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REVIEW ARTICLE

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Effectiveness and safety of vonoprazan-based regimen for *Helicobacter pylori* eradication: A meta-analysis of randomized clinical trials

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Abstract

What is known and objective: The *Helicobacter pylori* (*H. pylori*) eradication rate of proton pump inhibitor (PPI)-based regimen remains decreasing. Vonoprazan (VPZ), a stronger and longer-lasting acid blocker, has been proposed to treatment of *H. pylori* infection. However, previous reviews did not have a pre-established study protocol and did not conduct a comprehensive search of the database, so the results obtained were not robust. We aimed to perform a meta-analysis to assess the effectiveness and safety of VPZ-based regimens for treatment of *H. pylori* infection in comparison with other regimens.

Methods: We conducted a systematic literature search on PubMed, Embase, Cochrane Library, Web of Science, ClinicalTrials and ChiCTR Register. Randomized clinical trials comparing VPZ-based regimens with similar eradication regimens without VPZ in the treatment of *H. pylori* infection were included. Eradication rate, compliance of the patients and side effects were specified as the primary outcomes. RevMan 5.4 software was used to analyze the RCTs and provide pooled risk ratio (RR) with 95% confidence intervals (CI). Systematic searches, study selection, data extraction, risk of bias assessment and statistical analysis were performed by two independent researchers according to the predesigned criteria on the PROSPERO.

Results and discussion: A total of 8 RCTs with 2012 patients qualified for evaluation. The results showed that the eradication rate of VPZ-containing regimens was significantly superior to PPI-containing regimens for both intention-to-treat (RR, 1.14; 95% CI: 1.06–1.23; $p = 0.0006$) and per-protocol analyses (RR, 1.12; 95% CI: 1.04–1.20; $p = 0.003$). Subgroup analysis based on treatment regimens, eradication experience and clarithromycin resistance, as well as sensitivity analysis further confirmed this finding. In addition, there was no significant difference in compliance (RR, 1.02; 95% CI: 0.98–0.1.05; $p = 0.35$) and the frequency of adverse events (RR, 0.84; 95% CI: 0.70–1.00; $p = 0.05$) between the regimens.

What is new and conclusion: Compared with PPI-based regimens, the VPZ-containing regimens showed a comparable or even superior eradication rate of *H. pylori* in terms of overall comparison and comparison of different treatment regimens, eradication

Chen Yang and Sai Li are contributes equally to this work.

experience and clarithromycin resistance. In addition, VPZ-based regimens have better tolerability and fewer adverse events. More future studies are needed to evaluate the impact of some differences in patient characteristics.

Trial registration: PROSPERO CRD42021229598.

KEYWORDS

Helicobacter pylori eradication, meta-analysis, proton-pump inhibitor, vonoprazan

1 | INTRODUCTION

According to the US Centers for Disease Control and Prevention, about two-thirds of the world's human population is colonized by *Helicobacter pylori*, especially in developing countries.[1] As a human carcinogen, *H. pylori* has been confirmed to be closely related to the occurrence of peptic ulcer, gastric cancer, distal gastric adenocarcinoma and B cell mucosa-associated lymphoid.[2] Multitudes of studies clearly indicate that the eradication of *H. pylori* is beneficial to the prevention and treatment of gastrointestinal diseases, such as reducing the incidence of gastric cancer and preventing the recurrence of peptic ulcer.[3–5] Therefore, it is recommended that patients with *H. pylori* infection receive eradication treatment.[5,6]

For *H. pylori* infection, PPI-based triple therapy and bismuth-containing quadruple therapy have recommended first-line eradication regimen in different countries.[6–9] However, the success ratio of PPI-containing regimens has gradually declined in recent years, and the insufficient acid suppression effect is considered to be non-negligible.[10–12] Sustained and sufficient acid suppression can make *H. pylori* in a drug-susceptible replicative state, while increasing the intragastric pH levels can improve the stability and concentration of antibiotics such as clarithromycin and amoxicillin.[12,13] However, the acid suppression effect of the prodrug PPI is affected by diet and CYP2C19 polymorphisms, with a late onset of action and a short half-life.[14] Excellent acid inhibitors urgently need to be found and used in the eradication strategies of *H. pylori*.

