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RESEARCH

Effectiveness and safety of vonoprazan-based regimens compared with those of proton pump inhibitor (PPI)–based regimens as first-line agents for *Helicobacter pylori*: a meta-analysis of randomized clinical trials

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Abstract

Purpose Vonoprazan (VPZ), a reversible H^+–K^+ ATPase inhibitor, has a relatively fast and sustained acid-suppression action that is unaffected by diet or gene polymorphisms. Several randomized controlled trials have evaluated the difference in the eradication rate of *Helicobacter pylori* (HP) between VPZ-based and proton pump inhibitor (PPI)–based regimens. The present review aimed to (1) evaluate the efficacy, safety, and compliance of VPZ-based regimens compared with those of PPI-based regimens as first-line treatments for HP infection and (2) perform a subgroup analysis to examine the influence of differences in clarithromycin-resistance status, treatment duration, treatment regimens, and research region on treatment outcomes.

Methods We conducted a systematic literature search on PubMed, Embase, Cochrane Library, Web of Science, and ChiCTR Register. Systematic searches, study selection, data extraction, risk of bias assessment, and statistical analysis were performed according to pre-registered protocol on the PROSPERO (CRD42022336608).

Results Eight studies and 2956 HP-infected patients were enrolled. Only first-line therapy and RCT study were considered. VPZ-based group had a superior eradication efficacy compared to PPI-based group by intention-to-treat (ITT) (pooled risk ratio (RR): 1.14, 95% CI: 1.08–1.21, $p < 0.00001$) and per-protocol analysis (pooled RR: 1.13, 95% CI: 1.07–1.20, $p < 0.00001$). This finding was further validated by subgroup analysis depending on treatment regimens, duration, region, and clarithromycin resistance. In addition, there was no significant difference in adverse events ($p = 0.33$) and compliances ($p = 0.30$) between the regimens.

Conclusion The VPZ-based regimens showed a superior eradication efficacy compared to the already frequently used PPI-based regimens. Furthermore, VPZ-based therapy showed comparable tolerability and incidence of adverse events.

Keywords *Helicobacter pylori* eradication · Meta-analysis · Proton-pump inhibitor · Vonoprazan · First-line therapy

Introduction

Helicobacter pylori (HP) infection has been identified as a major cause of multiple diseases, with a lifetime risk of approximately 17% for peptic ulcers and 0.6–22% for gastric cancer in patients with HP infection [1]. Following the formal recognition of HP gastritis as an infectious disease in 2015, all patients were recommended eradication medications [2, 3].

For HP infection, multiple therapies have been widely researched, including proton pump inhibitor (PPI) triple therapy; bismuth-containing quadruple therapy; dual therapy with high-dose PPIs combined with amoxicillin; and a group of four-drug therapies, including metronidazole, known as sequential, concomitant, and hybrid therapies [4]. However,

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the eradication rate of PPI-based regimens has gradually decreased owing to widespread antibiotic resistance [5] and insufficient acid suppression [6]. In addition, the primary and secondary resistance rates to common antibiotics (clarithromycin, metronidazole, and levofloxacin) have been reported to exceed 10% in all World Health Organization regions [7]. These data are higher in China, with antibiotic resistance approaching 20–40% [8].

Vonoprazan (VPZ), a reversible H^+–K^+ ATPase inhibitor, has a relatively fast and sustained acid-suppression action that is unaffected by diet or gene polymorphisms [9, 10]. After 7 days of repeated administration of VPZ 40 mg daily, the mean 24-h intragastric pH > 4 holding-time ratios in Japanese and United Kingdom volunteers were found to be 100% and 93.2%, respectively [11]. The generation of VPZ has rekindled debate regarding existing treatment regimens, as significant acid-suppression capacity has been observed to lead to increased efficacy of amoxicillin-containing regimens. Many randomized controlled trials (RCTs) are currently underway to determine the efficacy and safety of VPZ and amoxicillin regimens.

According to the present meta-analysis, VPZ-based regimens appeared to be more effective than PPI-based regimens. This conclusion was reached based on data from various retrospective studies [12], and no pooled analysis of RCTs has been conducted. Moreover, the only available RCT-based meta-analysis did not consider treatment experience [13]. Several RCTs on the effectiveness of VPZ-based regimens have recently been conducted, and the results have been updated. Therefore, we evaluated the efficacy and safety of VPZ-based regimens compared with those of PPI-based regimens in HP-infected individuals who had not been previously treated. Furthermore, a subgroup analysis was performed to determine the influence of differences in clarithromycin resistance status, treatment duration, and treatment regimens on treatment outcomes.

Methods

Systematic searches, study selection, data extraction, risk of bias assessment, and statistical analysis were performed according to pre-registered protocol on the PROSPERO (CRD42022336608).

Search strategy

Relative RCT studies were searched through PubMed, Embase, Cochrane Library, and Web of Science (updated to May 23, 2022). In addition, unpublished studies were found by searching ClinicalTrials.gov and the ChiCTR Register. The search strategy, including medical subject heading (Mesh) and entry terms, was as follows: "*Helicobacter pylori*, *Helicobacter nemestrinae*, *Campylobacter pylori*, *Campylobacter pylori* subsp. *pylori*, *Campylobacter pyloridis*," "1-(5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl)-N-methylmethanamine, Vonoprazan, TAK 438, TAK438, TAK-438, potassium-competitive acid blocker, Takecab," and "randomized controlled trial controlled clinical trial, random allocation, double-blind, single-blind, placebo, randomized, randomly, random, RCT, clinical trial*,trial*, Random*." The full search strategy in PubMed was shown in Supplementary Table S1.

