

Efficacy and Safety of Vonoprazan-Based Bismuth-Containing Quadruple Therapy for Helicobacter Pylori Eradication: A Meta-Analysis

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Abstract: Aims: To compare the efficacy and safety of vonoprazan-based bismuth-containing quadruple therapy (VBCQ) versus proton pump inhibitor (PPI)-based bismuth-containing quadruple Therapy (PBCQ) for Helicobacter pylori eradication. **Methods:** We performed a systematic search in PubMed, Embase, Web of Science, Cochrane Library, CNKI, Wanfang databases for relevant randomized controlled trials up to March 2024. Meta-analysis by RevMan 5.4 software. **Results:** Ten randomized controlled trials were evaluated in this meta-analysis. In intention-to-treat (ITT) analysis and per-protocol (PP) analysis, the eradication rate of VBCQ was significantly higher than PBCQ [ITT overall eradication rate: 86.7% vs 82.8%, RR: 1.05, 95% CI (1.05, 1.09), $P < 0.05$; PP overall eradication rate: 92.0% vs 88.0%; RR = 1.05, 95% CI (1.05, 1.08), $P < 0.05$]. The incidence of adverse events in VBCQ was higher than PBCQ (36.7% vs 36.5%), there was no significant difference ($P > 0.05$). **Conclusions:** VBCQ has a higher eradication rate and comparable safety.

Keywords: Vonoprazan; Helicobacter Pylori; Proton Pump Inhibitor; Quadruple Therapy; Efficacy; Safety

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Helicobacter pylori (H. pylori, Hp) infection has a global prevalence of approximately 50%, varying across regions and populations. In mainland China, over 500 million individuals are infected with Hp^[1]. Digestive diseases such as gastritis, peptic ulcer disease, and gastric cancer are closely associated with Hp infection. The "National Sixth Consensus" recommends eradication therapy for confirmed Hp infections in the absence of contraindications^[2]. Vonoprazan (VPZ), a potassium-competitive acid blocker (P-CAB), was introduced in China in December 2019. Compared to proton pump inhibitors (PPIs), VPZ offers more potent and prolonged acid suppression. The 2022 Chinese guidelines recommend a VPZ-based bismuth quadruple therapy for Hp eradication^[3]. However, the efficacy and safety differences between VPZ-based and PPI-based quadruple regimens remain unclear. Comparative studies between VPZ-based bismuth quadruple therapy (VBCQ) and PPI-based bismuth quadruple therapy (PBCQ) are limited, and the superiority of VPZ-based therapy in improving eradication rates remains uncertain. This study systematically analyzes randomized controlled trials (RCTs) comparing VPZ- and PPI-based bismuth quadruple therapies to provide evidence-based recommendations for clinical application.

1. Materials and Methods

1.1 Search Strategy

This study was registered in the International Prospective Register of Systematic Reviews (ID: CRD42024501043). Literature search was conducted up to March 2024 in both Chinese and English databases, including PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Database. Keywords used in the search included "Helicobacter pylori," "H. pylori," "Hp," "Vonoprazan," "TAK-438," "Potassium-competitive acid blocker," and "Quadruple".

1.2 Inclusion and Exclusion Criteria

Inclusion criteria:(1) Patients of any age or gender with confirmed Hp infection via the urea breath test (UBT), stool antigen test, or histopathological examination;(2) Treatment group receiving VBCQ for 14 days;(3) Control group receiving PBCQ for 14 days;(4) Primary outcome: Hp eradication rate; Secondary outcome: adverse event (AE) incidence;(5) RCTs.

Exclusion criteria:(1) Non-RCT studies;(2) Incomplete data or unavailable full text.

1.3 Literature Screening and Data Extraction

Two independent reviewers screened studies and extracted relevant data, including study author, location, sample size, treatment regimen, and eradication confirmation method. Discrepancies were resolved through discussion. The primary outcome was Hp eradication rate, analyzed via intention-to-treat (ITT) and per-protocol (PP) methods. The secondary outcome was AE incidence.

1.4 Quality Assessment

The methodological quality of RCTs was evaluated based on:(1) Randomization method;(2) Allocation concealment;(3) Blinding of participants and investigators;(4) Blinding of outcome assessors;(5) Completeness of outcome data;(6) Selective reporting;(7) Other potential biases.