Vonoprazan (VPZ), a reversible H^+-K^+ ATPase inhibitor, have a faster and longer-lasting acid suppressive effect, which is not affected by diet and genes polymorphisms.[15,16] It has been approved in China for the treatment of reflux esophagitis in 2019 and considered to be an ideal candidate to improve the *H. pylori* eradication rate. Several meta-analysis have showed that superior efficacy of VPZ-based eradication regimens compared to PPI-based conventional regimens.[17–20] However, these meta-analyses either mainly included nonrandomized controlled trials, or insufficient subgroup discussion for various situations. Thus, we conducted a meta-analysis using RCTs to investigate the efficacy and safety of VPZ-based therapy for *H. pylori* eradication, and sufficient subgroup discussions were conducted on various situations.

2 | METHODS

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Cochrane handbook for systematic reviews of interventions. We prospectively documented this meta-analysis on the PROSPERO (CRD42019133002).

2.1 | Search strategy

Two independent researchers performed systematic searches of PubMed, Embase, Web of Science and Cochrane Library to identify relevant RCTs without language restrictions (updated to June 15, 2021). In addition, the ClinicalTrials.gov and ChiCTR Register were searched for unpublished studies. The search strategy combined terms related to *H. pylori*, vonoprazan and RCT. The details of search strategy on PubMed were described in the Table S1.

2.2 | Study selection

All papers were assessed by two independent researchers using predesigned criteria. The included criteria were as follows: (1) patients: *H. pylori* infection was diagnosed based on one or more confirmatory tests that included urea breath test, biopsy/bacterial culture, histological examination, rapid urea test, Anti-*H. pylori* IgG antibody test or stool antigen test; (2) intervention: VPZ-based therapy; (3) comparison: eradication therapy without VPZ which included the triple therapy, bismuth quadruple therapy, concomitant therapy, high dose dual therapy, sequential therapy and hybrid therapy; (4) outcomes: eradication rate, compliance of the patients and adverse events. (5) study design: RCT. Any disagreement was resolved by discussion between the two researchers.

2.3 | Data extraction

Data were extracted separately by two researchers through a predefined excel table containing the following information: first author, year of publication, trial registration number, study period, setting (country), age, treatment experience, test to diagnose, details

of each arm (drugs, doses, frequencies, and duration of medicine dosing), sample size, time to test after therapy, test to confirm eradication, funding. Authors or directors of the included studies were contacted via E-mail if needed.

2.4 | Risk of bias assessment

Two researchers independently performed the risk of bias assessment according to the Cochrane risk of bias tool (NOS), with any discrepancies resolved by consensus.

2.5 | Statistical analysis

The endpoints of interest in the pooled analysis were eradication rate, compliance of the patients and side effects. To identify potential sources of heterogeneity, sensitivity analysis and subgroup analysis were further performed. There were two ways of sensitivity analysis employed in the study. One was omitting one study in each turn and the other was simultaneously excluding small sample studies (less than 50 per group) and conference abstracts to examine the impact on the overall results. Subgroup analysis was performed according to the following items: treatment regimens (triple therapy versus bismuth quadruple therapy) or duration of treatment (7 days vs. 14 days), eradication experiences (treatment-naive vs. treatment-experienced vs. treatment-unclear), clarithromycin-resistant status (clarithromycin-susceptibility strains vs. clarithromycin-resistant strains).

Meta-analysis was performed by using RevMan software version 5.4 (provided by the Cochrane Collaboration 2020, Copenhagen, Denmark). In tests for overall heterogeneity, the Chi^2 (χ^2) test and inconsistency index (I^2) statistic were calculated. When the p-value for the χ^2 was bigger than 0.1 or I^2 value less than 50%, heterogeneity was considered acceptable. The pooled risk ratios (RRs) along with 95% confidence intervals (CI) were calculated using fixed-effect models when there was acceptable heterogeneity among studies. Otherwise, random-effect models were used. In the subgroup analysis, random-effect models were always used. In tests for overall effect, p values less than 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Study selection and characteristics of included studies

In all, 159 studies were yielded using the defined terms. Forty-four studies were removed using Endnote software Version X9. After screening the titles and abstracts, another 101 studies were further excluded because they did not meet with the inclusion criteria of the current meta-analysis. The remaining 14 studies were reassessed and 6 were further excluded because they were the same studies of different versions. The flow diagram of study selection was summarized in Figure 1.