Study selection

In the first stage, we eliminated irrelevant articles by reading the titles and abstracts. Following that, we chose the final RCT study based on pre-registered inclusion and exclusion criteria. The included criteria were as follows: (1) patients: initial HP infection was diagnosed based on confirmatory tests; (2) intervention: HP eradication therapy through VPZ-based regimens, included triple therapy, bismuth quadruple therapy, dual therapy, sequential therapy; (3) comparison: PPI-based regimens; (4) outcomes: eradication rate by intention-to-treat (ITT) analysis and per-protocol (PP) analysis, adverse events, and compliance; and (5) study design: RCT. The exclusion criteria were as follows: healthy population or younger than 18, reviews and meta-analyses, and full-text unavailable. Two investigators (Y. C. S. and L. Y.) independently evaluated the studies for eligibility; any disagreements were resolved by third investigator (W. L. H.).

Data extraction

The following data were extracted: first author, year of publication, trial registration number, study period, research region, mean age, gender, drug type, dose and frequency, testing time after treatment, and test to diagnose (Table 1; Supplementary Table S2).

Risk-of-bias assessment

Two researchers (Y. C. S. and L. Y.) independently evaluate the risk of bias in individual studies, with any discrepancies resolved by consensus. RCTs were assessed using the Cochrane Risk of Bias Assessment Tool for the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias [14].

Endpoint

The primary endpoint of this study was to compare the eradication rate of VPZ-based regimens and PPI-based regimens by the ITT and PP analysis, and the secondary endpoint was to compare adverse events and the compliance.

Table 1 Characteristics of the studies included in the meta-analysis

Study	Purpose	Period	Country	VPZ group	PPI group	Duration (days)	Age	Gender (M/F)	Sample	Time and test
Murakami (2016)	Verify the non-inferiority of VPZ to Lan (NCT01505127)	2012–2013	Japan	VAC	LAC	7	55.2 ± 12.3 53.9 ± 12.9	196/133 194/127	329/321	≥4 weeks UBT
Maruyama (2017)	Compare the eradication rate between VPZ and PPI	2015–2016	Japan	VAC	RAC/LAC	7	58 60	41/29 40/29	72/69	8 weeks UBT
Sue (2018) UMIN000016337	Compare the eradication rate between VPZ and PPI in the CAM-susceptible patients	2015–2016	Japan	VAC	RAC/LAC/EAC	7	64.3 ± 12.3 61.9 ± 13.3	37/18 35/16	55/51	8 weeks UBT
Bunchorntavakul (2021)	Compare the efficacy of 7-VAC with 14-OAC. TCTR20210219007	2019–2021	Thailand	VAC	OAC	7 vs. 14	54.21 ± 12.3 56.79 ± 13.25	26/35 31/30	61/61	4–6 weeks UBT
Hou (2022) NCT03050359	Verify the non-inferiority of VPZ to Lan in non-Japanese Asian patients	2017–2020	China, South Korea	VACB, followed by VPZ	LACB, followed by Lan	14, follow 4 weeks	NA	NA	211/204	4 weeks UBT
Chey (2021) NCT04167670	Compare the eradication rate between VPZ triple therapy and PPI triple therapy Compare the eradication rate between VPZ dual therapy and PPI triple therapy	2019–2022	The USA and Europe	a: VAC b: VA	c: LAC	14	a: 50.7 ± 13.88 b: 51.9 ± 13.47 c: 51.6 ± 13.61	a: 123/226 b: 139/210 c: 132/216	a: 349 b: 349 c: 348	4 weeks UBT
Zuberi (2022)	To verify the non-inferiority of 7-day VPZ-based triple therapy versus 14-day PPI-based triple therapy	2021.6–2021.9	Pakistan	VA	OAC	14	NA	NA	96/96	4 weeks Hp antigen test
Ang (2022)	To verify the non-inferiority of 7-day VPZ-based triple therapy versus 14-day PPI-based triple therapy NCT 03908619	2019.6–2021.6	Asian	VAC	OAC/EAC/RAC	7 vs. 14	51.5 ± 14.7 52.0 ± 14.6	68/51 82/43	119/125	4 weeks UBT

A amoxicillin, *B* bismuth, *C* clarithromycin, *E* esomeprazole, *L* lansoprazole *O* omeprazole, *R* rabeprazole

Statistical analysis

This meta-analysis was performed by Revman software (version Mac5.4.1; Cochrane Collaboration, Copenhagen, Denmark), and $p < 0.05$ was regarded as a significant difference. Risk ratios (RRs) and corresponding 95% CIs were used to determine the effect of VPZ-based regimen and PPI-based regimen. Heterogeneity was detected by the Cochrane's Q test and I^2 statistics; once there was significant heterogeneity ($p < 0.1$ or $I^2 > 50\%$), a random-effect model was used to combine the effect sizes of the included studies. Otherwise, a fixed-effect model was used. Publication bias was estimated by a funnel plot. The sensitivity analysis was plotted in the "R" version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) with the "meta" package.

Results

Study selection and characteristics

Using ENDNOTE software (version X9), 351 records were identified, and 174 were excluded because of duplication (Fig. 1). In the first stage, 77 studies were removed after title and abstract screening, and 158 were removed for the following reasons: reviews or meta-analyses ($n = 53$), healthy participants or those aged < 18 years ($n = 14$), non-HP eradication initial treatment ($n = 6$), non-RCT study ($n = 38$), non-referral to HP eradication rate ($n = 20$), and treatment intervention not involving VPZ vs. PPI comparison ($n = 27$). Subsequently, 19 studies were further reviewed, after which four studies were removed due to the lack of detailed eradication rate data, and seven were excluded due to duplication of clinical trials. Finally, eight studies [4, 15–21] involving 2956 HP-infected patients were included; 1656 and 1648 patients were assigned to VPZ- and PPI-based groups, respectively.

