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SYSTEMATIC REVIEWS

Treatment of *Helicobacter pylori* with potassium competitive acid blockers: A systematic review and meta-analysis

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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) infects over half the global population, causing gastrointestinal diseases like dyspepsia, gastritis, duodenitis, peptic ulcers, G-MALT lymphoma, and gastric adenocarcinoma. Eradicating *H. pylori* is crucial for treating and preventing these conditions. While conventional proton pump inhibitor (PPI)-based triple therapy is effective, there's growing interest in longer acid suppression therapies. Potassium competitive acid blocker (P-CAB) triple and dual therapy are new regimens for *H. pylori* eradication. Initially used in Asian populations, vonoprazan (VPZ) has been recently Food and Drug Administration-approved for *H. pylori* eradication.

AIM

To assess the efficacy of regimens containing P-CABs in eradicating *H. pylori* infection.

METHODS

This study, following PRISMA 2020 guidelines, conducted a systematic review and meta-analysis by searching MEDLINE and Scopus libraries for randomized clinical trials (RCTs) or observational studies with the following command: [("*Helicobacter pylori*" OR "H pylori") AND ("Treatment" OR "Therapy" OR "Eradication") AND ("Vonaprazan" OR "Potassium-Competitive Acid Blocker" OR "P-CAB" OR "PCAB" OR "Revaprazan" OR "Linaprazan" OR "Soraprazan" OR "Tegoprazan")]. Studies comparing the efficacy of P-CABs-based treatment to classical PPIs in eradicating *H. pylori* were included. Exclusion criteria included case reports, case series, unpublished trials, or conference abstracts. Data variables encompassed age, diagnosis method, sample sizes, study duration, intervention and control, and *H. pylori* eradication method were gathered by two independent reviewers. Meta-analysis was performed in R software, and forest plots were generated.

RESULTS

A total of 256 references were initially retrieved through the search command. Ultimately, fifteen studies (7 RCTs, 7 retrospective observational studies, and 1 comparative unique study) were included, comparing P-CAB triple therapy to PPI triple therapy. The intention-to-treat analysis involved 8049 patients, with 4471 in the P-CAB intervention group and 3578 in the PPI control group across these studies. The analysis revealed a significant difference in *H. pylori* eradication between VPZ triple therapy and PPI triple therapy in both RCTs and observational studies [risk ratio (RR) = 1.17, 95% confidence interval (CI): 1.11-1.22, $P < 0.0001$] and (RR = 1.13, 95%CI: 1.09-1.17, $P < 0.0001$], respectively. However, no significant difference was found between tegoprazan (TPZ) triple therapy and PPI triple therapy in both RCTs and observational studies (RR = 1.04, 95%CI: 0.93-1.16, $P = 0.5$) and (RR = 1.03, 95%CI: 0.97-1.10, $P = 0.3$), respectively.

CONCLUSION

VPZ-based triple therapy outperformed conventional PPI-based triple therapy in eradicating *H. pylori*, positioning it as a highly effective first-line regimen. Additionally, TPZ-based triple therapy was non-inferior to classical PPI triple therapy.

Key Words: *Helicobacter pylori* infection; Potassium competitive acid blockers; Proton pump inhibitors; Vonoprazan; Amoxicillin

Core Tip: In the systematic review and meta-analysis on the treatment of *Helicobacter pylori (H. pylori)* with potassium competitive acid blockers, vonoprazan-based triple therapy demonstrated superior efficacy over conventional proton pump inhibitor (PPI)-based triple therapy, establishing itself as a highly effective first-line regimen. Conversely, tegoprazan-based triple therapy was found to be non-inferior to classical PPI triple therapy. These findings signify a potential paradigm shift in *H. pylori* eradication strategies.

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INTRODUCTION

Helicobacter pylori (*H. pylori*), a gram-negative bacterium, which infects over 50% of the global population, with a prevalence in approximately half of the world's inhabitants. The primary mode of transmission is person-to-person through fecal/oral exposure[1]. The presence of *H. pylori* in the stomach is associated with the onset of various gastroduodenal conditions, including chronic gastritis, peptic ulcers (10%-15% incidence), and gastric adenocarcinomas (less than 1% occurrence)[2].

Early childhood infection with *H. pylori*, ranging from 30% to 50%, significantly elevates the infection rate to over 90% during adulthood. This phenomenon is closely linked to adverse socioeconomic conditions and overcrowded living environments commonly found in developing countries[3]. As a result, while the incidence and prevalence of this infection have notably decreased in the developed world, the decline is not as pronounced in developing countries[3].

Successful eradication of *H. pylori* not only enhances the mucosal healing of ulcers and gastritis but also diminishes the incidence of gastric cancer[4,5]. Nevertheless, achieving successful *H. pylori* eradication poses challenges, leading to a rise in resistance rates to multiple antibiotics. This is compounded by factors such as host CYP2C19 gene polymorphisms and inadequate therapeutic regimens, contributing to a gradual decline in *H. pylori* eradication rates[6].

Vonoprazan (VPZ) stands out as an orally active, innovative potassium competitive acid blocker (P-CAB), distinguishing itself from conventional proton pump inhibitors (PPIs). Its mechanism involves binding to and inhibiting H^+, K^+-ATPase in the gastric parietal cells, marking the final step in the acid secretory cascade[7]. VPZ's independence from pre or post-meal conditions allows for rapid absorption post-oral administration, achieving peak plasma levels in under 2 h and exhibiting an extended plasma half-life of 9 h. This unique pharmacokinetic profile grants VPZ a prolonged acid suppression effect compared to PPIs, and it remains unaffected by CYP2C19 polymorphisms[7].

