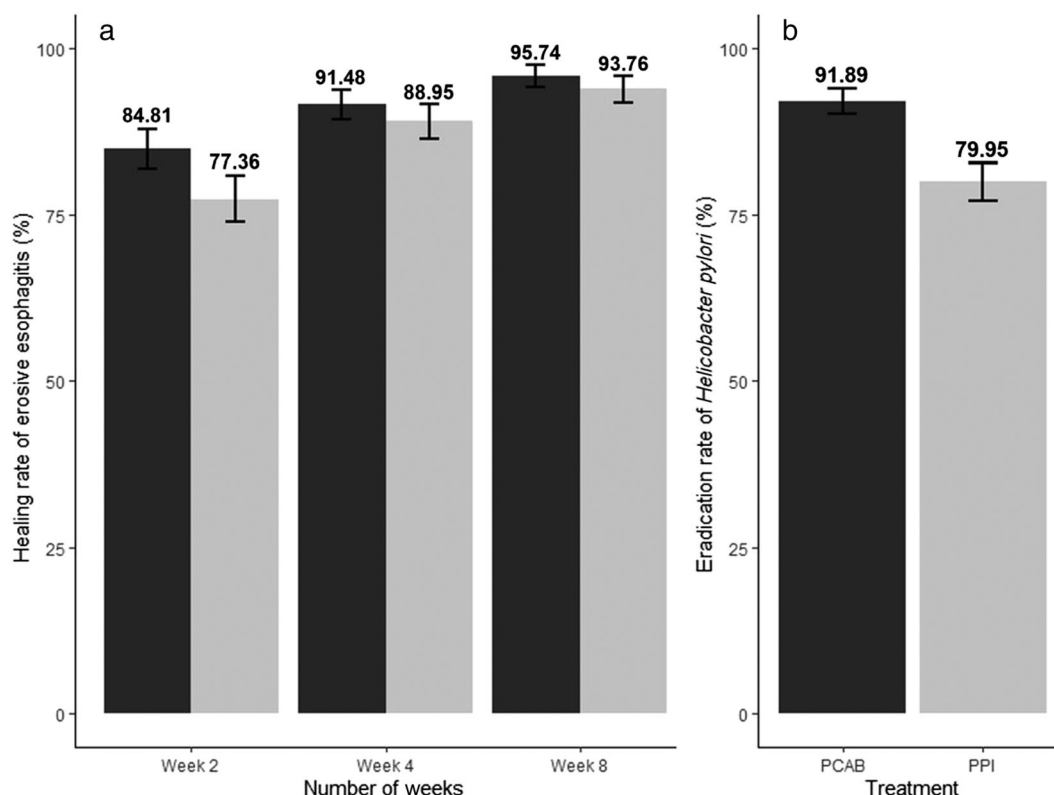
2, 4, and 8). The pooled healing rates of erosive esophagitis were higher in the Vonoprazan group than in the PPI group for all the three different endpoints (Fig. 2a; Week 2: 84.81% vs 77.36%; Week 4: 91.48% vs 88.95%; Week 8: 95.74% vs 93.76%). However, the pooled RRs showed better healing rates in the Vonoprazan group only in Week 2 (RR 1.09; 95% CI 1.03–1.14) compared with Week 4 (RR 1.03; 95% CI 1.00–1.07) and Week 8 (RR 1.02; 95% CI 1.00–1.05) (Fig. 3). Sensitivity analysis did not show any significant changes to the pooled RR, and the conclusion of the findings for healing rates at Weeks 2, 4, and 8 (Fig. S3).

At Week 4, there were no differences in the healing rates of erosive esophagitis between PPI, and Linaprazan (RR 1.00; 95% CI 0.93–1.07), Tegoprazan (RR 1.00; 95% CI 0.90–1.11), and Keverprazan (RR 1.01; 95% CI 0.90–1.14). Non-inferiority was also shown at Week 8 between PPI, and Tegoprazan (RR 1.03; 95% CI 0.96–1.10) and Keverprazan (RR 1.07; 95% CI 0.99–1.14).