This study's characteristics are presented in Table 1. All studies were published between 2012 and 2022, with seven of them conducted in Asia (three in Japan) and one each in the USA and Europe. One study comprised two studies with independently controlled designs, including VPZ dual therapy vs. PPI triple therapy and VPZ triple therapy vs. PPI triple therapy. As they were conducted using strict randomization, we treated them as two separate studies to assess efficacy and bias. Resultantly, this meta-analysis included eight RCTs and nine studies. Of the interventions administered in these nine studies, six entailed VPZ triple therapy vs. PPI triple therapy, two entailed VPZ dual therapy vs. PPI triple therapy, and one entailed VPZ bismuth-containing quadruple therapy vs. bismuth-containing quadruple therapy with PPIs. In terms of treatment duration, three studies compared 7-day VPZ triple therapy with 7-day PPI triple therapy, two compared 14-day VPZ dual therapy with 14-day PPI triple therapy, one compared 14-day VPZ triple therapy with 14-day PPI triple therapy, and two compared 7-day VPZ triple therapy with 14-day PPI triple therapy.

Comparison of VPZ and PPI

HP eradication according to intention-to-treat and per-protocol analyses

As shown in Fig. 2, the pooled HP eradication rates were 83.5% and 72.6% in the VPZ- and PPI-based groups, respectively, according to ITT analysis. The VPZ-based group had