Finally, there were 8 studies including 6 full-length articles,[21–26]1 conference abstract[27] and 1 unpublished clinical trial[28] met with the inclusion criteria and enrolled in this meta-analysis. The characteristics of the included studies were shown in Table 1. These studies were published between 2016 and 2021, and their enrolment periods ranged from 2012 to 2019. A total of 1023 participants received VPZ-based therapies, and 989 patients received PPI-containing therapies as control group. Of the 8 studies, five studies recruited treatment-naive patients,[21,22,26–28]two recruited treatment-experienced patients[23,25] and one did not report treatment experience of enrolled patients.[24] Six trials using the triple therapy were lasted for 7 days[21–23,25–27] and the other two trials using the bismuth quadruple therapy were lasted for 14 days.[24,28]

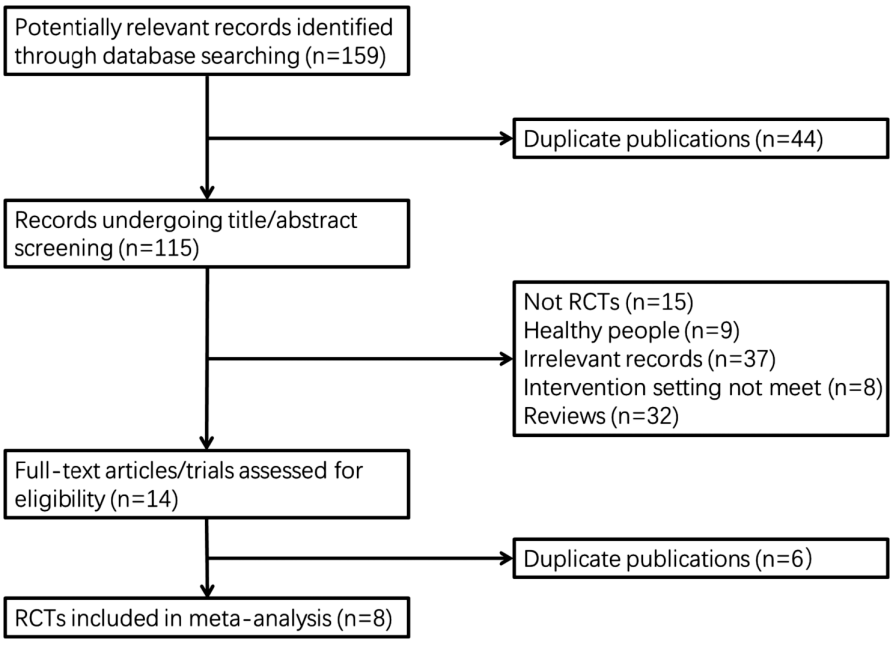

FIGURE 1 Flow diagram of study selection

TABLE 1 Characteristics of included RCT studies in this meta-analysis

Study	Trial registration number	Study period	Setting (country)	Age	Treatment experience	Test to diagnose
Murakami 2016[21]	NCT01505127	201202–201306	Multicentre (46 sites in Japan)	≥20	First	RUT/UBT/C/SAT
Maruyama 2017[22]	ID21148	201504–201602	Single-centre (Japan)	<80	First	UBT
Sue 2018[26]	UMIN000016337	201502–201610	Multicentre (3 sites in Japan)	≥20	First	AB/RUT/C/H/UBT
Sue 2019[23]	UMIN000016336	201502–201709	Single-centre (Japan)	≥20	Third	UBT/SAT/AB/RUT/C
Tamaki 2019[a,27]	NA	201506–201805	Multicentre (Japan)	NA	First	UBT
Hojo 2020[25]	UMIN000016601	201503–201703	Two-centres (Japan)	NA	Second	UBT/SAT/RUT/H
Huh 2021[24]	NCT02892409	201609–201705	Single-centre (Korea)	19–60	Unclear	UBT
NCT03050359[b,28]	NCT03050359	201704–201907	Multicentre (52 sites in China and Korea)	≥18	First	UBT

Abbreviations: AB, anti-*H. pylori* IgG antibody testing; Amo, amoxicillin; C, biopsy/bacterial culture; Cla, clarithromycin; Eso, esomeprazole; H, histological examination; Lan, lansoprazole; Met, metronidazole; NA, not available; Rab, rabeprazole; RUT, rapid urea test; SAT, stool antigen test; Sit, sitafloxacin; UBT, urea breath test; VPZ, vonoprazan.