**Gastroesophageal reflux disease.** The two included studies have used different endpoints to improve GI symptoms, and, due to the heterogeneity between studies, these were not pooled into the meta-analysis (Table S2). In the first study, Sakurai *et al.*<sup>24</sup> reported no significant differences in symptom relief at 4 weeks between patients receiving Vonoprazan 20 mg and Esomeprazole 20 mg (sufficient relief 81.8% vs 88.0% and

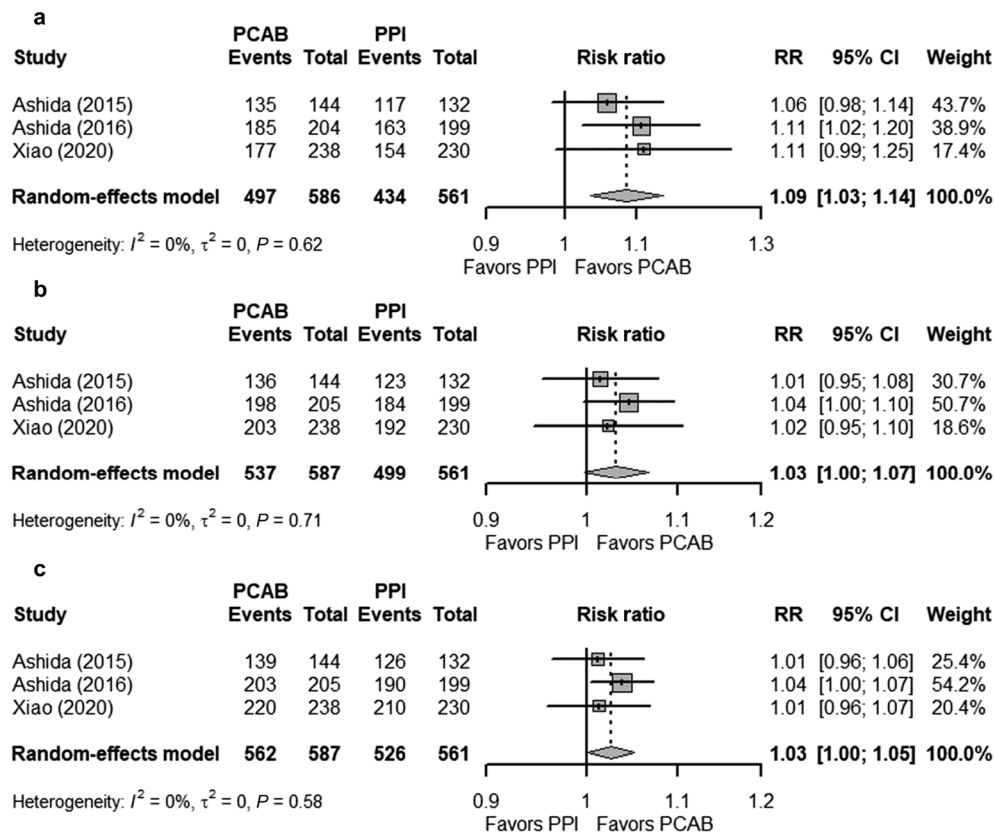
complete resolution 50% vs 64%). Furthermore, the numerical change in the Frequency Scale for the Symptoms of GERD (FSSG) between the Vonoprazan group and the Esomeprazole group (71.9% vs 72.8%) was not statistically different. Likewise, in the second unpublished clinical trial (NCT02743949) comparing Vonoprazan 40 mg or Vonoprazan 20 mg with Esomeprazole 40 mg, the 24-h heartburn-free periods (Vonoprazan 40 mg 38.4% or 20 mg 36.7% vs Esomeprazole 40 mg 36.5%) were not significantly different between the groups. Similarly, the percentage of participants with > 1 sustained resolution of heartburn (Vonoprazan 40 mg 31.8% or 20 mg 30.6% vs Esomeprazole 32.6%) was not significantly different between the groups.

***Helicobacter pylori* eradication.** A total of 869 and 846 patients from nine studies were randomized to PCAB-based and PPI-based therapy, respectively. Seven of the nine studies investigated first-line treatment for *H. pylori*, while one study investigated second-line and third-line treatment. The pooled eradication rate of *H. pylori* for first-line treatment was 91.89% in the PCAB-based group and 79.95% in the PPI-based group (Fig. 2b). The overall RR comparing the two groups was 1.13 (95% CI 1.04–1.22) in first-line treatment, 0.89 (95% CI 0.66–1.22) in second-line treatment, and 1.42 (95% CI 0.97–2.09) in third-line treatment (Fig. 4). There was significant heterogeneity among studies exploring first-line treatment of