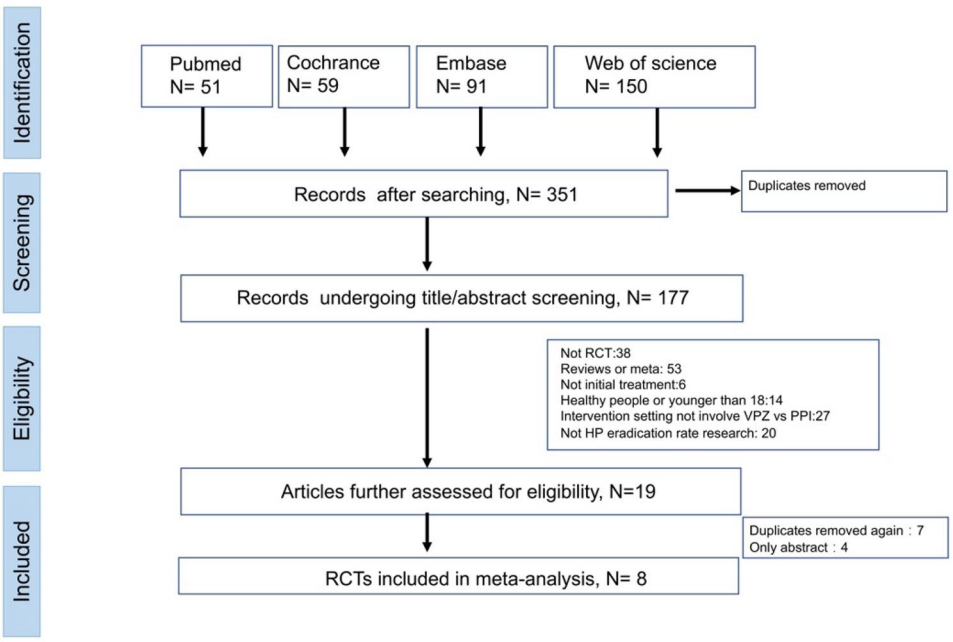

Fig. 1 A flowchart of the study-selection process

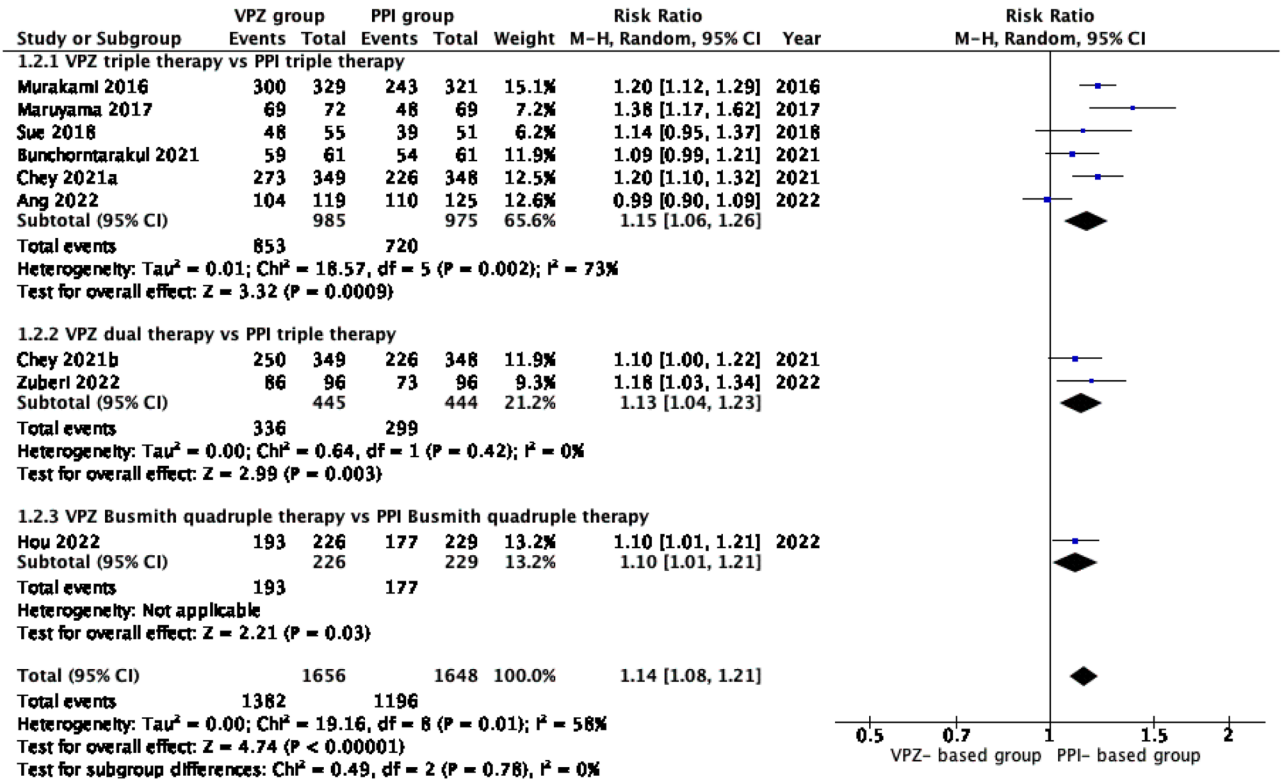

Fig. 2 Forest plots comparing HP eradication rates between the VPZ- and PPI-based groups according to intention-to-treat (ITT) analysis. *PPI*, proton pump inhibitor; *ITT*, intention-to-treat; *CI*, confidence interval

a significantly higher cure advantage than the PPI-based group (pooled risk ratio (RR): 1.14, 95% confidence interval [CI]: 1.08–1.21, $p<0.00001$).

According to PP analysis, the pooled HP eradication rates were 87.1% and 76.4% in the VPZ- and PPI-based groups, respectively. As shown in Supplementary Figure S2, the VPZ-based group had a superior eradication efficacy to the PPI-based group (pooled RR: 1.12, 95% CI: 1.05–1.19, $p=0.0003$), and significant heterogeneity (chi-squared test, $p<0.0001$, $I^2=76\%$) was also observed.

Sensitivity analysis

A sensitivity analysis separates data items to examine whether any has a substantial impact on the pooled RR. Sensitivity analysis revealed no significant changes in studies involving the HP eradication rate based on ITT and PP analyses (Supplementary Figure S3).

Subgroup analysis

A subgroup analysis was conducted according to the treatment regimens used in all studies. As shown in Fig. 2 and Supplementary Figure S2, the VPZ group exhibited superior eradication efficacy to the PPI group in terms of triple therapy (VPZ/PPI + amoxicillin + clarithromycin) according to ITT (pooled eradication rates: 86.6% vs. 73.8%, pooled RR: 1.15, 95% CI: 1.06–1.26, $p=0.0009$) and PP (pooled eradication rates 89.9% vs. 76.5%, pooled RR: 1.14, 95% CI: 1.03–1.25, $p=0.010$) analyses. On analyzing the VPZ dual-therapy subgroup (VPZ + amoxicillin) vs. the PPI triple-therapy subgroup (PPI + amoxicillin + clarithromycin), the VPZ group also demonstrated a better eradication efficacy (ITT analysis: 75.5% vs. 67.3%, pooled RR: 1.13, 95% CI: 1.04–1.23, $p=0.003$; PP analysis: 78.9% vs. 71.0%, pooled RR: 1.11, 95% CI: 1.03–1.19, $p=0.004$). Similarly, on analyzing the bismuth-containing quadruple-therapy subgroups, the VPZ group also exhibited significant superiority (ITT analysis: 83.2% vs. 71.9%, RR: 1.10, 95% CI: 1.01–1.21, $p=0.03$; PP analysis: 91.5% vs. 86.8%, RR: 1.05, 95% CI: 0.99–1.13, $p=0.13$).

Of the eight included studies, four RCTs [4, 15, 17, 21] provided eradication rates based on clarithromycin susceptibility, and three [4, 15, 21] availed data based on clarithromycin-resistant patients. Among patients with clarithromycin-resistant strains, the VPZ group demonstrated significant superiority over the control group (pooled eradication rates: 73.7% vs. 38.0%, RR: 1.74, 95% CI: 1.23–2.47, $p=0.002$; Fig. 3). In contrast,

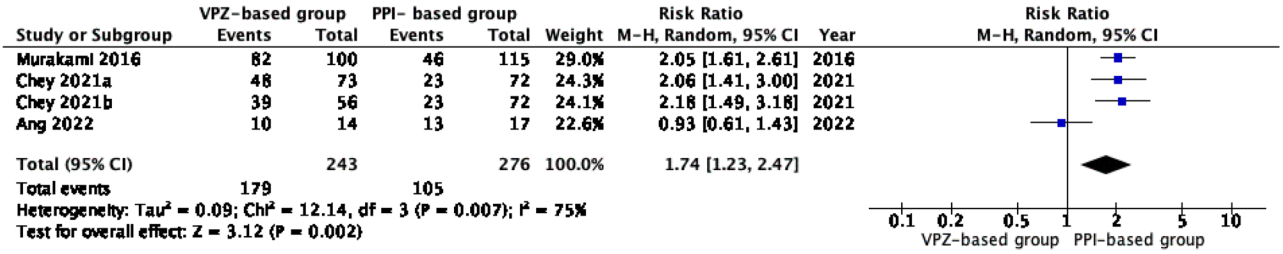

Fig. 3 Forest plot comparing HP eradication rates between the VPZ-based and control groups within the clarithromycin-resistant population

no significant superiority was shown in the eradication rate of clarithromycin susceptibility (pooled eradication rates: 86.5% vs. 83.8%, RR: 1.03, 95% CI: 0.99–1.07, $p=0.14$; Supplementary Figure S4).

