Incidence and type of adverse events in patients taking vonoprazan: A systematic review and meta-analysis

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Wentao Xu*, **Zhaohui Bai***, **Yiyang Shang***, **Jing Wang***, **Yujun Wong** and **Xingshun Qi**

Abstract

Background: Vonoprazan, a novel acid-suppressive drug, is non-inferior to proton pump inhibitors (PPIs) for the management of gastric acid-related diseases. However, the safety of vonoprazan has not been systematically evaluated yet.

Objectives: To elucidate the incidence and type of adverse events (AEs) in patients taking vonoprazan.

Design: Systematic review and meta-analysis.

Data sources and methods: PubMed, EMBASE, and Cochrane Library databases were searched for all studies reporting the safety of vonoprazan. The incidences of any AEs, drug-related AEs, serious AEs, AEs leading to drug discontinuation, and common AEs were pooled. Odds ratios (ORs) were calculated to compare the incidence of AEs between patients taking vonoprazan and PPIs.

Results: Seventy-seven studies were included. The pooled incidences of any AEs, drug-related AEs, serious AEs, and AEs leading to drug discontinuation were 20, 7, 1, and 1%, respectively. The incidences of any AEs (OR = 0.96, $p = 0.66$), drug-related AEs (OR = 1.10, $p = 0.44$), serious AEs (OR = 1.14, $p = 0.36$), and AEs leading to drug discontinuation (OR = 1.09, $p = 0.55$) were not significantly different between patients taking vonoprazan and PPIs. In subgroup analyses, patients with peptic ulcer disease (PUD) had higher incidences of any AEs, serious AEs, and AEs leading to drug discontinuation than those with gastroesophageal reflux disease (GERD), *Helicobacter pylori* (*H. pylori*) infection, and artificial ulcer after gastric endoscopic submucosal dissection (ESD), but patients with *H. pylori* infection had a higher incidence of drug-related AEs than those with PUD, GERD, and artificial ulcer after gastric ESD. The incidence of AEs was higher in patients taking long-term use of vonoprazan than those taking short-term use of vonoprazan.

Conclusion: Vonoprazan is well tolerated and shows similar safety compared to PPIs. The safety of vonoprazan may be primarily influenced by its indications and duration.

Registration: PROSPERO CRD42022314982.

Keywords: adverse event, gastric acid, proton pump inhibitor, vonoprazan, safety

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Correspondence to:
Xingshun Qi
Department of Gastroenterology, General Hospital of Northern Theater Command, No. 83 Wenhua Road, Shenyang, Liaoning 110840, China
xingshunqi@126.com

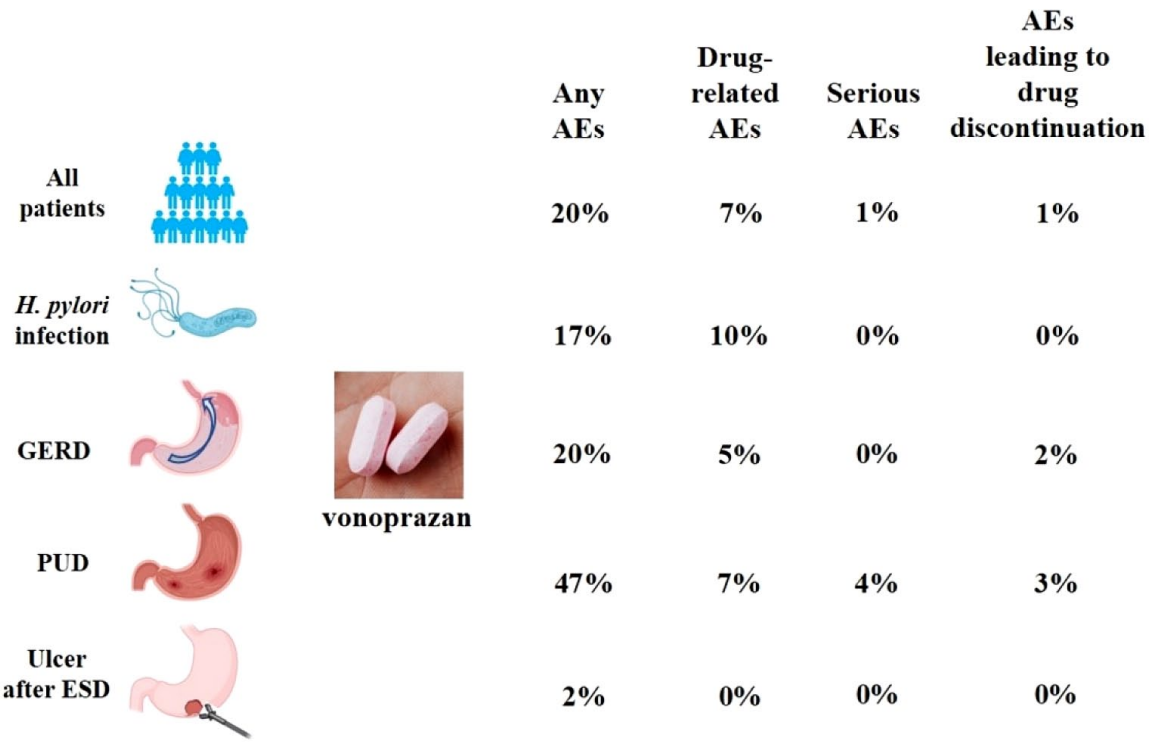
Wentao Xu
Zhaohui Bai
Yiyang Shang
Department of Gastroenterology, General Hospital of Northern Theater Command, Shenyang, China

Department of Life Sciences and Biopharmaceutics, Shenyang Pharmaceutical University, Shenyang, China

Jing Wang
Department of Gastroenterology, The 960th Hospital of the PLA, Jinan, China

Yujun Wong
Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore, Singapore

*Co-first authors



Graphical abstract

Introduction

Acid-suppressive agents are widely used for the management of various upper gastrointestinal diseases, such as peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), *Helicobacter pylori* (*H. pylori*) infection, artificial ulcers after gastric endoscopic submucosal dissection (ESD), and Zollinger–Ellison syndrome. Histamine-2 receptor antagonists, the first class of acid-suppressive agents, have limited efficacy and poor tolerance.[1] Subsequently, in the late 1980s, proton pump inhibitors (PPIs) were introduced into our clinical practice, which strengthened the efficacy of management of gastric acid-related disorders.[2] However, several gaps remained, such as insufficient inhibition of gastric acid, nocturnal acid breakthrough, poor compliance, slow onset of action, and drug efficacy by CYP2C19 gene polymorphisms.[1,3] Vonoprazan, a new potassium-competitive acid blocker, has been approved for the management of acid-related diseases in Asia, South America, and some parts of North America.[4] It acts on the key enzyme H^+/K^+-ATPase in the final step of gastric acid secretion by parietal cells, thereby hindering the exchange of H^+ and K^+ and inhibiting gastric acid secretion.[5] Notably, vonoprazan has some advantages as compared to PPIs.[1,6–9] First, its activation is independent of acidic environment. Second, its onset of action is rapid, because its peak concentration can be reached quickly after 2 h of oral administration. Third, its efficacy is not affected by meals. Fourth, it can inhibit both activated and resting proton pumps in the gastric parietal cells, and the first dose can achieve the maximum acid-suppression and maintain its stability. Its plasma elimination half-life time is 5.7–8.8 h. Fifth, it is mainly metabolized by hepatic CYP3A4/5 enzyme, but not affected by CYP2C19 gene polymorphisms. Taken together, vonoprazan seems to exert more potent and prolonged acid-suppressing effects than PPIs.[5] Current evidence has suggested that vonoprazan can be non-inferior to PPIs for the management of gastric acid-related disorders and more effective than PPIs for healing severe erosive esophagitis (EE) and eradicating *H. pylori*.[10–15] Several practice guidelines have also recommended vonoprazan as the first-line choice for the management of EE and *H. pylori* infection.[16,17] However, until now,

the safety of vonoprazan has not been systematically evaluated yet. Therefore, we performed a systematic review and meta-analysis to elucidate the incidence and type of adverse events (AEs) in patients receiving vonoprazan, and to explore the risk factors affecting the safety of vonoprazan.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items Systematic Reviews and Meta-Analyses (PRISMA) statement. The PRISMA checklist was shown in the Supplemental Material.

Registration

This meta-analysis was registered in PROSPERO with a registration number of CRD42022314982.

Literature search

Three major electronic databases (i.e., EMBASE, PubMed, and Cochrane Library) were searched. The following keywords were used: 'Vonoprazan', 'Takecab', and 'TAK-438'. The last search was performed on 19 June 2022.