[a]Conference abstract.

[b]Unpublished clinical trial.

3.2 | Risk of bias in included studies

Risks of bias within individual studies were shown in Figure 2. Blinding of participants and personnel was the main source of potential bias according to the Cochrane Risk of Bias tool. Five studies used open-labelled design, whereas three studies were double-blinded. The study of Tamaki et al. might have a high risk of other bias, as it was only a conference abstract with no trial registration number.[27]

3.3 | Sensitivity analysis

Two ways of sensitivity analysis were performed. The statistical significance of the pooled RR was not changed by excluding one study at a time (Table S2) or simultaneously excluding all small sample studies and conference abstracts (Figure S2).

3.4 | Meta-analysis of eradication rate

In the ITT analysis, random-effect model was used as the heterogeneity was significant ($\chi^2 = 0.01$, $p = 0.03$, $I^2 = 55\%$, Figure 3). *H. pylori* eradication rate of VPZ group was higher than control group (pooled eradication rates, 87.0% vs. 75.4%; RR, 1.14; 95% CI: 1.06–1.23; $p = 0.0006$). A similar tendency was found in the PP analysis (pooled eradication rates, 90.0% vs. 79.0%; RR, 1.12; 95% CI: 1.04–1.20; $p = 0.003$) and significant heterogeneity was observed among these studies ($\chi^2 = 0.01$, $p = 0.003$, $I^2 = 67\%$) as shown in Figure S1.

3.5 | Meta-analysis of compliance

In the meta-analysis of 8 studies with 2012 participants, high compliance was shown in both group (pooled compliance, 96.5% vs. 95.0%; RR, 1.02; 95% CI: 0.98–1.05; $p = 0.35$). Heterogeneity test was found significant among these studies ($\chi^2 = 0.00$, $p = 0.003$, $I^2 = 68\%$, Figure 4).

3.6 | Meta-analysis of the adverse effects

There were 4 studies[21,22,24,25] providing information of overall incidence of adverse events during treatment and 6 studies[21–26] providing details of incidences of common adverse events. The overall incidence of adverse events in VPZ group was significantly lower than that in control group (pooled incidences, 33.5% vs. 40.0%; RR, 0.84; 95% CI: 0.70–1.00; $p = 0.05$) with low heterogeneity

VPZ group	Control group	Sample size (V/P)	Time to test after therapy	Test to confirm eradication	Funding
VPZ 20 mg, Amo 750 mg, Cla 200/400 mg, b.i.d. for 7 days	Lan 30 mg, Amo 750 mg, Cla 200/400 mg, b.i.d. for 7 days	329/321	≥4 weeks	UBT	Takeda
VPZ 20 mg, Amo 750 mg, Cla 200/400 mg, b.i.d. for 7 days	Rab 20 mg/Lan 30 mg, Amo 750 mg, Cla 200/400 mg, b.i.d. for 7 days	72/69	8 weeks	UBT	NA
VPZ 20 mg, Amo 750 mg, Cla 200/400 mg, b.i.d. for 7 days	Lan 30 mg/Rab 10 mg/Eso 20 mg, Amo 750 mg, Cla 200/400 mg, b.i.d. for 7 days	55/51	~8 weeks	UBT	Yokohama City University
VPZ 20 mg, Amo 750 mg, Sit 100 mg, b.i.d. for 7 days	Eso 20 mg/Rab 10 mg/Lan 30 mg, Amo 750 mg, Sit 100 mg, b.i.d. for 7 days	33/30	~8 weeks	UBT	Yokohama City University
VPZ 20 mg, Amo 750 mg, Cla 200 mg, b.i.d. for 7 days	Eso 20 mg, Amo 750 mg, Cla 200 mg, b.i.d. for 7 days	270/251	8–12 weeks	UBT	NA
VPZ 20 mg, Amo 750 mg, Met 250 mg, b.i.d. for 7 days	Rab 10 mg, Amo 750 mg, Met 250 mg, b.i.d. for 7 days	23/23	≥4 weeks	UBT	None
VPZ 20 mg, Amo 1 g, Cla 500 mg, Tripotassium bismuth dicitrate 600 mg, b.i.d. for 14 days	Lan 30 mg, Amo 1 g, Cla 500 mg, Tripotassium bismuth dicitrate 600 mg, b.i.d. for 14 days	15/15	42 days	UBT	Takeda
VPZ 20 mg, Amo 1 g, Cla 500 mg, Bismuth potassium citrate/ bismuth tripotassium dicitrate 600 mg, b.i.d. for first 2 weeks, followed by VPZ 20 mg q.d. for up to 4 weeks	Lan 30 mg, Amo 1 g, Cla 500 mg, Bismuth potassium citrate/ bismuth tripotassium dicitrate 600 mg, b.i.d. for first 2 weeks, followed by Lan 30 mg q.d. for up to 4 weeks	226/229	4 weeks	UBT	Takeda