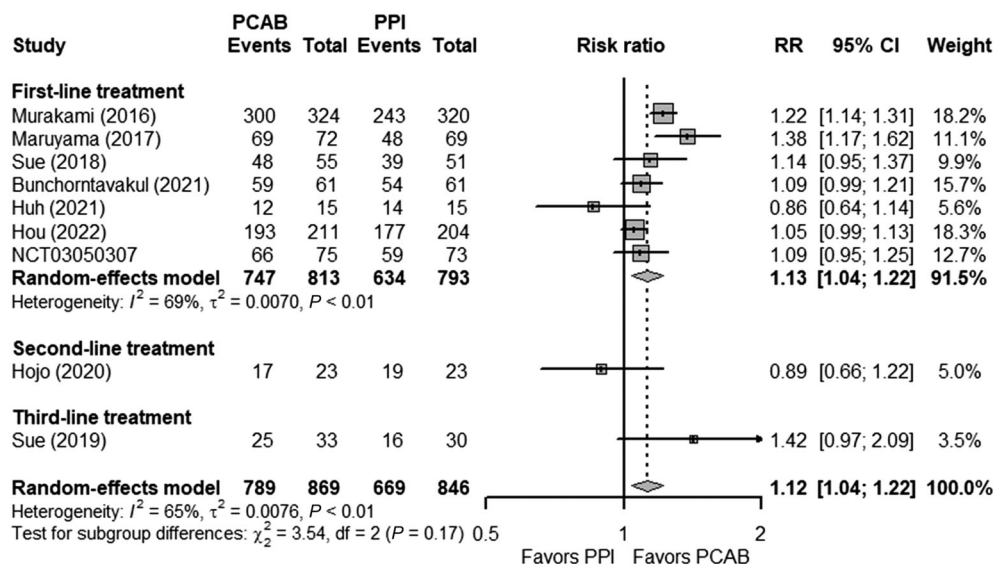


**Figure 2** Bar graphs denoting (a) the crude/pooled healing rate of erosive esophagitis in patients receiving Vonoprazan and PPI and (b) the crude/pooled eradication rate of *Helicobacter pylori* infection in patients receiving first-line treatment of (■) Vonoprazan (PCAB) and (□) PPI. The healing rate and eradication rate are presented in % with its 95% confidence interval. PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.





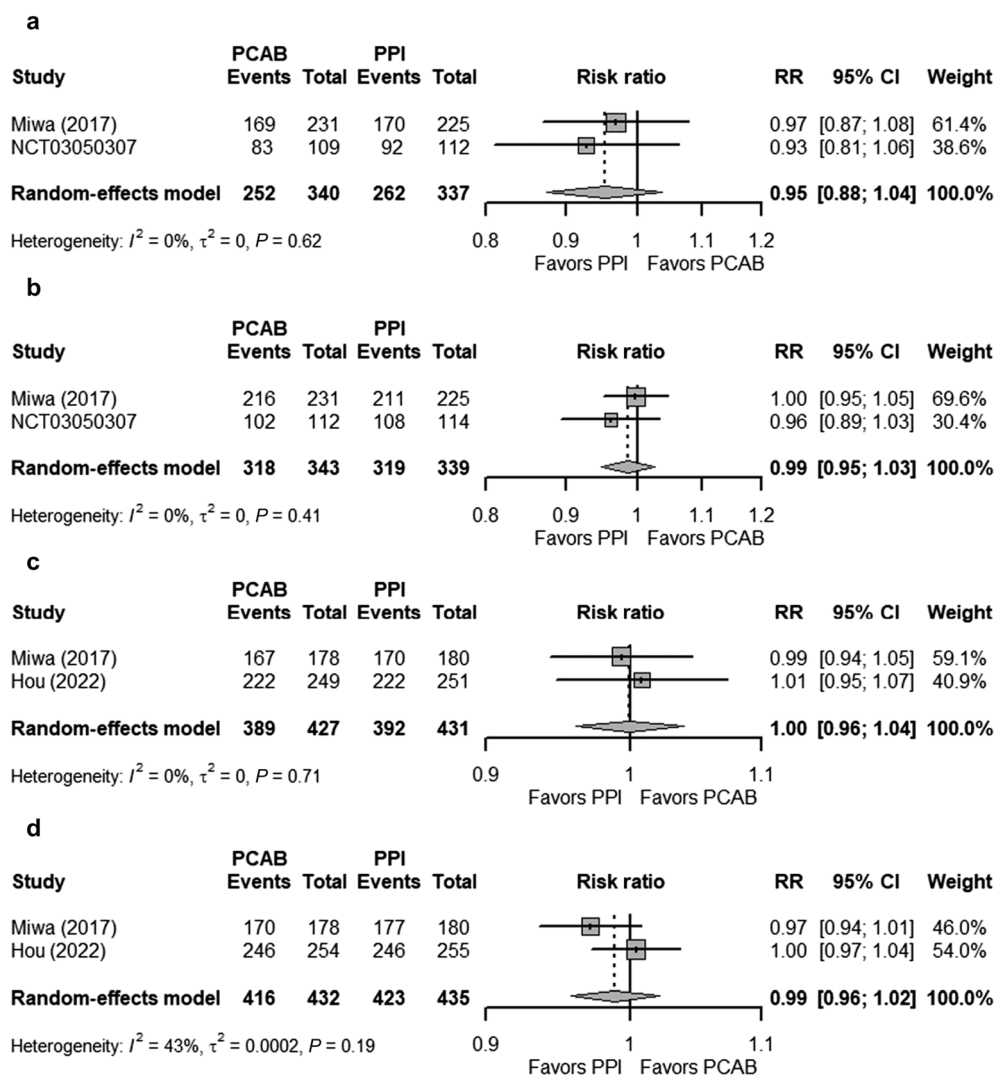
**Figure 3** Forest plots comparing the healing rates of erosive esophagitis in patients receiving Vonoprazan and PPI at (a) Week 2, (b) Week 4, and (c) Week 8. The RR and 95% CI for each study are presented in logarithmic scale. The pooled RRs are derived from the random-effects model. CI, confidence interval; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; RR, risk ratio.