Study selection criteria

All eligible studies should evaluate the use of vonoprazan and report its safety data. Exclusion criteria were as follows: (1) duplicates; (2) guidelines, reviews, or meta-analyses; (3) case reports, comments, notes, letters, or protocols; (4) experimental or animal studies; (5) clinical trial registration alone; (6) the study population was healthy people; (7) vonoprazan was not used; and (8) the safety data could not be extracted. Publication language was not restricted.

Data extraction

Two researchers (WX and YS) independently extracted the following information from each included study: first author; publication year; type of publication; country; study design; enrollment period; sample size; indications for acid-suppressing agents; dose, frequency, and duration of vonoprazan, PPIs, or placebo; combined medications; total number and age range of patients taking vonoprazan, PPIs, or placebo; number of patients who experienced any AEs, drug-related AEs, serious AEs, AEs leading to drug discontinuation, and common AEs. Any AEs, drug-related AEs, serious AEs, and AEs leading to drug discontinuation are defined in accordance with the reports of each included study. Disagreement was resolved after discussion with another researcher (ZB).

Study quality assessment

The Cochrane Risk of Bias tool was used for assessing the quality of randomized controlled trials (RCTs) in terms of seven domains, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. The risk of bias is graded as 'low risk', 'high risk', and 'uncertainty'.

The Newcastle–Ottawa Scale (NOS) was used for assessing the quality of cohort studies. It uses a semi-quantitative system to evaluate the quality of studies in the parts of selection, comparability, exposure, and outcomes. A total of nine stars is the highest score. A NOS score of 0–3, 4–6, and 7–9 represents low, moderate, and high quality, respectively.

The Johanna Briggs Institute Scale was used for assessing the quality of single-arm studies.[18] It includes 10 questions addressing the internal validity and risk of bias of case series, particularly confounding, selection, and information bias, in addition to the importance of clear reporting. If a study had a score of $\leqslant$4, 5–6, and $\geqslant$7, it would be of low, moderate, and high quality, respectively.

Outcomes

The primary outcome of this meta-analysis was the incidence of AEs, including any AEs, drug-related AEs, serious AEs, AEs leading to drug discontinuation, and common AEs, in patients taking vonoprazan.

The secondary outcome was the difference in the incidence of AEs between patients taking vonoprazan *versus* those taking PPIs.

Statistical analyses

Meta-analyses were performed using Stata software version 12.0 (Stata Corp, College Station, TX, USA), RStudio version 4.2.0 (R Foundation

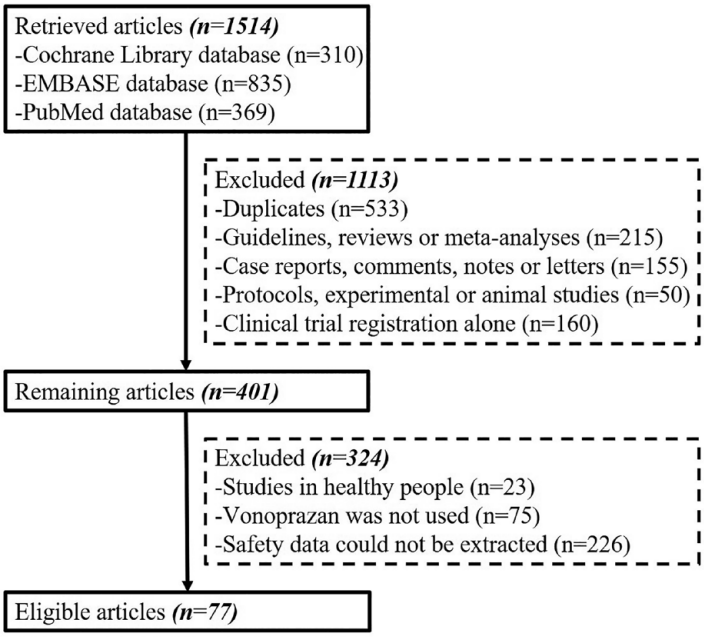


Figure 1. Flow chart of study selection.

for Statistical Computing, Vienna, Austria), and Review Manager software version 5.4 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects model was employed. Dichotomous outcomes were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Cochrane Q test and the I^2 statistics were employed to assess heterogeneity among studies, and $p < 0.1$ or $I^2 > 50\%$ was considered as statistically significant heterogeneity. Publication bias was evaluated with the Eggers' test, and $p < 0.1$ was considered as significant publication bias. Meta-regression analyses were employed to explore the sources of heterogeneity according to the pre-specified covariates, which included type of publication (Full-text *versus* Abstract *versus* Unpublished), study design (RCT *versus* non-RCT), sample size (>200 *versus* ⩽200), indications for vonoprazan (*H. pylori* infection *versus* GERD *versus* PUD *versus* Artificial ulcers after gastric ESD), duration of vonoprazan (>8 weeks *versus* ⩽8 weeks), ethnicity (Asian *versus* non-Asian), and age group (Adult *versus* Adolescent). If the number of included studies was ⩾2, subgroup analyses would be conducted according to the covariates mentioned above. In addition, we performed further subgroup analyses according to the duration of vonoprazan for the management of EE (short-term healing *versus* long-term maintenance) and PUD (short-term healing *versus* long-term prevention). $p < 0.1$ was considered as statistically significant interaction.

Results

Study selection and characteristics

Initially, 1514 papers were identified. Finally, 77 studies were included (Figure 1).[10–15,19–89] The characteristics of included studies were listed in Table 1. These included studies which were published between 2015 and 2022. Seventy-four studies were conducted in Asia,[10–15,19–22,24–28,30–53,55–89] and three in non-Asian countries.[23,29,54] Thirty-four studies were RCTs,[10–14,19–23,32–35,38,42–44,46,52,54,55,57,60,61,63,72,74,77,80,83,85,86,89] 24 cohort studies,[15,24,27,31,36,37,41,47,50,51,53,56,59,62,64–67,71,75,79,81,84,87] and 19 single-arm studies.[25,26,28–30,39,40,45,48,49,58,68–70,73,76,78,82,88] The indications for vonoprazan included *H. pylori* infection ($n = 49$),[11,15,19,22–27,29,30,33,34,36,37,39–41,45–47,50–53,56,58,59,62–67,71–75,77–82,84,85,87,89] GERD ($n = 18$),[10,14,20,21,28,38,43,44,48,49,54,57,60,61,68–70,86] PUD ($n = 6$),[12,13,32,42,55,76] and artificial ulcers after gastric ESD ($n = 4$).[31,35,83,88] The sample size ranged from 12 to 2715. The duration of vonoprazan ranged from 1 to 104 weeks.

Table 1. Characteristics of included studies.