1.5 Statistical Analysis

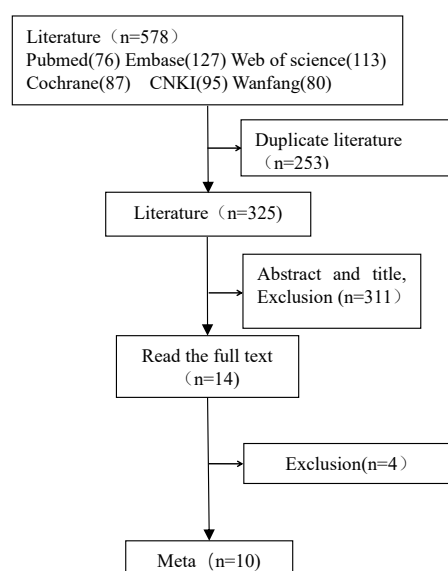
Risk ratio (RR) with a 95% confidence interval (CI) was used to assess eradication rates and safety. Heterogeneity was evaluated using I^2 statistics: $I^2 \leq 50\%$ indicated a fixed-effects model, while $I^2 > 50\%$ necessitated a random-effects model. A significance level of $P < 0.05$ was set. Funnel plots assessed publication bias. Sensitivity analysis was conducted by changing effect models. Data analysis was performed using RevMan 5.4 software.

2.Results

2.1 Literature Search Results

A total of 578 articles were obtained from the search, which were introduced into EndNote 20.6 and NoteExpress 3.7 literature manager. 253 duplicate articles were removed by software and manual removal. 311 articles were excluded from reviews, comments, letters, case reports and research contents, 4 articles were excluded, and 10 studies were finally included. Figure 1.

Figure 1. The literature search process



2.2 Characteristics of Included Studies

Ten studies (6 in English, 4 in Chinese) published between 2022 and 2024 were included^[4-13], involving 8 studies from China, 1 from South Korea, and 1 multinational East Asian study. Most studies confirmed Hp eradication using the ¹³C-UBT test. Table 1

Table 1 Basic characteristics of literature

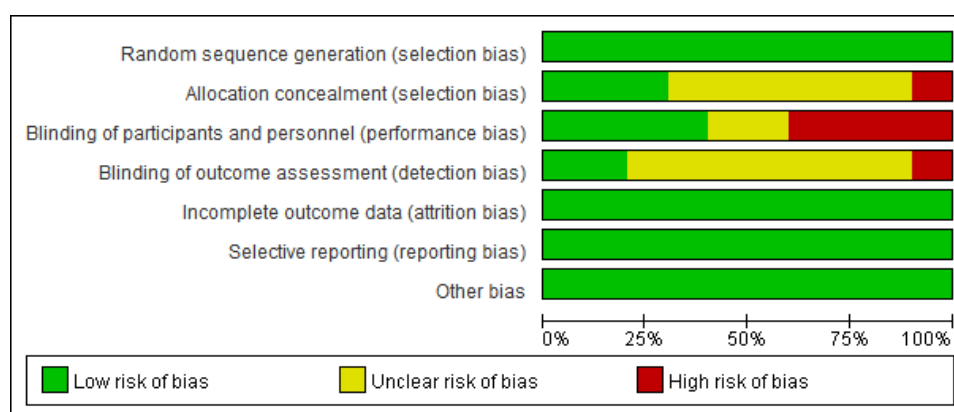
	Age	Country / region	Sample	experimental / control	VPZ	PPI	Confirmation of eradication
Chen et al[4]	18-75	China	90	45/45	V 20mg bid,14d	I 5mg bid,14d	¹³ C-UBT
Deng et al[5]	19-78	China	222	113/109	V 20mg qd,14d	R 20mg bid,14d	¹³ C-UBT
Hou et al[6]	≥18	East Asia	415	211/204	V 20mg bid,14d	L 30mg bid,14d	¹³ C-UBT
Huh et al[7]	18-60	Korea	30	15/15	V 20mg bid,14d	L 30mg bid,14d	¹³ C-UBT
Lian et al[8]	19-70	China	214	107/107	V 20mg bid,14d	E 20mg bid 14d	¹³ C-UBT
Li ea al[9]	60-75	China	60	30/30	V 20mg bid,14d	L 30mg bid,14d	¹³ C/ ¹⁴ C-UBT HpSAT
Lu et al[10]	18-65	China	156	78/78	V 20mg bid,14d	E 20mg bid,14d	¹³ C/ ¹⁴ C-UBT
Miao et al[11]	18-60	China	44	22/22	V 20mg bid,14d	E 20mg bid,14d	¹³ C-UBT
Ran et al[12]	20-70	China	160	80/80	V 20mg bid,14d	O 20mg bid,14d	¹³ C-UBT
Song et al[13]	≥18	China	510	256/254	V 20mg bid,14d	E 20mg bid,14d	¹³ C-UBT

Note: V: vororacin; E: esomeprazole; L: lansoprazole; O: omeprazole; R: rabeprazole; I: eprazole;; qd: 1 per day; bid: 2 per day; UBT urea breath test; HpSAT: antigen test for H. pylori stool.