**Figure 4** Forest plots comparing the eradication rates of *Helicobacter pylori* in patients receiving Vonoprazan and PPI as first-line, second-line, and third-line treatment. The RR and 95% CI for each study are presented in logarithmic scale. The pooled RRs are derived from the random-effects model. CI, confidence interval; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; RR, risk ratio.

*H. pylori* ( $P < 0.01$ ;  $I^2 = 69\%$ ). Sensitivity analysis comparing the eradication rate of *H. pylori* did not yield any substantial changes to the primary analysis for first-line treatment (Fig. S4A). Subgroup analyses for first-line treatment by drug–drug comparison and risk of bias of included studies did not show any significant subgroup differences (Fig. S4B). However, studies from Japan were shown to have a significantly higher RR than those conducted outside of Japan (1.24; 95% CI 1.14–1.34 vs 1.06; 95% CI 1.01–1.12; subgroup interaction  $P < 0.01$ ). Additionally, restricting the analysis to studies that compared only triple therapies with the same treatment duration in both the PCAB and PPI groups showed a greater pooled RR of 1.24 (95% CI 1.14–1.34) (Fig. S5).

**Gastric and duodenal ulcers.** Of four studies, two were gastric ulcers, one was duodenal ulcer, and one analyzed both gastric and duodenal ulcers. All studies investigated Vonoprazan as the PCAB, while only one study by Cho *et al.* used Tegoprazan and thus was not included in the pooled analysis. The healing rates of GI ulcers were assessed at Weeks 2, 4, and 6 for duodenal ulcers but at Week 8 for gastric ulcers. In Week 2, for the Vonoprazan group, the healing rates of gastric ulcers and duodenal ulcers were 29.9% and 66.3%, respectively, compared with the PPI group, 32.4% and 63.9%, respectively. At Weeks 4 and 8, the healing rates of gastric and duodenal ulcers did not differ between the two groups (Fig. 5). The healing rates of gastric ulcers at Weeks 4 and 8 also did not differ in those receiving Tegoprazan and PPI.



**Figure 5** Forest plots comparing the healing rates of gastrointestinal ulcers in patients receiving Vonoprazan and PPI at (a) GU - Week 4, (b) GU - Week 8, (c) DU - Week 4, and (d) DU - Week 8. The RR and 95% CI for each study are presented in logarithmic scale. The pooled RRs are derived from the random-effects model. CI, confidence interval; DU, duodenal ulcer; GU, gastric ulcer; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; RR, risk ratio.