Study identifier	Type of publication	Country	Study design	Enrollment period	Population	Sample size	VPZ group (*n*)	Control group (*n*)	Duration of treatment
Ang *et al.*[19]	Full text	Singapore	RCT	2019.6–2021.6	Patients aged 21–88 years with *H. pylori* infection	244	20 mg, b.i.d.: 119	OPZ, 20 mg/EPZ, 20 mg/ RPZ, 20 mg, b.i.d.: 125	VPZ: 1 week PPI: 2 weeks
Ashida *et al.*[20]	Full text	Japan	RCT	2011.11–2013.3	Patients aged ⩾20 years with endoscopically-confirmed healed EE	607	10 mg, q.d.: 202; 20 mg, q.d.: 204	LPZ, 15 mg, q.d.: 201	24 weeks
Ashida *et al.*[21]	Full text	Japan	RCT	2011.10–2012.8	Patients aged ⩾20 years with endoscopically confirmed EE	409	20 mg, q.d.: 207	LPZ, 30 mg, q.d.: 202	8 weeks
Ashida *et al.*[21]*	Full text	Japan	RCT	2011.11–2013.7	Patients aged ⩾20 years with endoscopically healed EE	305	10 mg, q.d.: 154; 20 mg, q.d.: 151	NA	52 weeks
Ashida *et al.*[10]	Full text	Japan	RCT	NA	Patients aged ⩾20 years with endoscopically confirmed EE	731	5 mg, q.d.: 145; 10 mg, q.d.: 148; 20 mg, q.d.: 154; 40 mg, q.d.: 145	LPZ, 30 mg, q.d.: 139	8 weeks
Bunchorntavakul and Buranathawornsom[22]	Full text	Thailand	RCT	2019.11–2021.1	Patients aged ⩾18 years with *H. pylori* infection	122	20 mg, b.i.d.: 61	OPZ, 20 mg, b.i.d.: 61	VPZ: 1 week OPZ: 2 weeks
Chey *et al.*[23]	Full text	US and European	RCT	2019.12–2021.1	Patients aged ⩾18 years with *H. pylori* infection	1039	20 mg, b.i.d.: 346 (VPZ-triple); 20 mg, b.i.d.: 348 (VPZ-dual)	LPZ, 30 mg, b.i.d.: 345 (LPZ-triple)	2 weeks
Endo *et al.*[24]	Abstract	Japan	Cohort	2012–2016	Patients with *H. pylori* infection	1774	20 mg, b.i.d.: 410 (first line); 20 mg, b.i.d.: 58 (second line)	EPZ, 20 mg, b.i.d.: 259 (first line) RPZ, 10 mg, b.i.d.: 482 LPZ, 30 mg, b.i.d.: 334; EPZ, 20 mg, b.i.d.: 100 (second line) RPZ, 10 mg, b.i.d.: 74 LPZ, 30 mg, b.i.d.: 57	1 week
Furuhashi *et al.*[25]	Abstract	Japan	Single-arm	2016.1–2018.12	Patients with *H. pylori* infection	189	20 mg, b.i.d.: 189	None	1 week
Furuta *et al.*[26]	Abstract	Japan	Single-arm	2015.4–2016.3	Patients with *H. pylori* infection and allergic to penicillin	39	20 mg, b.i.d.: 39	None	1 week
Gotoda *et al.*[27]	Full text	Japan	Cohort	2015–2019	Second-year junior high-school students aged 12–18 years with *H. pylori* infection	221	20 mg, b.i.d.: 60 (VA-dual); 20 mg, b.i.d.: 161 (VAC-triple)	None	1 week
Gotoh *et al.*[28]	Full text	Japan	Single-arm	2016.8–2017.8	Patients aged ⩾20 years with EE, NERD, and PPI-resistant GERD	200	10 or 20 mg, q.d.: 200	None	28 weeks
Gunaratne *et al.*[29]	Full text	Australia	Single-arm	2017.1–2019.9	Patients aged ⩾18 years with *H. pylori* infection	153	20 mg, t.i.d.: 153	None	10 days
Hayashi *et al.*[30]	Abstract	Japan	Single-arm	2015.4–2017.1	Patients aged ⩾20 years with *H. pylori* infection	556	556	None	1 week

(Continued)

Table 1. (Continued)

Study identifier	Type of publication	Country	Study design	Enrollment period	Population	Sample size	VPZ group (*n*)	Control group (*n*)	Duration of treatment
Hojo *et al.*[11]	Full text	Japan	RCT	2015.3–2017.3	Patients with *H. pylori* infection	46	20 mg, b.i.d.: 23	RPZ, 10 mg, b.i.d.: 23	1 week
Horikawa *et al.*[31]	Abstract	Japan	Cohort	2015.4–2016.3	Patients with artificial ulcers after gastric ESD	60	20 mg: 30	LPZ, 30 mg: 30	4 weeks
Hou *et al.*[32]	Full text	China and South Korea	RCT	2017.4–2019.7	Patients aged ⩾18 years with active DU	531	20 mg, q.d.: 263 (patients with *H. pylori* infection: 20 mg b.i.d. for the first 2 weeks): 226	LPZ, 30 mg, q.d.: 268 (patients with *H. pylori* infection: 20 mg b.i.d. for the first 2 weeks): 229	6 weeks
Hu *et al.*[33]	Full text	China	RCT	2021.1–2021.10	Patients aged 18–70 years with *H. pylori* infection	119	20 mg, b.i.d.: 37; 20 mg, b.i.d.: 37; 20 mg, b.i.d.: 24; 20 mg, b.i.d.: 21	NA	10 days; 10 days; 1 week; 1 week
Huh *et al.*[34]	Full text	South Korea	RCT	NA	Patients aged ⩾18 years with *H. pylori* infection	30	20 mg, b.i.d.: 15	LPZ, 30 mg, b.i.d.: 15	2 weeks
Ichida *et al.*[35]	Full text	Japan	RCT	2015.9–2017.12	Patients aged ⩾52 years with artificial ulcers after gastric ESD	82	20 mg, q.d.: 43	EPZ, 20 mg, q.d.: 39	8 weeks
Inokuchi *et al.*[36]	Full text	Japan	Cohort	2016.12–2021.2 2013.10–2015.2	Patients aged ⩾20 years with *H. pylori* infection	86	20 mg, b.i.d.: 57	EPZ, 20 mg, q.i.d.: 12; EPZ, 20 mg, q.i.d.: 17	VPZ: 1 week; EPZ: 10 days; EPZ: 2 weeks
Ito *et al.*[37]	Abstract	Japan	Cohort	2014.6–2018.12	Patients aged ⩾18 years with *H. pylori* infection	1435	612	RPZ: 375; LPZ: 448	NA
Iwakiri *et al.*[38]	Full text	Japan	RCT	2012.8–2013.9	Patients aged ⩾20 years with PPI-resistant EE	19	20 mg, q.d.: 9; 40 mg, q.d.: 10	NA	8 weeks
Kakiuchi *et al.*[39]	Full text	Japan	Single-arm	2016–2018	Junior high school students aged 15–16 years with *H. pylori* infection	501	20 mg, b.i.d.: 501	None	1 week
Kakiuchi *et al.*[40]	Full text	Japan	Single-arm	2017–2019	Third-grade Junior high school students with *H. pylori* infection	274	20 mg, b.i.d.: 274	None	1 week
Kataoka *et al.*[41]	Abstract	Japan	Cohort	2012.5–2016.2	Patients with *H. pylori* infection	441	41 (first line); 11 (second line); 10 (third line)	PPIs: 279; PPIs: 75; PPIs: 25	1 week
Kataoka *et al.*[41]*	Abstract	Japan	Cohort	2012.5–2016.2	Patients with *H. pylori* infection and allergic to penicillin	26	7	PPIs: 19	1 week
Kawai *et al.*[42]	Full text	Japan	RCT	2011.10–2013.4	Patients aged ⩾20 years with endoscopically confirmed history of PUD and required long-term LDA therapy	621	10 mg, q.d.: 202; 20 mg, q.d.: 202	LPZ, 15 mg, q.d.: 217	52 weeks
Kinoshita *et al.*[43]	Full text	Japan	RCT	2011.11–2013.2	Patients aged ⩾20 years with NERD	827	10 mg, q.d.: 278; 20 mg, q.d.: 271	Placebo: 278	4 weeks

(Continued)

Table 1. (Continued)

Study identifier	Type of publication	Country	Study design	Enrollment period	Population	Sample size	VPZ group (*n*)	Control group (*n*)	Duration of treatment
Kinoshita *et al.*[44]	Full text	Japan	RCT	2016.11–2018.2	Patients aged ⩾20 years with NERD	483	10 mg, q.d.: 238	Placebo: 245	4 weeks
Kusano *et al.*[45]	Full text	Japan	Single-arm	2015.4–2017.3	Junior high school students with *H. pylori* infection	118	20 mg, b.i.d.: 118	None	1 week
Maruyama *et al.*[46]	Full text	Japan	RCT	2015.4–2016.2	Patients with *H. pylori* infection	141	20 mg, b.i.d.: 72	RPZ, 20 mg/LPZ, 30 mg, b.i.d.: 69	1 week
Matsumoto *et al.*[47]	Full text	Japan	Cohort	2013.8–2016.3	Patients with *H. pylori* infection	420	20 mg, b.i.d.: 125	RPZ, 10 mg/LPZ, 30 mg/EPZ, 20 mg, b.i.d.: 295	1 week
Miwa *et al.*[12]	Full text	Japan	RCT	2011.10–2013.2	Patients aged ⩾20 years with DU	368	20 mg, q.d.: 183	LPZ, 30 mg, q.d.: 185	6 weeks
Miwa *et al.*[12]*	Full text	Japan	RCT	2011.11–2012.12	Patients aged ⩾20 years with GU	482	20 mg, q.d.: 244	LPZ, 30 mg, q.d.: 238	8 weeks
Mizokami *et al.*[13]	Full text	Japan	RCT	2011.10–2013.6	Patients aged ⩾20 years with a history of PUD and required continuous long-term therapy with NSAIDs	640	10 mg, q.d.: 218; 20 mg, q.d.: 212	LPZ, 15 mg, q.d.: 210	104 weeks
Mizuno *et al.*[48]	Full text	Japan	Single-arm	2016.3–2017.9	Patients aged ⩾20 years with healed EE	50	10 mg, q.d.: 50	None	48 weeks
Mizuno *et al.*[49]	Full text	Japan	Single-arm	2015.3–2017.1	Patients aged ⩾20 years with healed EE	52	10 mg, q.d.: 52	None	24 weeks
Mori *et al.*[50]	Full text	Japan	Cohort	2014.1–2016.12	Patients aged 27–92 years with *H. pylori* infection	524	20 mg, b.i.d.: 277	LPZ, 30 mg, b.i.d.: 251	1 week
Mukai *et al.*[51]	Full text	Japan	Cohort	2015.1–2016.12	Patients aged 21–88 years with *H. pylori* infection	421	271	PPI: 150	NA
Murakami *et al.*[52]	Full text	Japan	RCT	2012.2–2013.6	Patients aged ⩾20 years with *H. pylori* infection	650	20 mg, b.i.d.: 329 (first line)	LPZ, 30 mg, b.i.d.: 321 (first line)	1 week
Murakami *et al.*[52]*	Full text	Japan	RCT	2012.2–2013.6	Patients aged ⩾20 years with *H. pylori* infection	50	20 mg, b.i.d.: 50 (second line)	NA	1 week
Nabeta *et al.*[53]	Full text	Japan	Cohort	2014–2017	Patients with *H. pylori* infection	583	20 mg, b.i.d.: 309 (second line)	RPZ, 20 mg/LPZ, 30 mg, b.i.d.: 274 (second line)	1 week
NCT02743949[54]	Unpublished	European	RCT	2016.7–2018.10	Patients aged ⩾18 years with GERD	256	20 mg, q.d.: 85; 40 mg, q.d.: 85	EPZ, 40 mg, q.d.: 86	4 weeks
NCT03050307[55]	Unpublished	China and South Korea	RCT	2017.4–2020.3	Patients aged ⩾18 years with GU	234	20 mg, q.d.: 115	LPZ, 30 mg, q.d.: 119	8 weeks