Subsequently, we performed a subgroup analysis of eight studies (seven RCTs) based on different treatment durations (7 or 14 days). As shown in Supplementary Figures S5 and S6, 7-day VPZ triple therapy had a significantly higher eradication rate than PPI triple therapy (ITT analysis: pooled RR: 1.22, 95% CI: 1.15–1.30, $p<0.00001$; PP analysis: pooled RR: 1.19, 95% CI: 1.05–1.35, $p=0.008$). Similar results were obtained in the 14-day subgroup. Interestingly, in our subgroup analysis, which included two RCTs, 7-day VPZ triple therapy achieved comparable efficacy to 14-day PPI triple therapy (ITT analysis: pooled RR: 1.03, 95% CI: 0.96–1.10, $p=0.47$; PP analysis: pooled RR: 1.04, 95% CI: 0.99–1.09, $p=0.14$).

Of the included RCTs, three were from Japan [15–17], four from Asian countries other than Japan [4, 18–20], and one from Europe [21]. HP eradication rates varied by region; therefore, we performed a subgroup analysis according to the region in which the studies were conducted. As shown in Supplementary Figures S7 and S8, in Japan, the VPZ group exhibited a higher eradication rate according to ITT and PP analyses (ITT analysis: pooled RR: 1.22, 95% CI: 1.15–1.30, $p<0.00001$; PP analysis: pooled RR: 1.19, 95% CI: 1.05–1.35, $p=0.008$). Similar findings were observed in other Asian (ITT analysis: pooled RR: 1.09, 95% CI: 1.03–1.15, $p=0.002$; PP analysis: pooled RR: 1.05, 95% CI: 1.01–1.09, $p=0.008$) and European (ITT analysis: pooled RR: 1.15, 95% CI: 1.08–1.24, $p<0.0001$; PP analysis: pooled RR: 1.16, 95% CI: 1.06–1.28, $p=0.002$) countries, and the differences were statistically significant.

Adverse events were recorded in five of the included studies. The VPZ group exhibited a lower incidence of adverse events than the PPI group; however, the difference was not statistically significant (pooled incidence rates: 20.4% vs. 24.9%, RR: 0.83, 95% CI: 0.58–1.20, $p=0.33$), with high heterogeneity ($p<0.0001$, $I^2=83\%$; Fig. 4).

Compliance

In this meta-analysis of nine studies involving 2956 participants, no significant difference in compliance was noted between the regimens (Fig. 5) (pooled compliance: 95.7% vs. 94.8%, pooled RR: 1.01, 95% CI: 0.99–1.04, $p=0.30$). Significant heterogeneity was exhibited across these studies ($p=0.01$, $I^2=59\%$; Fig. 5).

Discussion

Several meta-analyses comparing VPZ- and PPI-based regimens have been published in recent years; however, most of them were retrospective, and the credibility of meta-analyses of retrospective studies is questionable. For example, Jung

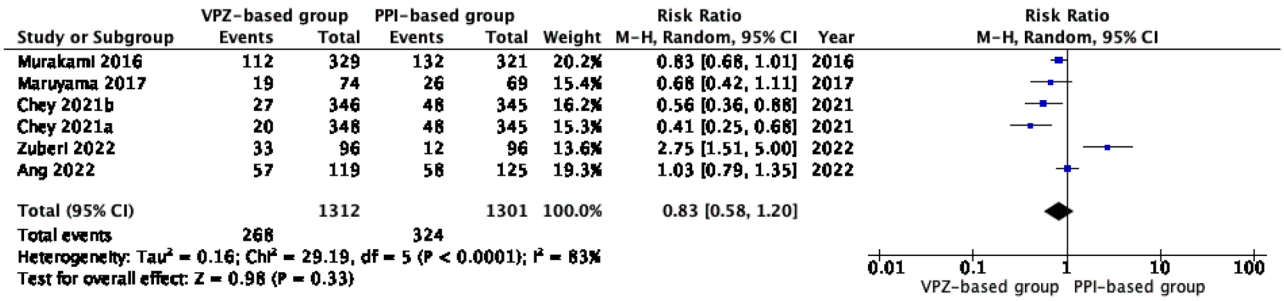

Fig. 4 Forest plot comparing adverse events associated with HP eradication therapy between the VPZ- and PPI-based groups

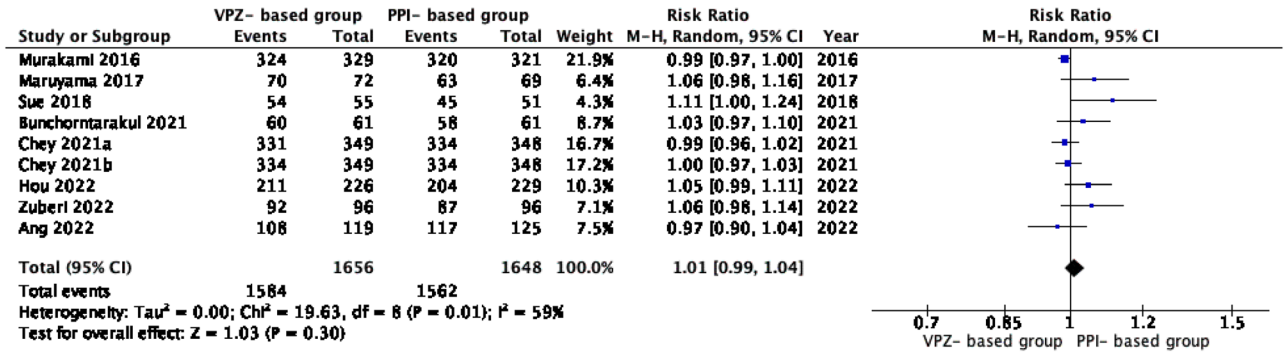

Fig. 5 Forest plot comparing compliance with HP eradication therapy between the VPZ- and PPI-based groups

et al. [12] conducted a meta-analysis that included one RCT and nine retrospective studies. Similarly, Dong et al. [22] included two RCTs and 12 non-randomized controlled trials (non-RCTs), with the non-RCTs and RCTs exhibiting heterogeneities of 65% and 26%, respectively. RCT-based meta-analyses potentially provide high-quality evidence. Based on three RCTs, Lyu et al. [23] conducted a meta-analysis and concluded that VPZ-based triple therapy was superior to PPI-based triple therapy as a first-line regimen; however, in one [17] of the three studies, all participants were sensitive to clarithromycin. Chen et al. (2022) [13] updated the meta-analysis data of VPZ versus PPIs for eradication therapy of HP infection to include 8 RCTs, three of which involved non-first-line treatments and included only one abstract article, greatly increasing heterogeneity. We focused on RCTs ($n=8$) investigating first-line HP-eradication treatment, three of which were published in 2022 and two in 2021.