VPZ exhibits versatile clinical applications, encompassing the treatment of gastroesophageal reflux disease, non-erosive reflux disease, erosive esophagitis, and peptic ulcer disease. It also serves as prophylaxis for upper gastrointestinal bleeding and has recently received Food and Drug Administration approval for dual and triple *H. pylori* eradication therapy[7,8]. This systematic review and meta-analysis aim to evaluate the effectiveness of regimens incorporating P-CABs in eradicating *H. pylori* infection.

MATERIALS AND METHODS

Data sources

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) guidelines[9], a systematic review and meta-analysis were conducted, searching the literature in MEDLINE and Scopus libraries.

Inclusion and exclusion criteria

Inclusion criteria encompassed randomized clinical trials (RCTs) or observational studies that compared the efficacy of P-CABs-based treatment with classical PPIs-containing regimens for *H. pylori* eradication. Exclusion criteria involved case reports, case series, unpublished trials, or those solely presented as conference abstracts (oral presentations or posters).

Study selection and data extraction

A comprehensive search of various databases including MEDLINE and Scopus was conducted using the search terms: ("*Helicobacter pylori*" OR "H pylori") AND ("Treatment" OR "Therapy" OR "Eradication") AND ("Vonaprazan" OR "Potassium-Competitive Acid Blocker" OR "P-CAB" OR "PCAB" OR "Revaprazan" OR "Linaprazan" OR "Soraprazan" OR "Tegoprazan").

The initial screening involved eliminating duplicates and non-RCTs or observational studies. Two independent reviewers then assessed titles and abstracts to exclude irrelevant papers. Subsequently, full papers were obtained, and the reviewers independently gathered data on the efficacy rates of regimens containing P-CABs for *H. pylori* eradication. Additional collected variables comprised age, diagnostic method, sample sizes, study duration, intervention, control group, and the method used to confirm the eradication of *H. pylori*.

Data processing and analysis

Data were subjected to analysis and summarization employing descriptive techniques, encompassing frequency, means, and median calculations. For the meta-analysis of *H. pylori* treatment efficacy rates, R software version 4.3.2 and the meta package were employed.

RESULTS

The search command yielded 256 references, ultimately resulting in the inclusion of 15 studies: 7 RCTs, 7 retrospective observational studies, and 1 unique study that compared an RCT with an observational study, as illustrated in the PRISMA flowchart (Figure 1). The majority of these studies were conducted in Asia, with nine in Japan, four in South Korea, and one in Thailand. Notably, only one study was conducted in a Western region.

For the intention-to-treat analysis (ITT), a total of 8049 patients were involved across the 15 included studies, with 4471 in the intervention group and 3578 in the control group. The mean study duration in the intervention arm was 8.4 d, while in the control arm, it was 9.3 d.

Regarding *H. pylori* diagnosis, thirteen studies employed upper gastrointestinal endoscopy, utilizing biopsy with either rapid urease test, histology, or culture. Additionally, nine studies utilized the urease breath test (UBT), and another nine studies employed the *H. pylori* stool antigen, while four studies reported the use of *H. pylori* serum immunoglobulin G as one of the diagnostic methods.

The duration for *H. pylori* eradication control varied, ranging from 4 wk to 8 wk after the completion of treatment, using either the UBT or *H. pylori* stool antigen. Notably, fourteen studies utilized the UBT to assess *H. pylori* eradication status, while four studies employed the *H. pylori* stool antigen.

In eleven studies, VPZ was utilized in the intervention group, while tegoprazan (TPZ) was employed in only four studies. Notably, all four studies implementing TPZ were conducted in South Korea. Regarding the eleven VPZ studies, nine were carried out in Japan, one in Thailand, and the remaining one included both the United States and Europe. Lansoprazole (LPZ) emerged as the most frequently used PPI, featured in eleven studies, followed by rabeprazole (RPZ), which was employed in seven studies.

In ten studies, it was indicated that first-line or second-line triple therapies containing P-CABs were non-inferior to conventional PPI regimens (six studies including VPZ and four containing TPZ). Additionally, five studies demonstrated the superiority of P-CABs, with all of them utilizing VPZ compared to classic PPI therapy. Furthermore, all included studies reported that P-CABs were well-tolerated and deemed safe, with a safety profile similar to PPI regimens.

RCTs: VPZ triple therapy vs conventional PPI triple therapy

In the four included RCTs in Figure 2A, the ITT analysis comprised a total of 719 patients in the VPZ group and 705 in the PPI control group. The analysis revealed a significant difference between VPZ triple therapy and PPI triple therapy for *H. pylori* eradication [risk ratio (RR) = 1.17, 95% confidence interval (CI): 1.11-1.22, P = 0.0001], indicating that VPZ-based triple therapy is statistically superior to conventional PPI triple therapy for *H. pylori* eradication.