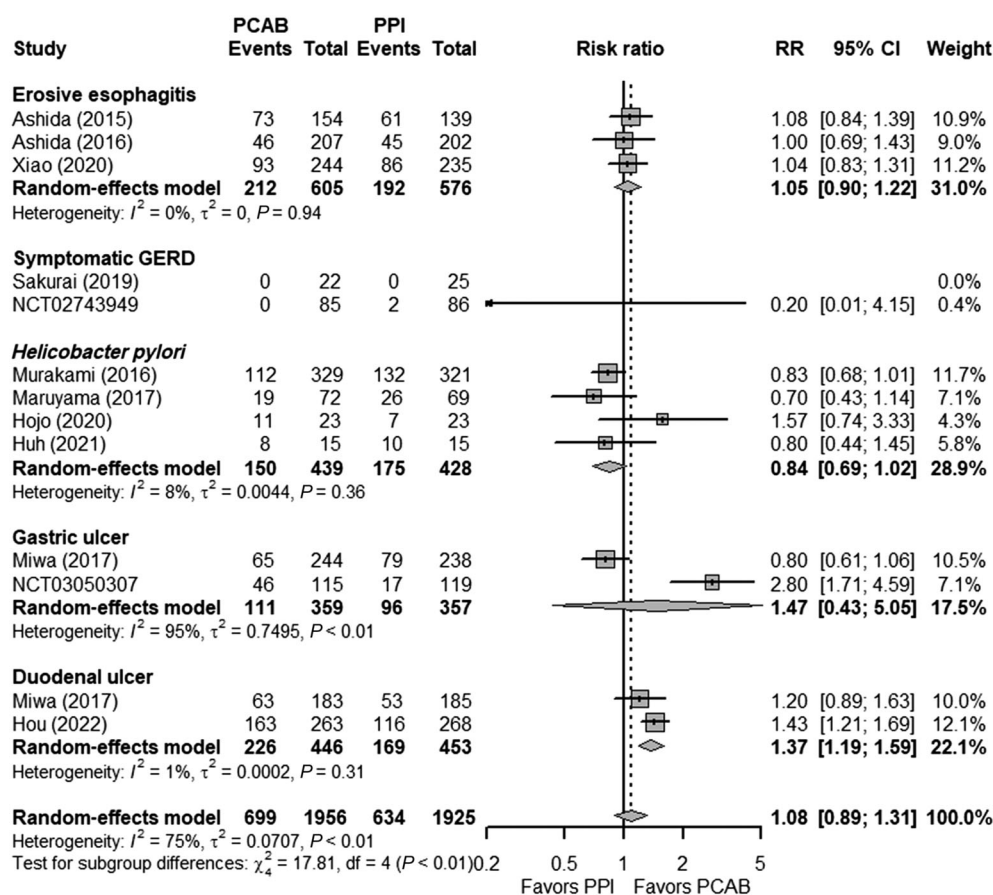
### Safety of potassium-competitive acid blocker versus proton pump inhibitor.

Fifteen studies reported TEAEs in 4519 patients receiving PCABs and PPIs, two and one studies of which reported safety endpoints on Tegoprazan and Keverprazan, respectively, while the remainder was done with Vonoprazan. The prevalence of TEAEs for the Vonoprazan and PPI groups was 35.7% and 32.9%, respectively. The RRs of TEAEs comparing the Vonoprazan group versus the PPI group were 1.05 (95% CI 0.90–1.22), 0.20 (95% CI 0.01–4.15), 0.84 (95% CI 0.69–1.02), 1.47 (95% CI 0.43–5.05), and 1.37 (95% CI 1.19–1.59) for erosive esophagitis, symptomatic GERD, *H. pylori* eradication, gastric ulcer, and duodenal ulcers, respectively (Fig. 6). The overall RR for all Vonoprazan studies reporting TEAEs was 1.08 (95% CI 0.89–1.31). There was significant heterogeneity between studies ( $P < 0.01$ ;  $I^2 = 75$ ). Sensitivity analysis did not change the conclusion (Fig. S6A). Furthermore, subgroup analyses by drug–drug comparison, study location, publication type, and risk of bias showed no significant difference in the RRs (interaction  $P > 0.10$ ) (Fig. S6B). The overall RR for all Tegoprazan and Keverprazan studies reporting TEAEs was 0.84 (95% CI 0.60–1.17) and 1.37 (95% CI 0.92–2.03), respectively (Fig. S7).