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Table 1. (Continued)

Study identifier	Type of publication	Country	Study design	Enrollment period	Population	Sample size	VPZ group (*n*)	Control group (*n*)	Duration of treatment
Nishizawa *et al.*[56]	Full text	Japan	Cohort	2002.2–2016.6	Patients with *H. pylori* infection	917	20 mg, b.i.d.: 154 (first line); 20 mg, b.i.d.: 50 (second line)	RPZ, 10 mg/LPZ, 30 mg, b.i.d.: 529 (first line); RPZ, 10 mg/LPZ, 30 mg, b.i.d.: 184 (second line)	1 week
Okanobu *et al.*[57]	Full text	Japan	RCT	2018.4–2020.3	Patients aged ⩾20 years with EE	73	20 mg (4 weeks) + 10 mg (8 weeks), q.d.: 37; 10 mg, q.d.: 36	NA	12 weeks
Okubo *et al.*[58]	Full text	Japan	Single-arm	2015.3–2017.9	Patients aged 22–85 years with *H. pylori* infection	131	20 mg, b.i.d.:131	None	1 week
Ono *et al.*[59]	Full text	Japan	Cohort	2009.3–2016.7	Patients with *H. pylori* infection and allergic to penicillin	88	20 mg, b.i.d.: 17; 20 mg, b.i.d.: 14	RPZ, 20 mg/LPZ, 30 mg, b.i.d.: 44; RPZ, 20 mg/LPZ, 30 mg, b.i.d.: 13	1 week
Oshima *et al.*[60]	Full text	Japan	RCT	2015.8–2017.9	Patients aged ⩾20 years with endoscopically-confirmed healed GERD and a recent history of at least weekly heartburn episodes	32	20 mg, q.d.: 16	LPZ, 30 mg, q.d.: 16	2 weeks
Sakurai *et al.*[61]	Full text	Japan	RCT	2016.5–2017.11	Patients aged ⩾20 years with GERD symptoms	60	20 mg, q.d.: 30	EPZ, 20 mg, q.d.: 30	4 weeks
Sakurai *et al.*[62]	Full text	Japan	Cohort	2014.4–2015.12	Patients aged ⩾20 years with *H. pylori* infection	1353	20 mg, b.i.d.: 546 (first line); 20 mg, b.i.d.: 76 (second line)	EPZ, 20 mg, b.i.d.: 507 (first line) RPZ, 10 mg, b.i.d.: 89 LPZ, 30 mg, b.i.d.: 211; EPZ, 20 mg, b.i.d.: 104 (second line) RPZ, 10 mg, b.i.d.: 24 LPZ, 30 mg, b.i.d.: 57	1 week
Sasaki *et al.*[63]	Abstract	Japan	RCT	NA	Patients with *H. pylori* infection	110	20 mg, b.i.d.: 57	EPZ, 20 mg, b.i.d.: 43	1 week
Sato *et al.*[64]	Abstract	Japan	Cohort	2014.4–2015.3	Patients with *H. pylori* infection	728	728	NA	NA
Sato *et al.*[65]	Abstract	Japan	Cohort	2014.8–2016.2	Patients with *H. pylori* infection	390	20 mg, b.i.d.: 155	RPZ, 10 mg, b.i.d.: 78; LPZ, 30 mg, b.i.d.: 157	1 week
Shichijo *et al.*[66]	Full text	Japan	Cohort	2013.3–2015.11	Patients aged 16–93 years with *H. pylori* infection	2715	20 mg, b.i.d.: 422	RPZ, 10 mg/LPZ, 30 mg/EPZ, 20 mg/OPZ, 20 mg, b.i.d.: 2293	1 week
Shimada *et al.*[67]	Abstract	Japan	Cohort	2015.2–2017.12	Patients with *H. pylori* infection	420	20 mg, b.i.d.: 265; 20 mg, b.i.d.: 155	NA	1 week
Shinozaki *et al.*[15]	Full text	Japan	Cohort	2013.4–2015.7	Patients with *H. pylori* infection	573	20 mg, b.i.d.: 117	EPZ, 20 mg, b.i.d.: 120; RPZ, 10 mg, b.i.d.: 138; LPZ, 30 mg, b.i.d.: 198	1 week
Shinozaki *et al.*[68]	Full text	Japan	Single-arm	2016.2–2020.10	Patients aged 35–86 years with PPI-resistant GERD	47	10 mg or 20 mg, q.d.: 47	None	1 year

(Continued)

Table 1. (Continued)

Study identifier	Type of publication	Country	Study design	Enrollment period	Population	Sample size	VPZ group (*n*)	Control group (*n*)	Duration of treatment
Shinozaki *et al.*[69]	Full text	Japan	Single-arm	2016.2–2017.2	Patients with PPI-resistant GERD	24	10 mg, q.d.: 24	None	1 month
Shinozaki *et al.*[70]	Full text	Japan	Single-arm	2016.1–2017.3	Patients with GERD	88	10 mg, q.d.: 88	None	1 month
Sue *et al.*[71]	Full text	Japan	Cohort	2015.2–2016.2	Patients aged ⩾20 years with *H. pylori* infection	1215	20 mg, b.i.d.: 612	EPZ, 20 mg/RPZ, 10 mg/LPZ, 30 mg/OPZ, 20 mg, b.i.d.: 603	1 week
Sue *et al.*[71]*	Full text	Japan	Cohort	2015.2–2016.2	Patients aged ⩾20 years with *H. pylori* infection	356	20 mg, b.i.d.: 211	EPZ, 20 mg/RPZ, 10 mg/LPZ, 30 mg/OPZ, 20 mg, b.i.d.: 145	1 week
Sue *et al.*[72]	Full text	Japan	RCT	2015.2–2016.10	Patients aged ⩾20 years with *H. pylori* infection	106	20 mg, b.i.d.: 55	EPZ, 20 mg/RPZ, 10 mg/LPZ, 30 mg, b.i.d.: 51	1 week
Sue *et al.*[73]	Full text	Japan	Single-arm	2015.2–2019.5	Patients aged ⩾20 years with *H. pylori* infection	16	20 mg, b.i.d.: 16	None	1 week
Sue *et al.*[74]	Full text	Japan	RCT	2015.2–2017.9	Patients aged ⩾20 years with *H. pylori* infection	63	20 mg, b.i.d.: 33	EPZ, 20 mg/RPZ, 10 mg/LPZ, 30 mg, b.i.d.: 30	1 week
Sue *et al.*[75]	Full text	Japan	Cohort	2015.2–2016.4	Patients aged ⩾20 years with *H. pylori* infection	50	20 mg, b.i.d.: 20	EPZ, 20 mg/LPZ, 30 mg, b.i.d.: 30	1 week
Sugawara *et al.*[76]	Full text	Japan	Single-arm	2016.9–2018.3	Patients aged 20–90 years with GU	162	20 mg, q.d.: 20	None	6 or 8 weeks
Suzuki *et al.*[77]	Full text	Japan	RCT	2018.10–2019.6	Patients aged 20–79 years with *H. pylori* infection	335	20 mg, b.i.d.: 168 (VA-dual); 20 mg, b.i.d.: 167 (VAC-triple)	NA	1 week
Suzuki *et al.*[78]	Abstract	Japan	Single-arm	2015.3–2016.1	Patients with *H. pylori* infection	253	20 mg, b.i.d.: 253 (first line)	None	1 week
Suzuki *et al.*[79]	Full text	Japan	Cohort	2013.1–2015.10	Patients with *H. pylori* infection	661	20 mg, b.i.d.: 181	EPZ, 20 mg/LPZ, 30 mg, b.i.d.: 480	1 week
Tamaki *et al.*[80]	Abstract	Japan	RCT	2015.6–2016.10	Patients aged 20–89 years with *H. pylori* infection	345	20 mg, b.i.d.:169	EPZ, 20 mg, b.i.d.: 176	1 week
Tanaka *et al.*[81]	Abstract	Japan	Cohort	2015.4–2017.12	Patients with *H. pylori* infection	55	20 mg, b.i.d.: 10	PPI, b.i.d.: 45	1 week
Tokunaga *et al.*[82]	Abstract	Japan	Single-arm	NA	Patients with *H. pylori* infection	12	10 mg, q.i.d.: 12	None	2 weeks
Tsuchiya *et al.*[83]	Full text	Japan	RCT	2015.4–2016.6	Patients with artificial ulcers after gastric ESD	80	20 mg, q.d.: 39	EPZ, 20 mg: 41	8 weeks
Tsujimae *et al.*[84]	Full text	Japan	Cohort	2013.11–2016.6	Patients with *H. pylori* infection	866	20 mg, b.i.d.: 439	EPZ, 20 mg: 427	1 week
Tungtrongchitr *et al.*[85]	Abstract	Thailand	RCT	NA	Patients with *H. pylori* infection	43	20 mg, b.i.d.: 22; 20 mg, b.i.d.: 21	NA	1 week; 2 weeks