($\chi^2 = 3.22$, $p = 0.36$, $I^2 = 7\%$, Figure 5). To further analyze the safety of the two regimens, we examined the occurrences of six common adverse events. Except for abdominal pain (9.8% vs. 16.8%; $p < 0.05$) and abdominal bloating (23.5% vs. 11.0%; $p < 0.05$), there was no difference in the incidence of the other four kinds of adverse events between two regimens (Table S3).

3.7 | Subgroup analysis

We performed subgroup analysis through different layering strategies. In a subgroup analysis of treatment regimen, the VPZ group had a significant higher cure advantage over the control group in the seven-day triple therapy (pooled eradication rates 87.6% vs. 74.5%; RR, 1.18; 95% CI: 1.08–1.28; $p = 0.0002$; Figure S3), while there was no significant difference in eradication rates between the 14-day bismuth quadruple therapy and the control group (pooled eradication rates 85.1% vs. 78.3%; RR, 1.01; 95% CI: 0.80–1.28; $p = 0.93$; Figure S3). In a subgroup analysis of eradication experience, forest plot analysis showed a significant superiority of VPZ group over control group in the treatment-naïve patients (pooled eradication rates 87.8% vs. 75.7%; RR, 1.17; 95% CI: 1.09–1.25; $p < 0.00001$; Figure S4), which was not observed in treatment-experienced patients or treatment-unclear patients. Of the eight included studies, three RCTs provided eradication rates according to the clarithromycin-susceptibility and two for clarithromycin-resistant. Among patients with clarithromycin-resistant strains, there was significant superiority of VPZ group over control group (pooled eradication rates 79.2% vs. 45.8%; RR, 1.66; 95% CI: 1.08–2.54; $p = 0.02$; Figure S5). In contrast, no significant superiority was shown for eradication rate of clarithromycin-susceptibility (pooled eradication rates 93.0% vs. 90.3%; RR, 1.03; 95% CI: 0.96–1.11; $p = 0.45$; Figure S5).

4 | DISCUSSION

Compared to previous meta-analysis,[17–20] We searched the database comprehensively to filter out published articles and unpublished grey data. Finally, eight RCTs with 2012 patients were included in our meta-analysis. In addition, the prespecified protocol of this study could strengthen the strength of the findings and reduce the risk of bias. In our study, the VPZ-based therapy was shown to have a higher eradication rate compared to the PPI-based therapy in ITT (87.0% vs. 75.4%) and PP (90.0% vs. 79.0%) analyses. According to the report card to grade *H. pylori* therapies proposed

FIGURE 2 Assessment of bias risk for the included studies

by Graham,[29] the eradication rate of VPZ-based therapy in ITT and PP analyses were acceptable grade (grade C) and good grade (grade B), respectively. On the contrary, the eradication rates of PPI-based therapy in ITT and PP analyses were lower than 80.0%, which was an unacceptable grade (grade F). Furthermore, this result was robust through the sensitivity analysis and removal of small sample we performed.

The recommended first-line treatment for *H. pylori* is different in different regions. Standard triple therapy with a treatment duration of 7 days is included in the Japanese health insurance system,[9] while the bismuth-containing quadruple therapy with 14 days is the most recognized therapy in Chinese.[8] According to our meta-analysis, the eradication rate of VPZ-containing triple therapies was superior to that of PPI (87.6% vs. 74.5%), which was similar to the results of a previous network meta-analysis.[17] Meanwhile, there was no significant difference in the eradication rate between the two in the bismuth-containing quadruple therapy (85.1% vs. 78.3%). The possible reason for this lack of a difference may be that the bismuth agent needs to form a protective film under the acidic environment, and the acid suppression effect of VPZ is rapid and long-lasting, which affects the effect of the bismuth agent. In addition, there are only two RCTs on bismuth-containing quadruple therapy in this article, and more studies are needed for verification.