2.3 Risk of Bias Assessment

All 10 studies implemented randomization. The risk of incomplete outcomes, selective reporting, and other biases was low, indicating high study quality. Figure 2.

Figure 2. Literature quality evaluation

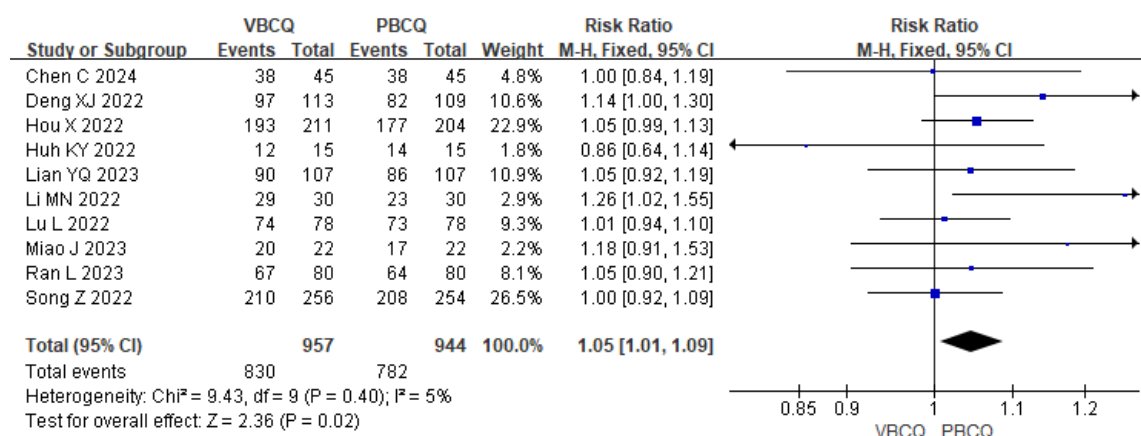


2.4 Meta-Analysis Results

2.4.1 Eradication Rate (ITT Analysis)

10 studies were included in the intention-to-treat (ITT) analysis. The eradication rates for VBCQ and PBCQ were 86.7% (830/957) and 82.8% (782/944), respectively. Heterogeneity testing indicated no significant variability among the studies ($I^2 = 5\%$, $P = 0.40$). The results from the fixed-effect model meta-analysis demonstrated that VBCQ had a significantly higher eradication rate compared to PBCQ (overall eradication rate: 86.7% vs. 82.8%, $RR = 1.05$, 95% CI: 1.01–1.09, $P < 0.05$), as shown in Figure 3.

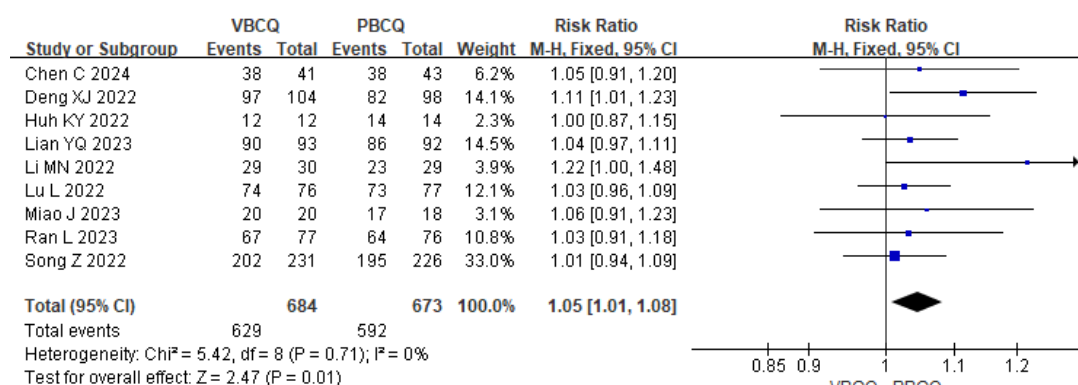
Figure 3. Forest plot of ITT analysis comparing eradication rates between VBCQ and PBCQ



2.4.2 Eradication Rate (PP Analysis)

9 studies were included in the per-protocol (PP) analysis. The eradication rates for VBCQ and PBCQ were 92.0% (629/684) and 88.0% (592/673), respectively. Heterogeneity testing indicated no significant differences among the studies ($I^2 = 0\%$, $P = 0.71$). The fixed-effect model meta-analysis showed that VBCQ had a higher eradication rate compared to PBCQ (overall eradication rate: 92.0% vs. 88.0%; $RR = 1.05$, 95% CI: 1.01–1.08, $P < 0.05$), Figure 4.