RCTs: TPZ triple therapy vs conventional PPI triple therapy

In the two RCTs included in Figure 2B, the ITT analysis involved a total of 280 patients in the TPZ group and 281 in the PPI control group. The analysis revealed no significant difference in *H. pylori* eradication therapy between the TPZ triple regimen and the PPI triple regimen (RR = 1.04, 95%CI: 0.93-1.16, P = 0.5324). Consequently, TPZ triple treatment is

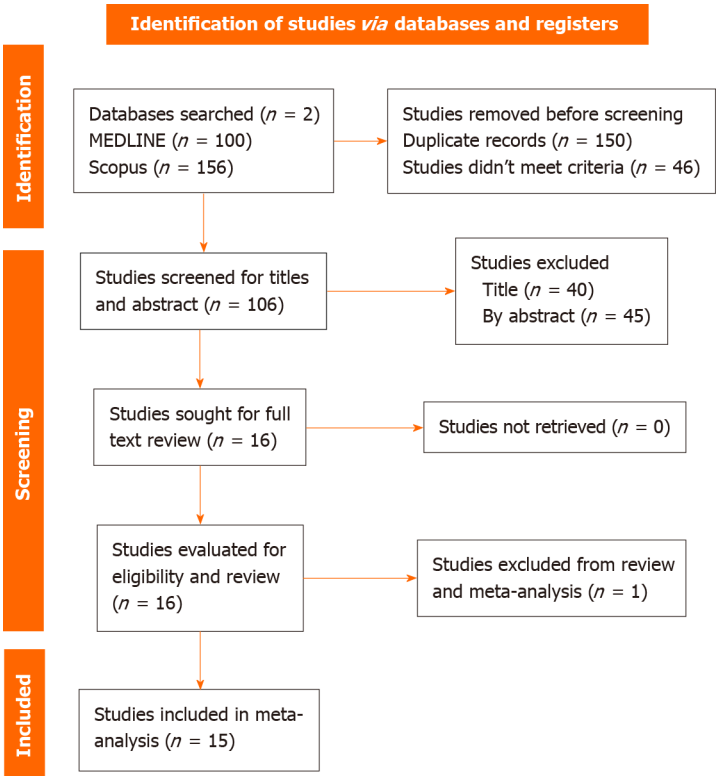

Figure 1 PRISMA flow diagram of the search strategy process.

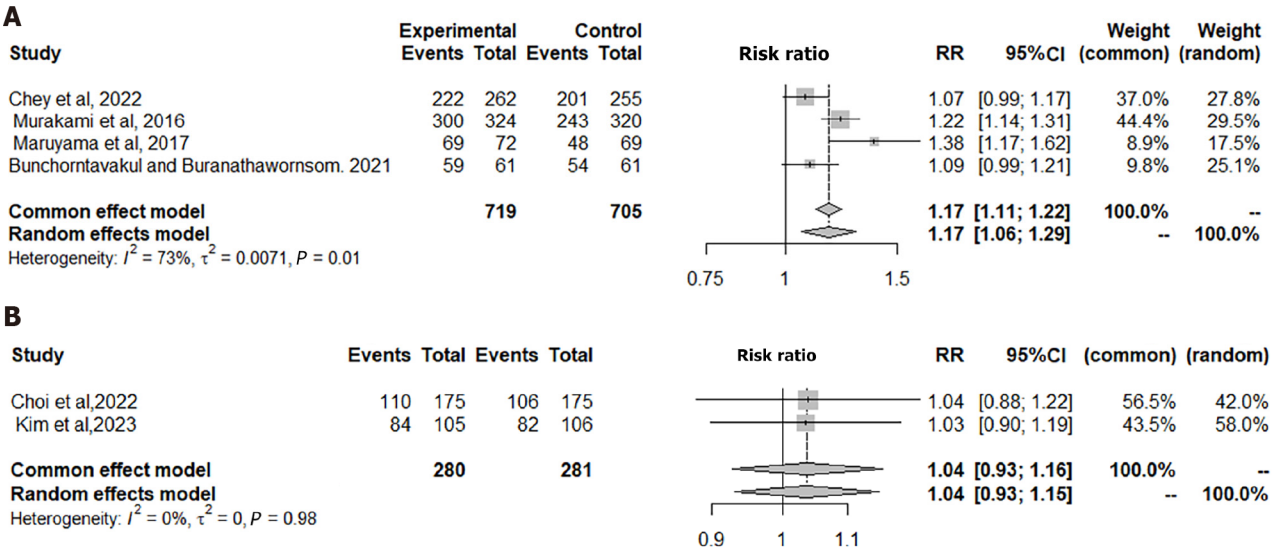

Figure 2 Vonoprazan triple therapy and tegoprazan triple therapy *vs* conventional proton pump inhibitor triple therapy - randomized controlled studies. A: Vonoprazan triple therapy; B: Tegoprazan triple therapy. RR: Risk ratio; CI: Confidence interval.

considered non-inferior to the classical PPI-based treatment.

Observational studies: VPZ triple therapy vs conventional PPI triple therapy

In the five observational studies included in Figure 3A, the ITT analysis encompassed a total of 2582 patients in the VPZ group and 1754 in the PPI control group. The analysis revealed a significant difference between VPZ triple therapy and PPI triple therapy for *H. pylori* eradication (RR = 1.13, 95%CI: 1.09-1.17, P = 0.0001). Consequently, VPZ-based triple therapy demonstrated superiority over conventional PPI triple therapy for *H. pylori* eradication in this context.