VPZ is the predominant regimen available in Japan, where the HP eradication regimen is 7-day triple therapy comprising PPI/VPZ + amoxicillin + clarithromycin (PPI–AC or VAC) as the first-line therapy [24]. Of the eight RCTs included in this meta-analysis, four were conducted in Japan; therefore, we initially analyzed the difference in eradication rates between VPZ and PPI triple therapies. VPZ emerged superior to PPIs in terms of eradication rate, and the results were consistent with those of previous studies. Jung et al. conducted a meta-analysis of 10 studies (10,644 patients) [12], nine of which were retrospective studies comparing the efficacy of VPZ-based triple therapy with that of PPI-based triple therapy. The eradication rates were 87.9% and 72.8%, which were similar to our 86.6% and 73.8%, respectively. Second, the antibiotic resistance rate has been increasing annually, thus considerably affecting HP eradication. Graham et al. [25] reported that the addition of clarithromycin to VPZ and amoxicillin as a triple therapy in the general population only added an approximately 12% benefit in cure rate, and 88% of the patients received clarithromycin unnecessarily. Moreover, more antibiotics may also lead to increased treatment toxicity, gut microbiota dysbiosis, and regimen complexity [25]. In our study, VPZ triple therapy exhibited a 10% cure-rate benefit compared with VPZ dual therapy (86.6% vs. 75.5%). However, compared with the PPI triple-therapy group, the VPZ dual group experienced a higher cure rate (both for 7 and 14 days) (pooled eradication rate 75.5% vs. 67.3%, RR: 1.13, $p=0.003$). Bismuth-containing quadruple therapy is the most commonly used regimen in China [26]. In the subgroup analysis, VPZ contributed to a higher eradication rate (83.2% vs. 71.9%) than PPIs; nonetheless, only one RCT was included [18], and more RCTs should be conducted in the future to investigate the effect of VPZ bismuth-containing quadruple therapy on the eradication rate in the Chinese population.

Antibiotic resistance has long been considered a major factor in HP eradication failures [27]. Xie et al. [28] reported crude pooled eradication rates of 59.35% (1044/1759) and 90.11% (6615/7341) in the clarithromycin-resistant and antibiotic-sensitive groups, respectively, based on 67 studies that explored clarithromycin-only resistance. In our meta-analysis, both regimens exhibited high eradication rates for clarithromycin-susceptible strains and were not statistically different. In contrast, regarding clarithromycin-resistant strains, the VPZ-based regimen potentially provided significantly higher eradication rates (pooled eradication rates: 73.7% vs. 38.0%, RR: 1.74, 95% CI: 1.23–2.47, $p=0.002$), demonstrating consistency with previous studies [12]. To overcome the insufficient eradication rate induced by antibiotic resistance, pre-treatment susceptibility testing should be considered [29].

The treatment duration of VPZ-based regimens exceeded that of PPI-based regimens in both the 7-day and 14-day subgroups. Seven-day and 14-day VPZ triple therapy had a significantly superior efficacy to PPI triple therapy (pooled RR: 1.22, 95% CI: 1.15–1.30, $p<0.00001$; pooled RR: 1.16, 95% CI: 1.09–1.23, $p<0.00001$, respectively). VPZ exhibits a faster acid-inhibitory capacity (intragastric pH increased to > 4.0 within 4 h) than PPIs [11], thus facilitating a shorter treatment duration. Interestingly, in our subgroup

analysis, which included two RCTs, 7-day VPZ triple therapy achieved comparable efficacy to 14-day PPI triple therapy (pooled RR: 1.03, 95% CI: 0.96–1.10, $p = 0.47$). Although Japanese guidelines [24] recommend a 7-day treatment duration for VPZ-based triple therapy, Western guidelines [30, 31] recommend a 14-day treatment duration for PPI-based triple therapy. As a result, more RCTs comparing 7-day VPZ-based therapy with 14-day PPI-based therapy are clinically relevant and required. To assess the improvement in HP eradication rates, more studies comparing VPZ dual therapy with VPZ triple therapy, concomitant therapy, and sequential therapy are also warranted.

Lyu et al. reported a significantly lower incidence of adverse effects and better tolerability with VPZ-based triple therapy than with PPI-based triple therapy [23]. However, in our study, the VPZ-based regimen was comparable to the control regimen in terms of compliance and adverse events, with no statistically significant differences. Diarrhea and abdominal distension are common side effects of VPZ but are acceptable and disappear after treatment.