### Discussion

There are several key findings in the current systematic review and meta-analysis. First, the comparative efficacy of Vonoprazan (most studied PCAB) versus PPI seems to vary among different gastric acid-related diseases. On the one hand, superiority in the eradication rate of *H. pylori* was demonstrated with Vonoprazan-based versus PPI-based first-line therapy (approximately 13% greater eradication rate). On the other hand, non-inferiority of PCAB over PPI was shown in the healing rates of erosive esophagitis, GERD, and gastric and duodenal ulcers. Second, the short-term safety rates based on TEAEs were comparable between the two treatment groups. Third, the sensitivity and subgroup analyses further confirmed the aforementioned observations.

The variations in comparative efficacy between PCAB and PPI in different disorders might not be all surprising. PCABs are faster in onset and more potent than PPIs. These properties likely impact therapy efficacy, as demonstrated in the current review. Furthermore, pH targets for healing of ulcers (pH > 3 for 12 h/day) are comparatively different from erosive esophagitis (pH > 4 for 18 h/day), as is time to response for gastric versus duodenal ulcers.<sup>5</sup> As such, PCABs may provide better responses to certain gastric acid-related diseases than others.



**Figure 6** Forest plots comparing the treatment-emergent adverse events in patients receiving Vonoprazan and PPI. The RR and 95% CI for each study are presented in logarithmic scale. The pooled RRs are derived from the random-effects model. Subgroup analysis was performed based on the specific gastric acid-related disease. CI, confidence interval; GERD, gastroesophageal reflux disease; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; RR, risk ratio.

There are other interesting findings. Of note, despite showing higher healing rates of erosive esophagitis in the Vonoprazan group compared with the PPI group across Weeks 2, 4, and 8, however, there was only substantial evidence to demonstrate superiority in Week 2. PCAB needed only 1 day to reach maximal acid suppression compared with 3–5 days with PPI.<sup>9,37</sup> Furthermore, PCAB does not require acid and proton pump activation to achieve the desired effect; thus, it has a faster acid-suppressive effect.<sup>37,38</sup> These pharmacokinetic characteristics of PCAB could explain the better and quicker healing of erosive esophagitis being evident by Week 2 over PPI. However, PPI was able to catch up with recovery over time, as evident from healing rates in Weeks 4 and 8.

In addition, PCAB showed comparable efficacy over PPI in treating and maintaining erosive esophagitis. For example, a follow-up study by Ashida *et al.* showed that Vonoprazan 20 mg was significantly more effective than Lansoprazole 15 mg in preventing erosive esophagitis recurrence at 24 weeks of maintenance period.<sup>39</sup> Despite the effectiveness in erosive esophagitis, the rate of symptom relief in GERD patients receiving PCAB *versus* PPI was similar or non-inferior. Sakurai *et al.* and an unpublished clinical trial failed to demonstrate any statistical significance of GERD symptoms in PCAB over PPI.<sup>25</sup> However, in smaller studies on PPI-resistant or refractory GERD patients, vonoprazan showed a more potent gastric suppression and better symptom improvement than PPI.<sup>40,41</sup> PCAB is probably the better choice because of the limitations of PPIs, such as short half-lives, requiring acid activation and inhibiting only activated proton pumps, and clinical variability of CYP2C19 polymorphism.<sup>41</sup> PCAB might be a suitable replacement for PPI in a subset of patients where refractory GERD is due to the extensive metabolism of the CYP2C19.<sup>40</sup> It can be concluded that while PPI remains effective for symptom relief of GERD, PCAB could be the alternative in cases where GERD is resistant or refractory to PPI because of its limitations.

A key finding in the current meta-analysis is the more effective eradication of *H. pylori* with Vonoprazan-based *versus* PPI-based first-line therapy. Effective acid suppression is an essential component of *H. pylori* eradication. More potent and quicker acid inhibition stimulates the growth of *H. pylori*, which in turn enhances the bactericidal effects of growth-dependent antibiotics such as amoxicillin.<sup>4,42</sup> In addition, our analysis suggested that Vonoprazan was similar or non-inferior to PPI for second-line and third-line treatment. The choice of antibiotics may explain the identical rates; however, we recognized that limited data were available for second-line and third-line therapy. Although amoxicillin is a known growth-dependent antibiotic, metronidazole, on the other hand, does not depend on the growth or stationary phase of *H. pylori*. Hence, the efficacy of metronidazole is unaffected by intragastric pH, which explains why acid suppression with PCAB could not improve the already high eradication rate of second-line therapy in Hojo *et al.*<sup>30</sup>

The healing rates of gastric and duodenal ulcers in patients receiving Vonoprazan *versus* PPI were similar for all weeks (Weeks 2, 4, and 6 for duodenal ulcers or Week 8 for gastric ulcers). However, the studies have combined both *H. pylori*-positive and *H. pylori*-negative ulcers. From the subgroup analyses focusing only on *H. pylori*-positive patients, PCAB was superior to PPI in the ulcer healing rates.