Observational studies: TPZ triple therapy vs conventional PPI triple therapy

In the two observational studies represented in Figure 3B, the ITT analysis incorporated a total of 537 patients in the TPZ group and 521 in the PPI control group. The analysis revealed no significant difference in *H. pylori* eradication therapy

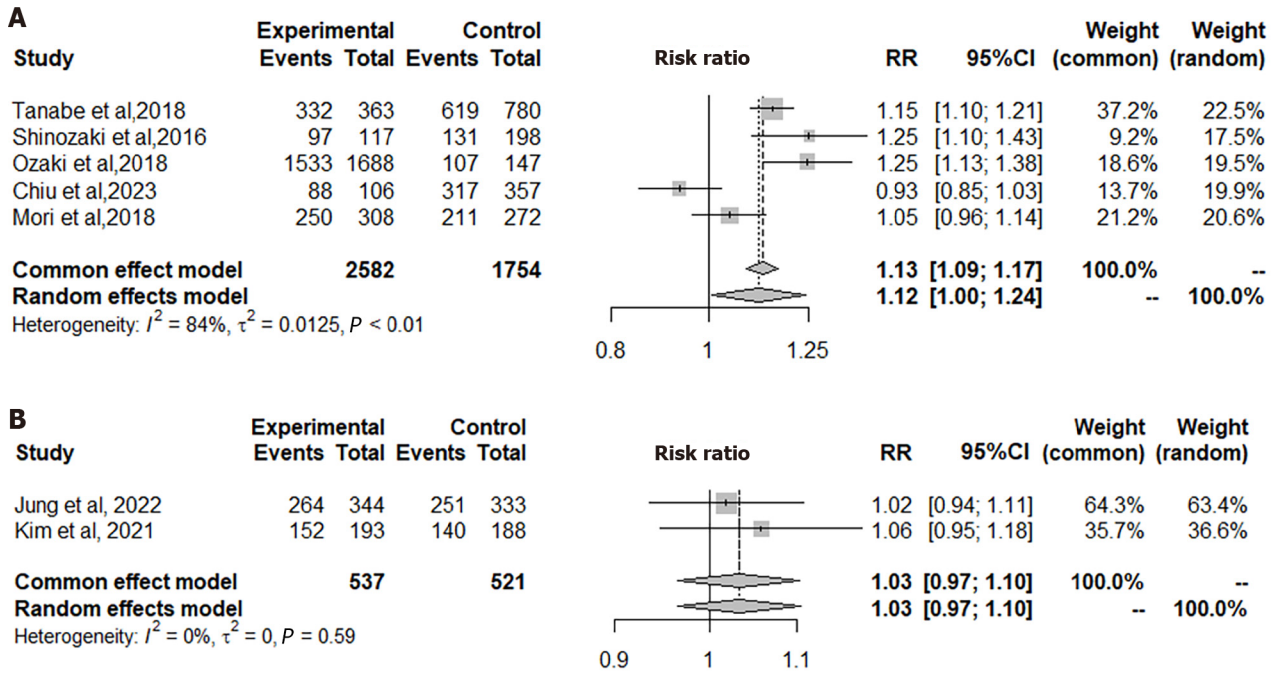

Figure 3 Vonoprazan triple therapy and tegoprazan triple therapy *vs* conventional proton pump inhibitor triple therapy - observational studies. A: Vonoprazan triple therapy; B: Tegoprazan triple therapy. RR: Risk ratio; CI: Confidence interval.

between the TPZ triple regimen and the PPI triple regimen (RR = 1.03, 95%CI: 0.97-1.10, P = 0.3555). Consequently, TPZ triple treatment demonstrated non-inferiority to classical PPI-based treatment in this context.

Second line therapy: VPZ second line triple therapy vs PPI second line triple therapy

In the two studies focusing on second-line *H. pylori* treatment, as illustrated in Figure 4, the ITT analysis encompassed a total of 353 patients in the VPZ group and 317 in the PPI control group. The analysis revealed no significant difference in *H. pylori* eradication therapy between the VPZ second-line regimen and the PPI second-line regimen (RR = 1.05, 95%CI: 0.99-1.11, P = 0.1001). Consequently, VPZ second-line treatment demonstrated non-inferiority to PPI second-line treatment for *H. pylori* eradication.

DISCUSSION

Eradicating *H. pylori* is of utmost significance, serving as the primary treatment for low-grade G-MALT, mitigating the recurrence of peptic ulcers, and lowering the risk of gastric adenocarcinoma in high-risk populations[10-12]. This critical therapeutic intervention not only addresses immediate health concerns but also plays a pivotal role in preventing more severe and potentially life-threatening conditions associated with *H. pylori* infection.

For years, PPI-based regimens have been the primary approach for both initial and secondary treatments in *H. pylori* eradication. However, the effectiveness of these regimens has declined recently, notably due to increasing resistance to clarithromycin and levofloxacin. The need for alternative treatments has become evident. Although there is an ongoing debate about the practicality of conducting susceptibility testing before starting PPI-based first-line triple therapy, especially in areas where clarithromycin resistance exceeds 15%, logistical and financial challenges present obstacles, particularly in developing nations. As a result, the prevailing practice in many settings involves empirical PPI-based triple therapy without susceptibility testing[11-14].

Given the increasing difficulties associated with PPI first-line triple therapy, P-CAB-based first-line therapy emerges as a viable alternative. In 2015, the VPZ-based triple regimen received approval in Japan, and in 2022, both triple and dual VPZ-containing therapies obtained approval in the United States for the treatment of *H. pylori* infection and associated diseases[6-8].