(Continued)

Table 1. (Continued)

Study identifier	Type of publication	Country	Study design	Enrollment period	Population	Sample size	VPZ group (*n*)	Control group (*n*)	Duration of treatment
Xiao *et al*.[86]	Abstract	China	RCT	NA	Adult patients with endoscopically-confirmed healed EE	536	10 mg, q.d.: 181; 20 mg, q.d.: 171	LPZ, 15 mg, q.d.: 184	24 weeks
Xiao *et al*.[14]	Full text	China, South Korea, and Malaysia	RCT	2015.3–2017.6	Patients aged ⩾18 years with endoscopically confirmed EE	479	20 mg, q.d.: 244	LPZ, 30 mg, q.d.: 235	8 weeks
Yamada *et al*.[87]	Full text	Japan	Cohort	2013.3–2015.9	Patients aged 18–94 years with *H. pylori* infection	2507	20 mg, b.i.d.: 335 (first line); 20 mg, b.i.d.: 66 (second line)	RPZ, 10 mg/ LPZ, 30 mg/ EPZ, 20 mg, b.i.d.: 1720 (first line); RPZ, 10 mg/ LPZ, 30 mg/EPZ, 20 mg, b.i.d.: 386 (second line)	1 week
Yoshii *et al*.[88]	Full text	Japan	Single-arm	2015.12–2018.6	Patients aged ⩾20 years with artificial ulcers after gastric ESD	49	20 mg, q.d.: 49	None	4 weeks
Zuberi *et al*.[89]	Full text	Pakistan	RCT	2021.6–2021.9	Patients aged 18–75 years with *H. pylori* infection	179	20 mg, b.i.d.: 92	OPZ, 20 mg, b.i.d.: 87	2 weeks

VPZ-triple, VAC-triple, VA-dual, LPZ-triple, first line, second line, and third line are the *H. pylori* eradication protocols in each study, which are defined in accordance with the reports of each study.
*Two cohorts in one study.
DU, duodenal ulcer; EE, erosive esophagitis; EPZ, esomeprazole; ESD, endoscopic submucosal dissection; GERD, gastroesophageal reflux disease; GU, gastric ulcer; *H. pylori*, *Helicobacter pylori*; LDA, low-dose aspirin; LPZ, lansoprazole; NA, not available; NERD, non-erosive reflux disease; NSAIDs, nonsteroidal anti-inflammatory drugs; OPZ, omeprazole; PPI, proton pump inhibitor; PUD, peptic ulcer disease; RCT, randomized controlled trial; RPZ, rabeprazole; VPZ, vonoprazan.

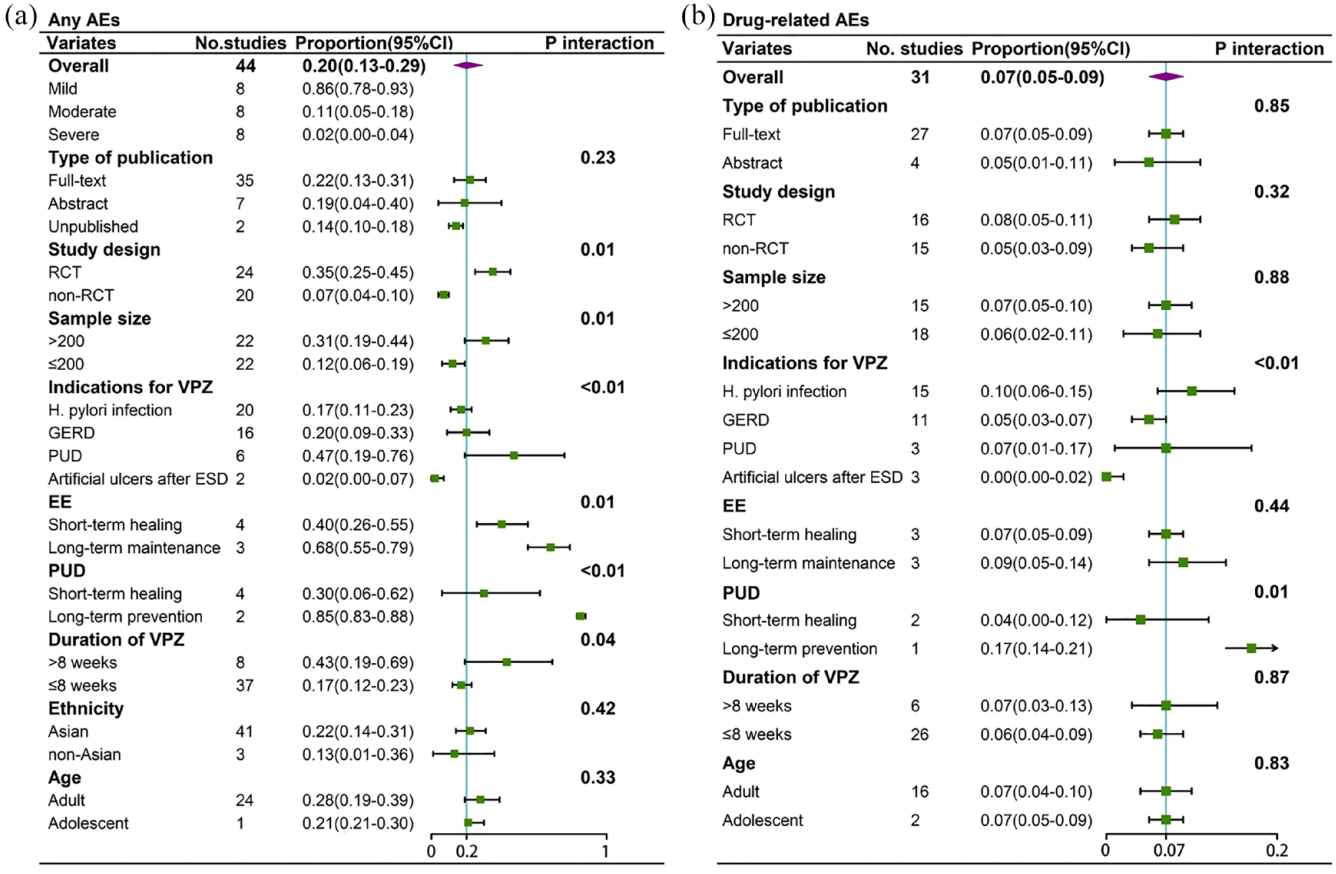

Figure 2. Forest plots of the incidences of any AEs (a) and drug-related AEs (b) in patients taking vonoprazan.
AE, adverse event; CI, confidence interval; EE, erosive esophagitis; ESD, endoscopic submucosal dissection; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; PUD, peptic ulcer disease; RCT, randomized controlled trial; VPZ, vonoprazan.