Vonoprazan was generally well tolerated; the overall prevalence of TEAE was 35.7% and 32.9% for PCAB and PPI, respectively, and did not significantly differ between the groups. TEAEs were substantially more significant in patients with duodenal ulcers receiving Vonoprazan than PPI. The RCTs in the current meta-analysis only reported short-term adverse events as the longest duration of PCAB use included in this study was 8 weeks. There is increasing safety concern associated with the long-term use of PPIs, especially the risk of osteoporotic fractures and kidney disease among the elderly and a likely more severe course of COVID-19 infection.<sup>6</sup> Unfortunately, the same cannot be inferred for the safety concerns related to long-term Vonoprazan use as the safety data are minimal. A profound gastric inhibition and hypergastrinemia associated with PCAB may result in longer-term issues, which have yet to be elucidated. However, from the present data, we may conclude that Vonoprazan is generally safe for short-term use in gastric acid-related diseases. Still, caution is needed if used for duodenal ulcer patients.

There are limitations to the current meta-analysis. First, studies published in a language other than English were excluded, which could result in potential geographical bias as other studies could be missed. Second, there were limited studies for erosive esophagitis, GERD, and GI ulcers, which could cause our results to be overestimated. However, compared with previous meta-analyses, which only included Vonoprazan as the only type of PCAB, other PCABs such as Linaprazan, Keverprazan, and Tegoprazan, which are available in markets outside of Japan, were also analyzed despite the limited studies available. Thus, more studies are needed to further establish the comparative efficacy and safety for other PCABs aside from Vonoprazan. Additionally, this meta-analysis utilized sensitivity analysis to confirm the robustness of the analysis. Third, analysis of efficacy of PPIs affected by CYP2C19 genotypes was not performed; furthermore, PCABs were generally not affected by CYP2C19 genotypes.<sup>43</sup> Finally, non-gastric acid-related disorders, including aspirin-induced or non-steroidal anti-inflammatory drug-induced gastric ulcers, and functional GI disorders were not included in the current meta-analysis.

## Conclusion

Vonoprazan is not inferior to PPI in healing erosive esophagitis and gastric and duodenal ulcers and improving GERD symptoms. Still, Vonoprazan is superior to PPI in the eradication rate of *H. pylori* infection using first-line treatment. Vonoprazan is also relatively safe compared with PPI; however, only short-term effects were evaluated. Further RCTs with larger samples, in different populations, and more variable use of PCABs (other than Vonoprazan) are needed to confirm findings of PCAB being the more potent and quicker acid suppressant and the alternative to PPIs in PPI-refractory conditions. Likewise, long-term safety data of PCABs are greatly needed.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Search strategy.

**Figure S2.** Cochrane Risk of Bias 2 (RoB2) tool assessment for included studies.

**Figure S3.** Leave-one-out analysis for studies comparing the healing rates of erosive esophagitis in patients receiving Vonoprazan and PPI at (A) Week 2, (B) Week 4 and (C) Week 8.

**Figure S4.** (A) Leave-one-out analysis for studies comparing the eradication rates of *Helicobacter pylori* in patients receiving first-line treatment Vonoprazan and PPI. (B) Subgroup analysis for the eradication rates of *Helicobacter pylori* in patients receiving first-line Vonoprazan and PPI by the drug–drug comparison, study location, and risk of bias.

**Figure S5.** Forrest plots showing the eradication rates of *Helicobacter pylori* in patients receiving first-line treatment of Vonoprazan and PPI. Analysis was restricted to studies which compared only triple therapies with the same treatment duration in both groups.

**Figure S6.** (A) Leave-one-out analysis for studies reporting the TEAEs in patients receiving PCAB and PPI. (B) Subgroup analysis for TEAEs in patients receiving PCAB and PPI by the drug–drug comparison, study location, publication type, and risk of bias.

**Figure S7.** Forrest plots comparing the TEAEs in patients receiving Tegoprazan and PPI.

**Table S1.** PRISMA Checklist.

**Table S2.** Summary of included studies in the systematic review.