In addition to the clinical complexities associated with *H. pylori* eradication therapy, economic considerations play a significant role, encompassing the substantial costs incurred for *H. pylori* testing, treatments, and follow-up requirements. A study aimed at assessing the cost-effectiveness of VPZ-based therapy compared to other first-line *H. pylori* eradication treatments in the United States utilized a Markov model to examine costs across various treatment options[15]. The cost analysis involved comparing VPZ-based triple therapy with alternatives such as VPZ-Amoxicillin dual treatment, rifabutin-based triple regimen, bismuth quadruple therapy, and PPI triple regimen. The study revealed that VPZ triple therapy had a higher expected cost of $1172 compared to $1048 with rifabutin triple therapy. However, VPZ triple therapy demonstrated a slightly higher expected quality-adjusted life years of 14.262 compared to 14.256 with rifabutin. The conclusion drawn from this investigation was that VPZ-based treatment is more cost-effective than the other options

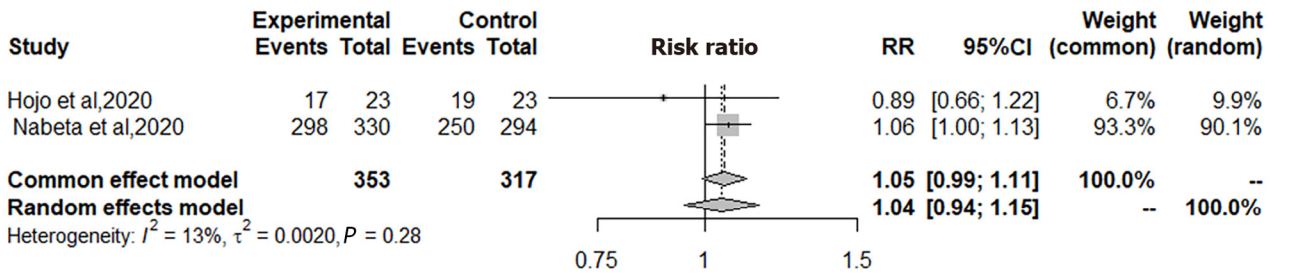

Figure 4 Vonoprazan second line triple therapy *vs* conventional proton pump inhibitor second line therapy. RR: Risk ratio; CI: Confidence interval.

[15].

It's worth noting that the cost of VPZ triple therapy (United States brand Voquezna Triple Pak) at $1172 could pose significant challenges in most developing countries, potentially limiting its prescription by clinicians even if the drugs are available. Therefore, the availability of highly government-subsidized generic forms of these drugs could prove beneficial in enhancing their utilization in the developing world.

This systematic review achieves a distinctive equilibrium by incorporating 7 RCTs, 7 retrospective observational studies, and 1 hybrid study (an RCT compared with observation). The cumulative sample size encompasses 8049 patients, with 55.5% (4471) allocated to the P-CAB group and 44.5% (3578) to the PPI control group. Notably, this review stands out from others by examining two different P-CABs, VPZ and TPZ, along with nearly all conventional PPIs, including omeprazole, esomeprazole, RPZ, LPZ, and pantoprazole.

The average duration of the studies in the experimental arm is 8.4 d, slightly shorter than the 9.3 d in the control arm. Despite its Asian dominance, this systematic review encompasses a diverse range of countries, including Japan, South Korea, and Thailand, offering a broader geographical perspective.

In this systematic review, 5 studies concluded that VPZ exhibited superiority over classical PPIs, while an additional 6 studies observed that VPZ was non-inferior to PPIs. Furthermore, TPZ was reported as non-inferior to typical PPIs in 4 other studies. The findings from this systematic review align with a previous one conducted in 2017[16]. In our meta-analysis, which included 4 RCTs and 5 observational studies comparing VPZ to PPI triple treatment, we found that VPZ-containing regimens are superior to conventional PPI-based triple therapy. Notably, in this current review, 3 studies involving VPZ were conducted outside Japan. In contrast, the previous meta-analysis from 2017 included 10 studies, all of which were conducted in Japan.

Results from this systematic review align with those published in 2022[17], suggesting that the VPZ-based triple regimen is superior to triple therapy containing PPIs. Furthermore, this meta-analysis conducted in 2022[17], which includes 7 studies from 3 countries, supports our findings. However, our systematic review provides updated data, incorporating 9 studies that compare VPZ to PPI in first-line triple therapy. Our meta-analysis reveals that TPZ-based triple therapy is non-inferior to the classical PPI-based triple regimen for *H. pylori* eradication. Similar results are observed for VPZ in second-line therapy, indicating its non-inferiority to PPI in the second-line *H. pylori* eradication treatment (Table 1).

VPZ-based dual therapy has emerged as a promising first-line treatment for *H. pylori* infection, involving the combination of VPZ and amoxicillin. Furthermore, one RCT compared a 10-d VPZ-amoxicillin dual therapy with a standard 14-d bismuth-based quadruple therapy, demonstrating noninferiority in eradication rates with fewer adverse events for the dual therapy[31]. A systematic review and meta-analysis conducted assessed the efficacy of this regimen compared to standard therapies for eradicating *H. pylori*. The pooled results from 15 studies involving 4568 patients demonstrated that VPZ-amoxicillin dual therapy achieved a high eradication rate of 85.0% and 90.0% by ITT and per-protocol analysis, respectively. Notably, this regimen outperformed PPIs-based triple therapy, showcasing its superiority [32]. A meta-analysis comparing VPZ-amoxicillin dual therapy with bismuth-containing quadruple therapy revealed similar eradication rates and improved safety profiles for the VPZ-based regimen. These findings collectively highlight the efficacy and safety of VPZ-based dual therapy as a compelling option for first-line *H. pylori* eradication[33].

Limitations of this study include the predominant focus on Eastern populations, hindering the generalization of the benefits of P-CABs to other demographic groups due to regional variations in genetics, diets, and lifestyle, which can influence gastric acidity levels. Moreover, the pooled sample size and the number of studies included in the analysis are limited. Additionally, the impact of antibiotic resistance, particularly clarithromycin resistance, wasn't thoroughly addressed in this systematic review.