Study quality

Quality of RCTs, cohort studies, and single-arm studies were summarized in Supplemental Figure 1, Supplemental Table 1, and Supplemental Table 2, respectively. Most of the included studies were of moderate and high quality.

Incidence of AEs in patients taking vonoprazan

Any AEs. Forty-four studies explored the incidence of any AEs in patients taking vonoprazan (Figure 2(a)). The pooled incidence of any AEs was 20% (95% CI = 13–29%) with significant heterogeneity ($I^2 = 98.9\%$; $p < 0.01$). Meta-regression analyses demonstrated that the heterogeneity might be attributed to the study design, sample size, and duration of vonoprazan (Supplemental Table 3). No significant publication bias was detected ($p = 0.483$).

Eight of the 44 studies reported the severity of any AEs. The pooled incidences of mild, moderate, and severe AEs were 86, 11, and 2%, respectively (Figure 2(a)).

In subgroup analyses, the pooled incidence of any AEs was 17, 20, 47, and 2% in patients taking vonoprazan for the management of *H. pylori* infection, GERD, PUD, and artificial ulcers after gastric ESD, respectively ($p_{interaction} < 0.01$); 40 and 68% in those for short-term healing of EE and long-term maintenance of healed EE, respectively ($p_{interaction} = 0.01$); 30 and 85% in those for short-term healing of PUD and long-term secondary prevention of PUD, respectively ($p_{interaction} < 0.01$); 43 and 17% in those for a duration of >8 weeks and ≤8 weeks, respectively ($p_{interaction} = 0.04$); 22 and 13% in Asian and non-Asian patients taking vonoprazan, respectively

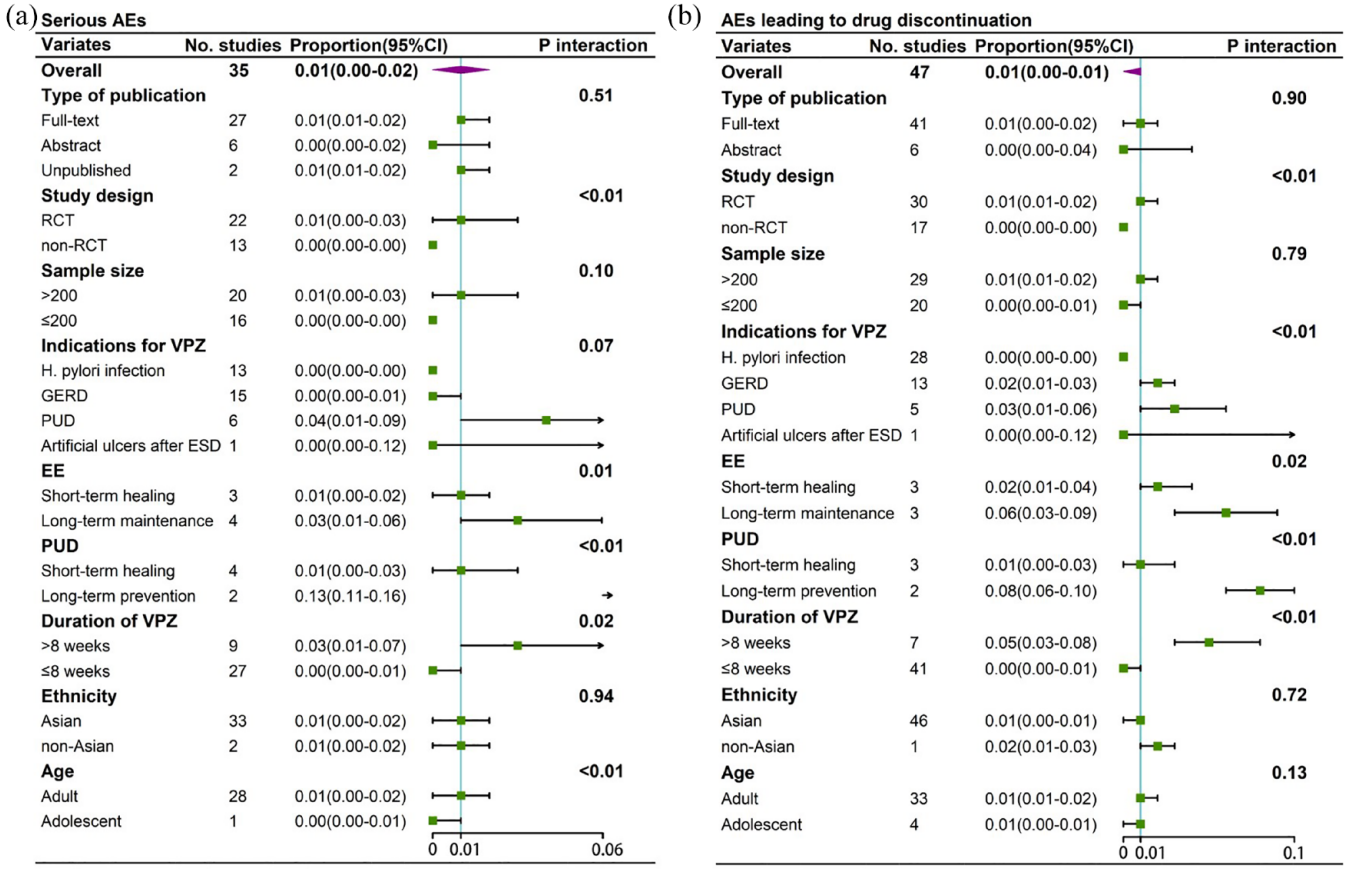

Figure 3. Forest plots of the incidences of serious AEs (a) and AEs leading to drug discontinuation (b) in patients taking vonoprazan.
AE, adverse event; CI, confidence interval; EE, erosive esophagitis; ESD, endoscopic submucosal dissection; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; PUD, peptic ulcer disease; RCT, randomized controlled trial; VPZ, vonoprazan.

($p_{interaction}$ = 0.42); and 28 and 21% in adult and adolescent patients taking vonoprazan, respectively ($p_{interaction}$ = 0.33) (Figure 2(a)).

Drug-related AEs. Thirty-one studies explored the incidence of drug-related AEs in patients taking vonoprazan (Figure 2(b)). Meta-analysis demonstrated that the pooled incidence of drug-related AEs was 7% (95% CI = 5–9%) with significant heterogeneity (I^2 = 88.8%; p < 0.01). Meta-regression analyses did not find any source of heterogeneity (Supplemental Table 3). No significant publication bias was detected (p = 0.987).

In subgroup analyses, the pooled incidence of drug-related AEs was 10, 5, 7, and 0% in patients taking vonoprazan for the management of *H. pylori* infection, GERD, PUD, and artificial ulcers after gastric ESD, respectively ($p_{interaction}$ < 0.01); 7 and 9% in those for short-term healing of EE and long-term maintenance of healed EE, respectively ($p_{interaction}$ = 0.44); 4 and 17% in those for short-term healing of PUD and long-term secondary prevention of PUD, respectively ($p_{interaction}$ = 0.01); 7 and 6% in those for a duration of >8 weeks and ≤8 weeks, respectively ($p_{interaction}$ = 0.87); and 7 and 7% in adult and adolescent patients taking vonoprazan, respectively ($p_{interaction}$ = 0.83) (Figure 2(b)).

Serious AEs. Thirty-five studies explored the incidence of serious AEs in patients taking vonoprazan (Figure 3(a)). Meta-analysis demonstrated that the pooled incidence of serious AEs was 1% (95% CI = 0–2%) with significant heterogeneity (I^2 = 90.8%; p < 0.01). Meta-regression analyses demonstrated that the heterogeneity might be attributed to the indications for vonoprazan and duration of vonoprazan (Supplemental Table 3). No significant publication bias was detected (p = 0.544).

In subgroup analyses, the pooled incidence of serious AEs was 0, 0, 4, and 0% in patients taking

vonoprazan for the management of *H. pylori* infection, GERD, PUD, and artificial ulcers after gastric ESD, respectively ($p_{interaction} = 0.07$); 1 and 3% in those for short-term healing of EE and long-term maintenance of healed EE, respectively ($p_{interaction} = 0.01$); 1 and 13% in those for short-term healing of PUD and long-term secondary prevention of PUD, respectively ($p_{interaction} < 0.01$); 3 and 0% in those for a duration of >8 weeks and ≤8 weeks, respectively ($p_{interaction} = 0.02$); 1 and 1% in Asian and non-Asian patients taking vonoprazan, respectively ($p_{interaction} = 0.94$); and 1 and 0% in adult and adolescent patients taking vonoprazan, respectively ($p_{interaction} < 0.01$) (Figure 3(a)).