Limitations

This study has certain limitations. First, our review included a small number of RCT studies, only one of the included studies was conducted in Europe, and the others were conducted in Asian countries. Therefore, since antibiotic resistance varies with country, the applicability of our findings worldwide may be limited. Second, we explored VPZ dual or triple therapy versus PPI triple therapy but included RCT studies did not consider the efficacy of sequential, concomitant, mixed, and reverse mixed therapies versus VPZ regimens. Therefore, we cannot conclude that VPZ-based regimens are superior to PPI-based regimens among all the currently available therapies. At the same time, the RCT involved regimens containing amoxicillin, so the results do not apply to patients allergic to penicillin. Third, we could not evaluate the relative efficacy of VPZ-based regimens based on PPI metabolism in patients. There was a difference in the representation of PPI in clinical trials. Omeprazole, lansoprazole, rabeprazole, and esoprazole were the PPI used in three, five, three, and two trials, respectively. It is well-known that the metabolism of the first-generation PPIs, including omeprazole, pantoprazole, and lansoprazole, was significantly affected by *CYP2C19* and *CYP3A4* gene polymorphisms, while the second-generation PPIs rabeprazole and esoprazole yielded lower efficacies [32]; nevertheless, genetic polymorphism was not analyzed in most of the included studies. Fourth, bismuth-containing quadruple therapy is the most used regimen in China, where the HP infection rate is currently 50%, but most of this meta-analysis is PPI triple therapy, and only one RCT involves bismuth quadruple therapy. Future RCT research on the impact of VPZ-based bismuth quadruple treatment on the eradication rate in the Chinese population should be undertaken. Fifth, heterogeneity was noted upon combining data from different studies, which may be attributed to the treatment regimen and study population. Sixth, our study was designed to compare the efficacy and safety of VPZ with those of PPIs as first-line therapies for HP eradication; thus, our results cannot be applied to second- or third-line therapy.

Conclusion

VPZ-based regimens demonstrated superior eradication efficacy compared with the frequently used PPI-based regimens. Furthermore, VPZ-based therapy exhibited comparable tolerability and adverse-event incidence rates.

Abbreviations VPZ: Vonoprazon; PPI: Proton pump inhibitor; HP: *Helicobacter pylori*; RCT: Randomized clinical trial; RR: Risk ratios; ITT: Intention-to-treat; CI: Confidence interval; PP: Per-protocol analysis

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-022-03430-y.

Author contribution W. L. H. was guarantor of the article. L. Y. and Y. C. S. performed the literature search with a systematic review. Y. C. S. performed the meta-analysis and extracted the data. L. Y. and Y. C. S. wrote the manuscript. And W. L. H. designed a systematic review and edited this manuscript. All authors approved the final version of this manuscript.

Data availability The data that support the findings of the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval Ethics statement is not needed for this type of study.

Competing interests The authors declare no competing interests.

References

1. Lee YC, Dore MP, Graham DY (2022) Diagnosis and treatment of *Helicobacter pylori* infection. Annu Rev Med 73:183–195. https://doi.org/10.1146/annurev-med-042220-020814
2. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, Haruma K, Asaka M, Uemura N, Malfertheiner P, Faculty members of Kyoto Global Consensus C, (2015) Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut 64(9):1353–1367. https://doi.org/10.1136/gutjnl-2015-309252
3. El-Serag HB, Kao JY, Kanwal F, Gilger M, LoVecchio F, Moss SF, Crowe SE, Elfant A, Haas T, Hapke RJ, Graham DY (2018) Houston Consensus Conference on testing for *Helicobacter pylori* infection in the United States. Clin Gastroenterol Hepatol 16 (7):992–1002 e1006. https://doi.org/10.1016/j.cgh.2018.03.013