CONCLUSION

This systematic review and meta-analysis indicate that VPZ-based triple therapy is statistically superior to classical PPI-based therapy, while TPZ-based triple therapy is non-inferior to PPI-based triple regimens. The superiority of VPZ-based therapy in *H. pylori* eradication is demonstrated with statistical significance, while TPZ triple therapy shows non-inferiority compared to PPI-based regimens. Nevertheless, further studies are needed to comprehensively evaluate the

Table 1 Summary of the main findings from studies

Ref.	Country	Methods	Results
Chey *et al*[8], 2022	United States and Europe	Intervention: VPZ 20 mg + AMX 1 g + CLR 500 mg BD 14 d. Control: LPZ 30 mg + AMX 1 g + CLR 500 mg BD 14 d	*H. pylori* eradication in VPZ triple therapy in 84.7% of patients' *vs* 78.8% for LPZ triple therapy (difference 5.9%; 95%CI: 0.8-12.6; noninferiority $P < 0.001$). VPZ triple therapy is non-inferior to LPZ triple therapy
Murakami *et al*[18], 2016	Japan	Intervention: VPZ 20 mg + AMX 750 mg + CLR 200 mg/400 mg BD 7 d. Control: LPZ 30 mg + AMX 750 mg + CLR 200 mg/400 mg BD 7 d	*H. pylori* eradication rate with VPZ was 92.6% (95%CI: 89.2%-95.2%) compare to 75.9% (95%CI: 70.9%-80.5%) with LPZ with the difference being 16.7% (95%CI: 11.2%-22.1%) indicating the non-inferiority of VPZ ($P < 0.0001$). VPZ tripple therapy is non-inferior to LPZ. VPZ is also well tolerated and safe
Maruyama *et al*[19], 2017	Japan	Intervention: VPZ 20 mg + AMX 750 mg, and CLR 200 mg/400 mg BD 7 d. Control: LPZ 30 mg + AMX 750 mg, and CLR 200 mg/400 mg BD 7 d	*H. pylori* eradication rate was significantly higher 95.8% in VPZ group compare to 69.6% in PPI group 95%CI: 88.3%-99.1%, $P = 0.00003$. VPZ-based therapy is superior to PPI as first line Pylori eradication and is safe
Bunchorntavakul *et al* [20], 2021	Thailand	Intervention: VPZ 20 mg + AMX 1 g + CLR 500 mg BD 7 d. Control: OPZ 20 mg + AMX 1 g + CLR 500 mg BD 14 d	The *H. pylori* eradication rates was 96.7% in VPZ group compare to 88.5% in OPZ group ($P = 0.083$). VPZ triple therapy is non-inferior to OPZ triple therapy and it is well tolerated and safe
Kim *et al*[21], 2023	South Korea	Intervention: TBMT group-TPZ 50 mg bid + TET 500 g qid, MTZ 500 mg tid + BBS 300 mg qid for 14 d. Control: LBMT group-LPZ 30 mg bid + TET 500 g qid, MTZ 500 mg tid + BBS 300 mg qid for 14 d	*H. pylori* eradication rates of TBMT group was 80.0% compare to LBMT group 77.4% with 95%CI: -8.4 to 13.7, $P = 0.0124$. Tegoprazan TBMT was non-inferior compare to lansoprazole LBMT and TBMT is also safe
Choi *et al*[22], 2022	South Korea	Intervention: TPZ 50 mg + AMX 1 g + CLR 500 mg bid 7 d. Control: LPZ 30 mg + AMX 1 g + CLR 500 mg bid 7 d	The *H. Pylori* eradication rates in the TPZ group was 62.86% and LPZ groups was 60.57% with 95%CI: -8.53 with non-inferiority test, $P = 0.009$. TPZ based triple therapy is non-inferior to LPZ triple regimen and TPZ is safe
Tanabe *et al*[23], 2018	Japan	Intervention: VPZ 20 mg + AMX 750 mg + CLR 200 mg/400 mg bid for 7 d. Control: PPI (LPZ 30 mg or RPZ 10 mg or EPZ 20 mg) + AMX 750 mg + CLR 200 mg/400 mg bid for 7 d	*H. pylori* eradication rates in VPZ based therapy group was 97.4% compare to the empirical PPI based therapy group 86.3% with 95%CI: 83.8-88.8 compare to with 95%CI: 95.7-99.1. The VPZ-based therapy was significantly more effective ($P < 0.001$) than PPI based empirical therapy
Shinozaki *et al*[24], 2016	Japan	Intervention: VAC group VPZ 20 mg + AMX 750 mg + CLR 200 mg for 7 d. Control: PPI group [(LAC) LPZ 30 mg + AMX 750 mg + CLR 200 mg for bid 7 d or (RAC) RPZ 10 mg + AMX 750 mg + CLR 200 mg bid for 7 d or (EAC) EPZ 40 mg + AMX 750 mg + CLR 200 mg bid for 7 d]	*H. pylori* eradication therapy was 83% in VAC with 95%CI: 75-89 compare to LAC 66% with 95%CI: 59-72; RAC 67% with 95%CI: 58-74; EAC 85% with 95%CI: 75-89. The VAC group showed a significantly higher eradication rate compared with the LAC and RAC groups VAC 83%, LAC 66% and RAC 67%, $P < 0.01$. Similar eradication rate were observed in VAC group 83% compare to EAC group 83%
Ozaki *et al*[25], 2018	Japan	Intervention: VPZ 40 mg + CLR 400 mg/800 mg + AMX 1500 mg daily for 7 d. Control: EPZ 40 mg + CLR 400 mg/800 mg + AMX 1500 daily for 7 d or RPZ 20 mg + CLR 400 mg/800 mg + AMX 1500 mg daily 7 d	*H. pylori* eradication rate in EPZ group 77.5% and the RPZ group 68.4%, no significant difference. There was a significantly superior eradication rate in VPZ group 90.8% compare to EPZ 77.5% and RPZ 68.4%. VPZ-based triple therapy eradication rates was remarkably higher compared with PPIs-based triple therapy in real world
Chiu *et al*[26], 2023	Japan	Intervention: VAC group-VPZ 20 mg + AMX 1 g + CLR 500 mg bid for 7 d. Control: PPI (LPZ 30 mg or RPZ 20 mg or PPZ 40 mg) + AMX 1 g bid daily for 7 d, followed by the same PPI + CLR 500 mg + MTZ 500 mg bid for 7 d	*H. pylori* eradication rate was 83.0% in the VAC compare to 88.8% in the PPI group. There was no significant difference in eradication rate between VAC 7 d therapy and LAC 14 d sequential therapy $P = 0.12$
Mori *et al*[27], 2018	Japan	Intervention: VPZ 20 mg + AMX 750 mg + CLR 200 mg/400 mg bid for 7 d. Control: LPZ 30 mg + AMX 750 mg + CLR 200 mg/400 mg bid for 7 d	*H. pylori* eradication rate with VPZ was significantly higher than the LPZ group 91.0% compare to 84.7% $P = 0.030$. VPZ was significantly more effective than LPZ for first-line treatment
Jung *et al*[10], 2023	South Korea	Intervention: TPZ 50 mg + AMX 1 g + CLR 500 mg bid for 14 d. Control: RPZ 20 mg + AMX 1 g + CLR 500 mg bid for 14 d	Eradication rate 76.7% in TPZ group with 95%CI: 72.1%-81.0% compare to 75.4% in RPZ group with 95%CI: 70.5%-79.8%, $P > 0.999$. The eradication rate of TPZ-based triple therapy was similar to that of RPZ-based triple therapy
Kim *et al*[28], 2021	South Korea	Intervention: TACB-TPZ 50 mg + AMX 1 g, CLR 500 mg, and BBS 300 mg bid for 7 d. Control: LACB LPZ 30 mg + AMX 1 g + CLR 500 mg, and BBS 300 mg bid for 7 d	Eradication rates were 78.8% in the tegoprazan TACB and 74.5% in the lansoprazole LACB group ($P = 0.323$). Both the tegoprazan and lansoprazole group showed simlar eradication rates
Hojo *et al*[29], 2020	Japan	Intervention: VPZ 20 mg + AMX 750 mg + MTZ 250 mg bid for 7 d - as 2nd line. Control: RPZ 10 mg + AMX 750 mg + MTZ 250 mg bid	Eradication rates in the was 73.9% in VPZ with 95%CI: 51.6%-89.8% compare to 82.6% in RPZ with 95%CI: 61.2%-95.0%, $P = 0.72$. VPZ based 2nd line therapy is non-inferior to RPZ 2nd