AEs leading to drug discontinuation. Forty-seven studies explored the incidence of AEs leading to drug discontinuation in patients taking vonoprazan (Figure 3(b)). Meta-analysis demonstrated that the pooled incidence of AEs leading to drug discontinuation was 1% (95% CI = 0–1%) with significant heterogeneity ($I^2 = 83.0\%$; $p < 0.01$). Meta-regression analyses demonstrated that the heterogeneity might be attributed to the duration of vonoprazan (Supplemental Table 3). No significant publication bias was detected ($p = 0.578$).

In subgroup analyses, the pooled incidence of AEs leading to drug discontinuation was 0, 2, 3, and 0% in patients taking vonoprazan for the management of *H. pylori* infection, GERD, PUD, and artificial ulcers after gastric ESD, respectively ($p_{interaction} < 0.01$); 2 and 6% in those for short-term healing of EE and long-term maintenance of healed EE, respectively ($p_{interaction} = 0.02$); 1 and 8% in those for short-term healing of PUD and long-term secondary prevention of PUD, respectively ($p_{interaction} < 0.01$); 5 and 0% in those for a duration of >8 weeks and ≤8 weeks, respectively ($p_{interaction} < 0.01$); 1 and 2% in Asian and non-Asian patients taking vonoprazan, respectively ($p_{interaction} = 0.72$); and 1 and 1% in adult and adolescent patients taking vonoprazan, respectively ($p_{interaction} = 0.13$) (Figure 3(b)).

Common AEs. Meta-analyses demonstrated that increased serum gastrin level was the most common AE (19%, 95% CI = 3–44%), followed by increased pepsinogen I level (17%, 95% CI = 2–43%), nasopharyngitis (14%, 95% CI = 7–22%), bloating (9%, 95% CI = 4–15%), loose stools (8%, 95% CI = 4–15%), diarrhea (7%, 95% CI = 4–9%), heart burn (6%, 95% CI = 3–9%), abdominal pain (5%, 95% CI = 2–9%), and upper respiratory tract infection (5%, 95% CI = 3–8%) (Table 2).

Difference in the incidence of AEs between patients taking vonoprazan versus *PPIs*

Any AEs. Twenty-six studies compared the incidence of any AEs between patients taking vonoprazan *versus* PPIs (Supplemental Figure 2). Meta-analysis demonstrated that the incidence of any AEs was statistically similar between patients taking vonoprazan *versus* PPIs (OR = 0.96, 95% CI = 0.80–1.15, $p = 0.66$) with significant heterogeneity ($I^2 = 69.0\%$; $p < 0.01$). Meta-regression analyses demonstrated that the heterogeneity might be attributed to the type of publication and study design (Supplemental Table 3). No significant publication bias was detected ($p = 0.768$).

Drug-related AEs. Twenty studies compared the incidence of drug-related AEs between patients taking vonoprazan *versus* PPIs (Supplemental Figure 3). Meta-analysis demonstrated that the incidence of drug-related AEs was statistically similar between patients taking vonoprazan *versus* PPIs (OR = 1.10, 95% CI = 0.87–1.39, $p = 0.52$) with significant heterogeneity ($I^2 = 42.0\%$; $p = 0.04$). Meta-regression analyses did not find any source of heterogeneity (Supplemental Table 3). No significant publication bias was detected ($p = 0.472$).

Serious AEs. Twenty-one studies compared the incidence of serious AEs between patients taking vonoprazan *versus* PPIs (Supplemental Figure 4). Meta-analysis demonstrated that the incidence of serious AEs was statistically similar between patients taking vonoprazan *versus* PPIs (OR = 1.14, 95% CI = 0.87–1.49, $p = 0.36$). There was no statistically significant heterogeneity ($I^2 = 0.0\%$; $p = 0.93$). No significant publication bias was detected ($p = 0.579$).

AEs leading to drug discontinuation. Thirty-one studies compared the incidence of AEs leading to drug discontinuation between patients taking vonoprazan *versus* PPIs (Supplemental Figure 5). Meta-analysis demonstrated that the incidence of AEs leading to drug discontinuation was statistically similar between patients taking vonoprazan *versus* PPIs (OR = 1.09, 95% CI = 0.82–1.45,

Table 2. Results of meta-analyses regarding common AEs.

Common AEs	No. studies	No. studies reporting the incidence	Effect size (95% CI)	Heterogeneity	
				I^2 (%)	*p* Value
Diarrhea	46	36	0.07 (0.04–0.09)	95.5	<0.01
Rash	30	24	0.02 (0.01–0.03)	56.0	<0.01
Nausea	22	15	0.03 (0.01–0.05)	85.5	<0.01
Abdominal pain	20	19	0.05 (0.02–0.09)	95.0	<0.01
Bloating	19	19	0.09 (0.04–0.15)	96.1	<0.01
Dysgeusia	19	19	0.03 (0.01–0.06)	92.6	<0.01
Increased serum gastrin level	14	3	0.19 (0.03–0.44)	97.7	<0.01
Constipation	13	13	0.02 (0.01–0.04)	82.9	<0.01
Vomiting	13	7	0.02 (0.01–0.03)	0.0	0.91
Headache	10	10	0.04 (0.01–0.07)	85.4	<0.01
Increased pepsinogen I level	9	3	0.17 (0.20–0.43)	97.9	0.01
Heart burn	8	7	0.06 (0.03–0.09)	48.8	0.07
Nasopharyngitis	8	6	0.14 (0.07–0.22)	96.9	<0.01
Loose stools	8	5	0.08 (0.04–0.15)	81.2	<0.01
Stomatitis	7	5	0.01 (0.00–0.02)	74.6	0.02
Increased pepsinogen II level	7	0	/	/	/
Upper respiratory tract infection	6	6	0.05 (0.03–0.08)	88.9	<0.01
Abnormal liver function	6	6	0.04 (0.02–0.05)	36.8	0.13

AE, adverse event; CI, confidence interval.

$p = 0.55$). There was no statistically significant heterogeneity ($I^2 = 5.0\%$; $p = 0.39$). No significant publication bias was detected ($p = 0.395$).

Common AEs. Meta-analyses demonstrated that the incidences of increased serum gastrin (OR = 6.25, 95% CI = 4.08–9.59, $p < 0.01$) and pepsinogen I levels (OR = 3.49, 95% CI = 2.40–5.10, $p < 0.01$) were significantly higher in patients taking vonoprazan than those taking PPIs. There was no statistically significant heterogeneity ($I^2 = 0\%$; $p = 0.45$ and $I^2 = 0\%$; $p = 0.66$, respectively). The incidence of diarrhea was significantly lower in patients taking vonoprazan than those taking PPIs (OR = 0.73, 95% CI = 0.57–0.94, $p = 0.32$) with significant heterogeneity ($I^2 = 57.7\%$; $p < 0.01$). The incidences of other common AEs were statistically similar between patients taking vonoprazan and PPIs (Figure 4).