4. Ang D, Koo SH, Chan YH, Tan TY, Soon GH, Tan CK, Lin KW, Krishnasamy-Balasubramanian JK, Wong YJ, Kumar R, R R, Tan Y, Ong PJ, Tan YJ, Li JW, Kwek AB, Ang TL, (2022) Clinical trial: seven-day vonoprazan- versus 14-day proton pump inhibitor-based triple therapy for first-line *Helicobacter pylori* eradication. Aliment Pharmacol Ther. https://doi.org/10.1111/apt.17070
5. Smith SM, O'Morain C, McNamara D (2014) Antimicrobial susceptibility testing for *Helicobacter pylori* in times of increasing antibiotic resistance. World J Gastroenterol 20(29):9912–9921. https://doi.org/10.3748/wjg.v20.i29.9912
6. de Boer W, Driessen W, Jansz A, Tytgat G (1995) Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. Lancet 345(8953):817–820. https://doi.org/10.1016/s0140-6736(95)92962-2
7. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E (2018) Prevalence of antibiotic resistance in *Helicobacter pylori*: a systematic review and meta-analysis in World Health Organization regions. Gastroenterology 155(5):1372–1382 e1317. https://doi.org/10.1053/j.gastro.2018.07.007
8. Bai P, Zhou LY, Xiao XM, Luo Y, Ding Y (2015) Susceptibility of *Helicobacter pylori* to antibiotics in Chinese patients. J Dig Dis 16(8):464–470. https://doi.org/10.1111/1751-2980.12271
9. Sue S, Maeda S (2021) Is a potassium-competitive acid blocker truly superior to proton pump inhibitors in terms of *Helicobacter pylori* eradication? Gut Liver 15(6):799–810. https://doi.org/10.5009/gnl20242
10. Kiyotoki S, Nishikawa J, Sakaida I (2020) Efficacy of vonoprazan for *Helicobacter pylori* eradication. Intern Med 59(2):153–161. https://doi.org/10.2169/internalmedicine.2521-18
11. Jenkins H, Sakurai Y, Nishimura A, Okamoto H, Hibberd M, Jenkins R, Yoneyama T, Ashida K, Ogama Y, Warrington S (2015) Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther 41(7):636–648. https://doi.org/10.1111/apt.13121
12. Jung YS, Kim EH, Park CH (2017) Systematic review with meta-analysis: the efficacy of vonoprazan-based triple therapy on *Helicobacter pylori* eradication. Aliment Pharmacol Ther 46(2):106–114. https://doi.org/10.1111/apt.14130
13. Yang C, Li S, Huang T, Lin H, Jiang Z, He Y, Yuan J, An H (2022) Effectiveness and safety of vonoprazan-based regimen for *Helicobacter pylori* eradication: a meta-analysis of randomized clinical trials. J Clin Pharm Ther. https://doi.org/10.1111/jcpt.13637
14. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods G, Cochrane Statistical Methods G (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928. https://doi.org/10.1136/bmj.d5928
15. Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M (2016) Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind study. Gut 65(9):1439–1446. https://doi.org/10.1136/gutjnl-2015-311304
16. Maruyama M, Tanaka N, Kubota D, Miyajima M, Kimura T, Tokutake K, Imai R, Fujisawa T, Mori H, Matsuda Y, Wada S, Horiuchi A, Kiyosawa K (2017) Vonoprazan-based regimen is more useful than PPI-based one as a first-line *Helicobacter pylori* eradication: a randomized controlled trial. Can J Gastroenterol Hepatol 2017:4385161. https://doi.org/10.1155/2017/4385161
17. Sue S, Ogushi M, Arima I, Kuwashima H, Nakao S, Naito M, Komatsu K, Kaneko H, Tamura T, Sasaki T, Kondo M, Shibata W, Maeda S (2018) Vonoprazan- vs proton-pump inhibitor-based first-line 7-day triple therapy for clarithromycin-susceptible *Helicobacter pylori*: a multicenter, prospective, randomized trial. Helicobacter 23(2):e12456. https://doi.org/10.1111/hel.12456
18. Hou X, Meng F, Wang J, Sha W, Chiu CT, Chung WC, Gu L, Kudou K, Chong CF, Zhang S (2022) Vonoprazan non-inferior to lansoprazole in treating duodenal ulcer and eradicating *Helicobacter pylori* in Asian patients. J Gastroenterol Hepatol. https://doi.org/10.1111/jgh.15837
19. Bunchorntavakul C, Buranathawornsom A (2021) Randomized clinical trial: 7-day vonoprazan-based versus 14-day omeprazole-based triple therapy for *Helicobacter pylori*. J Gastroenterol Hepatol 36(12):3308–3313. https://doi.org/10.1111/jgh.15700
20. Zuberi BF, Ali FS, Rasheed T, Bader N, Hussain SM, Saleem A (2022) Comparison of vonoprazan and amoxicillin dual therapy with standard triple therapy with proton pump inhibitor for *Helicobacter pylori* eradication: a randomized control trial. Pak J Med Sci 38 (4Part-II):965–969. https://doi.org/10.12669/pjms.38.4.5436
21. Chey WD, Megraud F, Laine L, Lopez LJ, Hunt BJ, Howden CW (2022) Vonoprazan triple and dual therapy for *Helicobacter pylori* infection in the US and Europe: randomized clinical trial. Gastroenterology. https://doi.org/10.1053/j.gastro.2022.05.055
22. Dong SQ, Singh TP, Wei X, Yao H, Wang HL (2017) Review: a Japanese population-based meta-analysis of vonoprazan versus PPI for *Helicobacter pylori* eradication therapy: is superiority an illusion? Helicobacter 22(6). https://doi.org/10.1111/hel.12438
23. Lyu QJ, Pu QH, Zhong XF, Zhang J (2019) Efficacy and safety of vonoprazan-based versus proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication: a meta-analysis of randomized clinical trials. Biomed Res Int 2019:9781212. https://doi.org/10.1155/2019/9781212
24. Kato M, Ota H, Okuda M, Kikuchi S, Satoh K, Shimoyama T, Suzuki H, Handa O, Furuta T, Mabe K, Murakami K, Sugiyama T, Uemura N, Takahashi S (2019) Guidelines for the management of *Helicobacter pylori* infection in Japan: 2016 revised edition. Helicobacter 24(4):e12597. https://doi.org/10.1111/hel.12597
25. Graham DY, Lu H, Shiotani A (2021) Vonoprazan-containing *Helicobacter pylori* triple therapies contribution to global antimicrobial resistance. J Gastroenterol Hepatol 36(5):1159–1163. https://doi.org/10.1111/jgh.15252
26. Liu WZ, Xie Y, Lu H, Cheng H, Zeng ZR, Zhou LY, Chen Y, Wang JB, Du YQ, Lu NH, Chinese Society of Gastroenterology CSGoHp, Peptic U (2018) Fifth Chinese National Consensus Report on the management of *Helicobacter pylori* infection. Helicobacter 23(2):e12475. https://doi.org/10.1111/hel.12475
27. Simala-Grant JL, Taylor DE (2004) Molecular biology methods for the characterization of *Helicobacter pylori* infections and their diagnosis. APMIS 112(11–12):886–897. https://doi.org/10.1111/j.1600-0463.2004.apm11211-1211.x
28. Zou Y, Qian X, Liu X, Song Y, Song C, Wu S, An Y, Yuan R, Wang Y, Xie Y (2020) The effect of antibiotic resistance on *Helicobacter pylori* eradication efficacy: a systematic review and meta-analysis. Helicobacter 25(4):e12714. https://doi.org/10.1111/hel.12714
29. Graham DY (2017) Vonoprazan *Helicobacter pylori* eradication therapy: ethical and interpretation issues. Gut 66(2):384–386. https://doi.org/10.1136/gutjnl-2016-311796
30. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM, European H, Microbiota Study G, Consensus P (2017) Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. Gut 66(1):6–30. https://doi.org/10.1136/gutjnl-2016-312288
31. Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, Jones NL, Render C, Leontiadis GI, Moayyedi P, Marshall JK (2016) The Toronto Consensus for the treatment of *Helicobacter pylori* infection in adults. Gastroenterology 151 (1):51–69 e14. https://doi.org/10.1053/j.gastro.2016.04.006

32. McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP (2012) Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection. Aliment Pharmacol Ther 36(5):414–425. https://doi.org/10.1111/j.1365-2036.2012.05211.x