		for 7 d - as 2nd line	line therapy and is safe
Nabeta *et al*[30], 2020	Japan	Intervention: VPZ 20 mg + MTZ 250 mg + AMX 750 mg bid for 7 d. Control: LPZ 30 mg or RPZ 10 mg + MTZ 250 mg + AMX 750 mg bid for 7 d	*H. pylori* eradication rate in VPZ 2nd line therapy 90% (298/330) compare to 85% in lansoprazole 2nd line therapy (250/294), $P = 0.045$. P-CAB-based (VPZ) second-line *H. pylori* eradication is significantly better than PPI-based (lansoprazole) therapy

VPZ: Vonoprazan; AMX: Amoxicillin; CLR: Clarithromycin; BD: Twice a day; LPZ: Lansoprazole; *H. pylori*: *Helicobacter pylori*; CI: Confidence interval; PPI: Proton pump inhibitor; RPZ: Rabeprazole; MTZ: Metronidazole; P-CAB: Potassium competitive acid blocker; LACB: Lanzoprazole + amoxicillin+ clarithromycin+ bismuth subsalicylate; TACB: Tegoprazan + amoxicillin + clarithromycin+ bismuth subsalicylate; TPZ: Tegoprazan; VAC: Vonoprazan + amoxicillin + clarithromycin + bismuth subsalicylate; LAC: Lansoprazole + amoxicillin+ clarithromycin; EPZ: Esomeprazole; EAC: Esomeprazole + amoxicillin + clarithromycin; RAC: Rabeprazole + amoxicillin + clarithromycin; LBMT: Lansoprazole + bismuth subsalicylate + metronidazole + tetracycline; TBMT: Tegoprazan + bismuth subsalicylate + metronidazole + tetracycline; BBS: Bismuth subsalicylate; TET: Tetracycline; OPZ: Omeprazole; tid: Three times in a day.

extent of P-CAB-based triple therapy's superiority over PPIs in eradicating *H. pylori*. The findings underscore the continued emphasis on the efficacy and safety of P-CABs, positioning P-CABs based triple therapy as a viable alternative to traditional PPI-based regimens for *H. pylori* eradication - being non-inferior and, in some instances, even superior to PPIs. Clinicians, especially in situations where VPZ-based therapy is available and affordable, should consider it as a viable option over traditional PPI-based therapy.