Discussion

Our study has systematically reviewed the currently available evidence regarding the safety profile of vonoprazan, and found that the pooled incidences of any AEs, drug-related AEs, serious AEs, and AEs leading to drug discontinuation

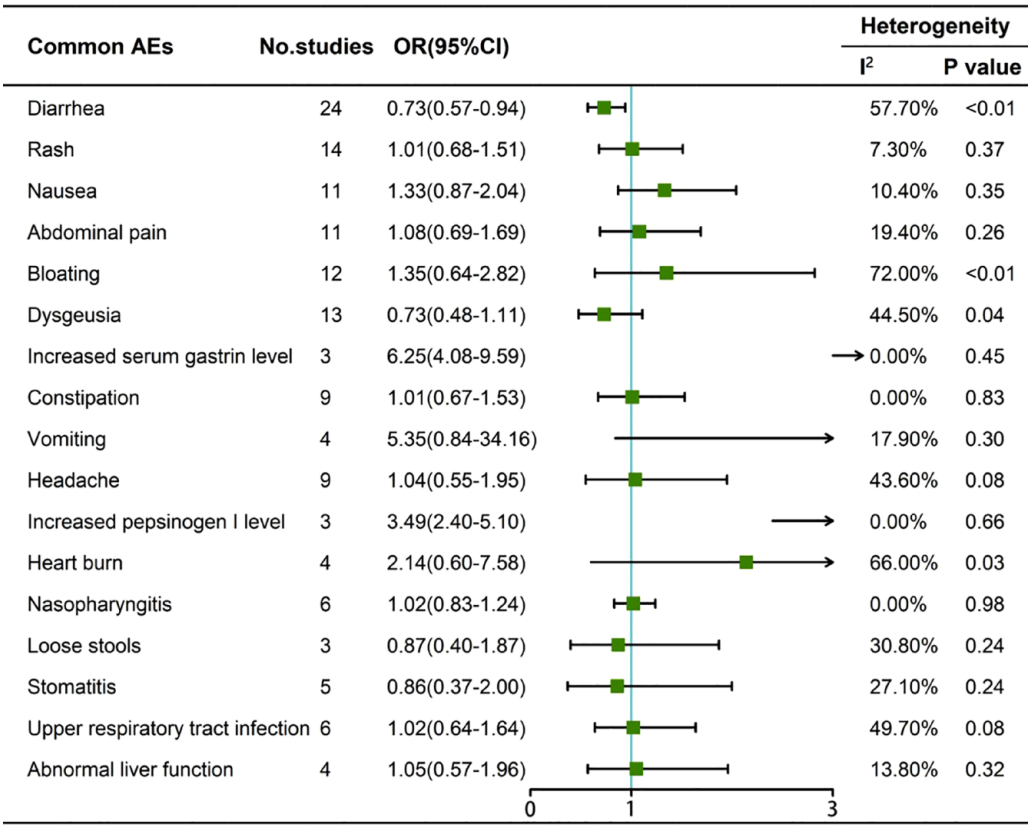

Figure 4. Difference in the incidence of common AEs between patients taking vonoprazan *versus* PPIs.
AE, adverse event; CI, confidence interval; OR, odds ratio; PPI, proton pump inhibitor.

were 20, 7, 1, and 1%, respectively; nearly all the reported AEs were mild; and its safety was similar to that of PPIs.

Our meta-analysis has some features as compared to previous ones, as follows. First, previous meta-analyses explored the safety of vonoprazan for a certain indication.[90–94] By comparison, our meta-analysis more comprehensively evaluated the safety of vonoprazan across multiple indications, including *H. pylori* infection, GERD, PUD, and artificial ulcers after gastric ESD. Second, previous meta-analyses only explored AEs leading to drug discontinuation and/or any AEs.[90–94] By comparison, our meta-analyses also evaluated drug-related and serious AEs. Third, our meta-analysis, but not previous meta-analyses,[90–94] evaluated a broader spectrum of common AEs and various severity of any AEs in patients taking vonoprazan.

Due to the lack of relevant data, we were not able to directly analyze the risk factors affecting the safety of vonoprazan. However, we performed subgroup analyses to evaluate the incidence of AEs in patients taking vonoprazan according to various conditions. First, patients with PUD had higher incidences of any AEs, serious AEs, and AEs leading to drug discontinuation than those with GERD, *H. pylori* infection, and artificial ulcer after gastric ESD. This might be because PUD is more complex and severe than other disease conditions, and requires a longer duration of vonoprazan.[95] Specifically, we included both studies regarding short-term healing of PUD and long-term secondary prevention of non-steroidal anti-inflammatory drugs or aspirin-induced PUD into the same subgroup. In short-term healing of PUD studies, some patients with PUD had concomitant *H. pylori* infection which needs to be eradicated by vonoprazan combined with other drugs.[32,55] In long-term secondary prevention of PUD studies, patients required a longer duration of vonoprazan.[13,42] Second, patients with *H. pylori* infection had a higher incidence of drug-related AEs than those with PUD, GERD, and artificial

ulcer after gastric ESD. This was mainly because multiple drugs, including antibiotics, bismuth, and probiotics, should be added along with vonoprazan for *H. pylori* eradication.[23,40] Third, it is readily understood that the incidence of AEs was higher in patients taking long-term (>8 weeks) use of vonoprazan than those taking short-term (⩽8 weeks) use of vonoprazan. This finding was also observed in patients taking vonoprazan for the management of EE and PUD. Fourth, the race of the population taking vonoprazan (i.e., Asian and non-Asian) might not influence the risk of AEs. Recently, a population pharmacokinetic model evaluated the impact of the population from Asia and Europe on vonoprazan exposure, and also showed that the population effect on vonoprazan exposure was limited.[96] Fifth, the incidence of AEs also seemed to be similar between adult and adolescent patients taking vonoprazan, which suggested that vonoprazan can be safe and well tolerated in both adults and adolescents. However, this finding required further validation in adolescents.

Increased serum gastrin and pepsinogen I levels might be the most common AEs, and their incidences were significantly higher in patients taking vonoprazan than those taking PPIs. They are believed to be a consequence of the potent gastric acid antisecretory effect of vonoprazan,[13] which is similar to PPIs,[10,14,32,42] but they do not cause any harmful effects on gastric mucosa.[13,21] The VISION trial evaluated the effect of vonoprazan on gastric mucosal tissue and its long-term safety. The four-year interim analysis found significantly higher levels of serum gastrin and pepsinogen I in the vonoprazan group than the lansoprazole group. Additionally, a case of foveolar-type adenoma developed in the vonoprazan group, and a case of oxyntic gland adenoma in the lansoprazole group. Histologically, hyperplasia of parietal cells and G cells was more frequently detected in the vonoprazan group. There was no neoplastic proliferation of endocrine cells in either group.[97] However, a case of foveolar-type gastric adenocarcinoma has recently been reported in a male patient with EE after a 156-week maintenance therapy of vonoprazan 10 mg daily.[98] In addition, gastric mucosal redness, 'stardust gastric mucosa', and white globe appearance can be observed in patients taking vonoprazan,[99–101] but they are not of major clinical significance. Other common AEs were infrequent, and their incidences were similar to that of PPIs.

It has been reported that long-term use of PPIs may also lead to clostridium difficile infection, osteoporosis, vitamin B_{12} deficiency, hypomagnesemia, and fundic gland polyp,[102] but they have never been found in our meta-analysis. Certainly, such AEs in patients receiving long-term use of vonoprazan deserves further observations.

PPIs exposure is associated with increased risk of infection, decompensation, and death in cirrhosis and that of progression to renal insufficiency in chronic kidney disease.[103–105] However, to date, no studies have reported that vonoprazan would cause such AEs. Indeed, patients with cirrhosis and chronic kidney disease were often excluded from our included studies, failing to evaluate the safety of vonoprazan in such patients. In future, prospective studies are needed to evaluate the safety of vonoprazan in patients with cirrhosis and chronic kidney diseases.

Our meta-analysis has some limitations as follows. First, a proportion of included studies were single-arm without control groups. Second, 18 studies were published as abstracts and 2 were unpublished clinical trials. Third, these included studies were mainly conducted in Japan. Fourth, we did not clearly discriminate which AEs were caused by PPIs/vonoprazan or antibiotics during *H. pylori* eradication therapy. Fifth, the heterogeneity among studies was statistically significant in most of our meta-analyses. Sixth, combined medication and underlying comorbidities, which might influence the safety of vonoprazan, could not be sufficiently evaluated in subgroup analyses.

Conclusion

Based on the current systematic review and meta-analysis, vonoprazan often has similar safety compared to PPIs, and rarely causes serious AEs and drug discontinuation. It seems that vonoprazan has a favorable safety profile in adolescent patients and non-Asian population. Furthermore, the safety of vonoprazan may be influenced by its indications and duration. However, more high-quality studies are necessary in future to validate these findings and to explore the risk factors affecting the safety of vonoprazan.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have made an intellectual contribution to the manuscript and approved the submission.

Author contributions

Wentao Xu: Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Writing – original draft; Writing – review & editing.

Zhaohui Bai: Data curation; Formal analysis; Methodology; Software; Supervision; Writing – review & editing.

Yiyang Shang: Data curation; Supervision; Validation.

Jing Wang: Formal analysis; Supervision; Writing – review & editing.

Yujun Wong: Investigation; Supervision; Writing – review & editing.

Xingshun Qi: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data sharing is not applicable to this article as no new data were created in this study.

ORCID iDs

Wentao Xu https://orcid.org/0000-0002-0156-791X

Zhaohui Bai https://orcid.org/0000-0001-6206-7153

Yiyang Shang https://orcid.org/0000-0003-3128-7991

Xingshun Qi https://orcid.org/0000-0002-9448-6739

Supplemental material

Supplemental material for this article is available online.

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