The increasing resistance to antibiotics is an important reason for the decline in eradicating *H. pylori* infection.[30] we conducted a subgroup analysis according to the clarithromycin-resistant status of *H. pylori*. These results showed that both regimens showed similarly high eradication rates for clarithromycin-susceptible strains (93.0% vs. 90.3%). In contrast, a significantly larger effect was observed in VPZ-based therapy in comparison with PPI-based therapy for clarithromycin-resistant strains (79.2% vs. 45.9%). This advantage of VPZ can undoubtedly be explained by its better acid suppression ability than PPI, thereby enhancing the efficacy of antibiotics to obtain a better eradication rate, which has been confirmed by clinical trials.[21,31] Moreover, this study showed that VPZ-based regimens were superior or equivalent to the control recommended eradication regimens in treatment-naïve and treatment-experienced patients. These collectively indicated that VPZ-based regimens could attain a better eradication rate in various populations. Therefore, the utility of VPZ as an alternative to PPI therapy has been considered in various situations.

When comparing with compliance and the frequency of adverse events, VPZ-containing regimens were comparable with the control regimens. The common adverse reactions of VPZ included diarrhoea and abdominal bloating, which were tolerable and disappeared after treatment.

We followed the prespecified protocol with minimal deviation and conducted a series of subgroup analyses to test the clinical heterogeneity and robustness of the research results. Nevertheless, this meta-analysis still has some limitations. First, only two included studies implemented explicit allocation hiding, and three studies were double-blind in design. Although the eradication rate data of *H. pylori* were based on the objective results of instrumental inspections, the risk of selection bias and implementation bias increased to a certain extent. Second, the number of studies and sample sizes for analyzing the difference between VPZ and PPI in subgroup analysis were limited. Third, all studies were conducted in Asia, mainly in Japan. Due to the antibiotic resistance and usual dosage varies depending on the countries, extrapolation of the result to other regions should be with caution, and further studies in multiple regions should be conducted to draw more general conclusions. Finally, we only compared conventional triple therapies and bismuth-containing quadruple therapy, thus other eradication regimens, such as concomitant therapy, sequential therapy, hybrid therapy, and high dose dual therapy, should be performed to evaluate whether VPZ is still superior.

5 | CONCLUSION

As mentioned above, VPZ-containing regimens are not inferior to the current widely used PPI-containing regimens in *H. pylori*

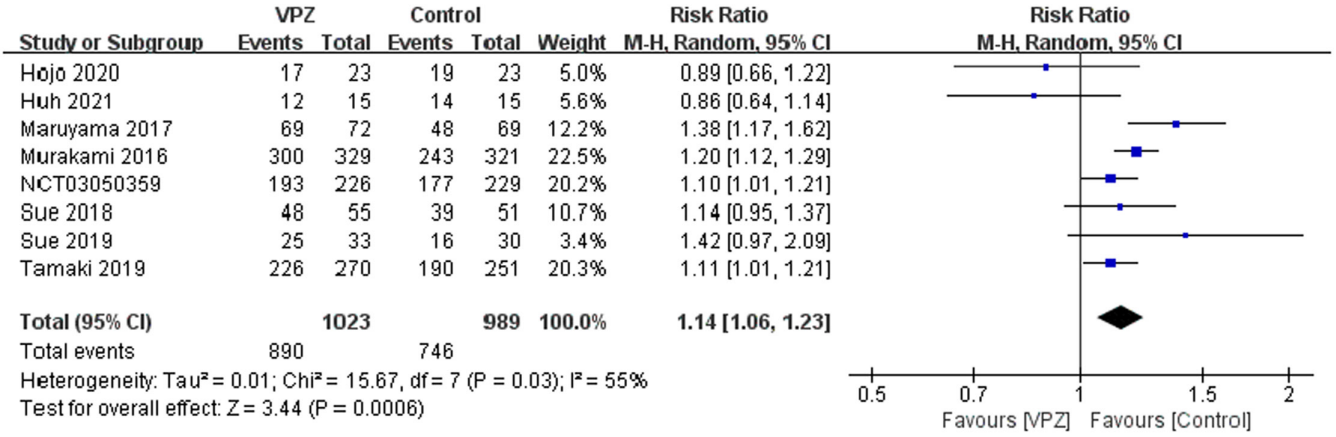

FIGURE 3 Forest plot for comparison of VPZ group with control group in *Helicobacter pylori* eradication rate according to intention-to-treat analysis