ARTICLE HIGHLIGHTS

Research background

Helicobacter pylori (*H. pylori*) infection affects over 50% of the global population, with varying prevalence worldwide. The bacterium is linked to gastroduodenal conditions, including chronic gastritis, peptic ulcers, and gastric adenocarcinomas. Childhood infection, particularly in socioeconomically challenged environments, significantly elevates adult infection rates. Successful *H. pylori* eradication is crucial for mucosal healing and reducing gastric cancer incidence. However, rising antibiotic resistance and suboptimal therapeutic regimens pose challenges to eradication. Vonoprazan (VPZ), a potassium-competitive acid blocker (P-CAB), offers a promising alternative to conventional proton pump inhibitors (PPIs). With unique pharmacokinetics and diverse clinical applications, VPZ has gained Food and Drug Administration approval for *H. pylori* eradication therapy.

Research motivation

The increasing prevalence of *H. pylori* antibiotic resistance and suboptimal therapeutic outcomes necessitate innovative eradication strategies. VPZ emerges as a novel, effective alternative with distinct pharmacokinetics and versatile clinical applications. Addressing the efficacy of regimens incorporating P-CABs in *H. pylori* eradication is crucial. This study seeks to unravel the potential of VPZ-based therapies in overcoming challenges associated with conventional treatments, impacting future research directions in the field of *H. pylori* eradication.

Research objectives

The primary objective of this study is to evaluate the efficacy of regimens containing P-CABs, particularly focusing on VPZ, in eradicating *H. pylori* infection. The study aims to analyze key parameters, including eradication rates, adverse events, and compliance, to provide a comprehensive understanding of VPZ-based therapies. By achieving these objectives, the study contributes valuable insights into optimizing *H. pylori* eradication strategies, guiding future research towards more effective and tailored therapeutic approaches in gastroenterology and infectious diseases.

Research methods

This systematic review and meta-analysis followed the PRISMA 2020 guidelines and conducted a comprehensive literature search in MEDLINE and Scopus libraries. Inclusion criteria encompassed randomized clinical trials (RCTs) or observational studies comparing the efficacy of P-CABs with classical PPIs for *H. pylori* eradication. Exclusion criteria ruled out case reports, case series, unpublished trials, and conference abstracts. Two independent reviewers screened titles, abstracts, and full papers, extracting data on efficacy rates and relevant variables. Descriptive techniques, including frequency, means, and medians, were employed for data summarization. The meta-analysis utilized R software version 4.3.2 and the meta package.

Research results

The systematic review and meta-analysis identified 15 studies, including 7 RCTs and 7 retrospective observational studies, contributing valuable insights into the efficacy and safety of regimens containing P-CABs for *H. pylori* eradication. The majority of studies were conducted in Asia, particularly in Japan and South Korea, with limited representation from Western regions. The analysis, comprising 8049 patients, demonstrated that VPZ triple therapy significantly outperformed conventional PPI triple therapy, showcasing its statistical superiority in *H. pylori* eradication.

Conversely, tegoprazan (TPZ) triple therapy was found to be non-inferior to classical PPI-based treatment. Observational studies reinforced these findings, emphasizing the superiority of VPZ triple therapy over PPI-based regimens. Additionally, second-line therapy with VPZ demonstrated non-inferiority to PPI-based second-line treatment for *H. pylori* eradication. Notably, all P-CAB regimens exhibited good tolerability and safety profiles, aligning with PPI treatments. These results contribute comprehensive evidence supporting the efficacy and safety of P-CABs, particularly VPZ, in *H. pylori* eradication therapy. Further research may explore the application of these findings in diverse populations and regions.

Research conclusions

This study advances the understanding of *H. pylori* eradication therapy by demonstrating the statistical superiority of VPZ-based triple therapy over conventional PPI-based regimens. The research concludes that TPZ-based triple therapy is non-inferior to PPI-based triple regimens. Notably, the study introduces the novel concept of P-CABs, specifically VPZ and TPZ, as effective alternatives in *H. pylori* eradication. By presenting robust evidence from 15 studies, including RCTs and observational studies, the research contributes to evolving treatment paradigms. The findings highlight VPZ's superior efficacy and TPZ's non-inferiority, offering clinicians valuable insights into alternative therapies amid rising antibiotic resistance. This study stands as a significant departure from conventional PPI-centric approaches and introduces P-CABs as viable options for *H. pylori* eradication, addressing the pressing need for alternative treatments in the face of declining PPI effectiveness.

Research perspectives

Future research should delve into the broader application of P-CAB-based triple and dual therapy beyond the predominantly studied Eastern populations. Assessing the generalizability of VPZ and TPZ efficacy to diverse demographic groups is crucial for informing global *H. pylori* eradication strategies. Additionally, further investigations should explore the impact of P-CABs in regions with varying genetic, dietary, and lifestyle factors, influencing gastric acidity levels. Addressing the limitations of this study, such as the limited pooled sample size and focused demographic representation, will enhance the external validity of findings. Future studies could integrate comprehensive analyses of antibiotic resistance, particularly clarithromycin resistance, to refine treatment recommendations. Economical considerations, emphasized in the study, warrant exploration through cost-effectiveness analyses in diverse healthcare settings. As the study hints at the potential affordability challenges of VPZ triple therapy in developing countries, future research could explore strategies for enhancing accessibility, such as government-subsidized generic forms. These perspectives collectively guide future research to broaden the scope, applicability, and accessibility of P-CAB-based therapies, fostering a more nuanced understanding of their role in global *H. pylori* eradication efforts.

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FOOTNOTES

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