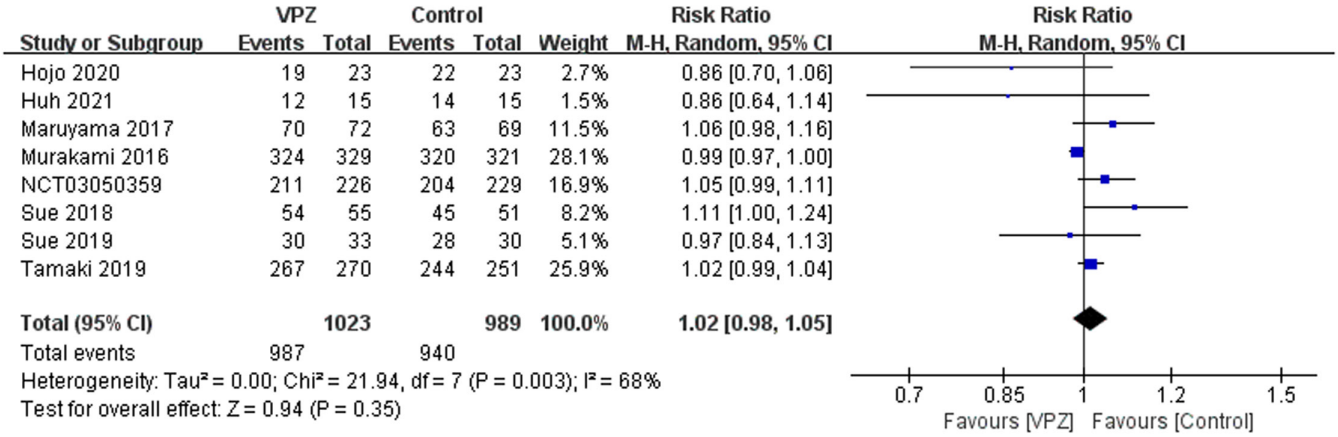

FIGURE 4 Forest plot for comparison of VPZ group with control group in compliance

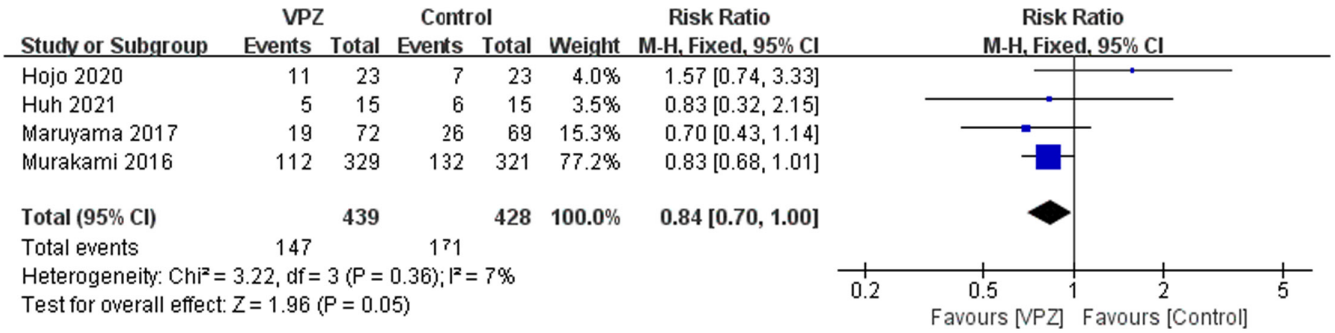

FIGURE 5 Forest plot for comparison of VPZ group with control group in adverse events

eradication. Meanwhile, VPZ has displayed well tolerated and safety. The evidence from this meta-analysis supports that VPZ is worth introducing into the clinical practice for *H. pylori* treatment.

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CONFLICT OF INTEREST

All authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data supporting this study are availability from the corresponding author (Huijie An) upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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