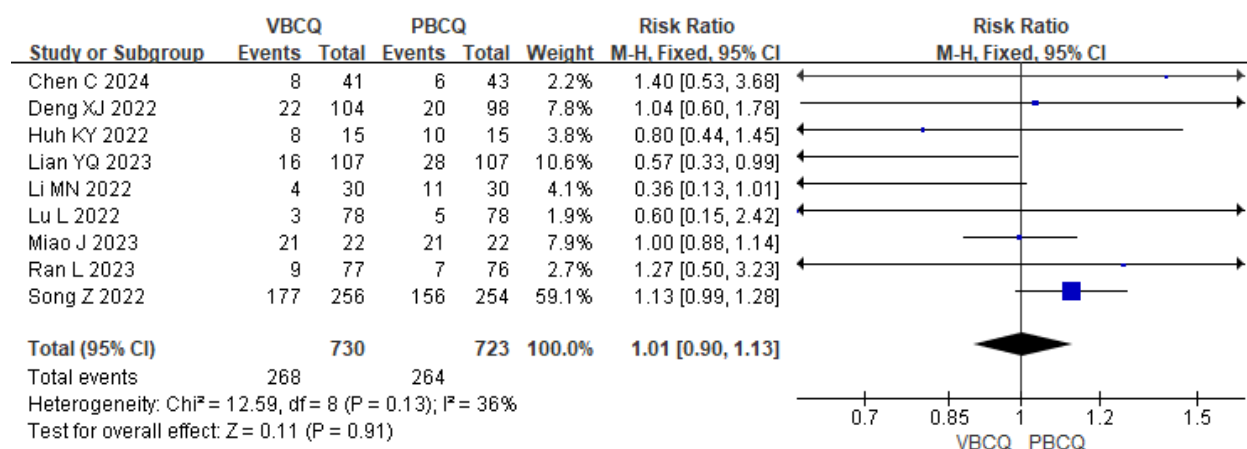
Figure 4. Forest plot of PP analysis comparing eradication rates between VBCQ and PBCQ



2.4.3 Safety Analysis

9 studies were included in the safety analysis. The incidence of adverse events for VBCQ and PBCQ was 36.7% (268/730) and 36.5% (264/723), respectively. Heterogeneity testing showed no significant differences among the studies ($I^2 = 36\%$, $P = 0.13$). The fixed-effect model meta-analysis indicated no significant difference in the incidence of adverse events between VBCQ and PBCQ (overall incidence: 36.7% vs. 36.5%; $RR = 1.01$, 95% CI: 0.90–1.13, $P > 0.05$), Figure 5.

Figure 5. Forest plot of safety analysis between VBCQ and PBCQ



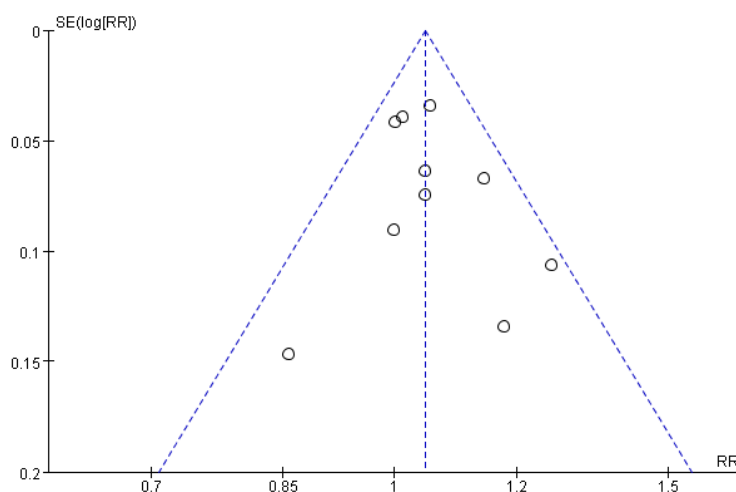
2.5 Sensitivity Analysis

Sensitivity analysis was conducted using model selection methods. In the ITT analysis, switching to a random-effects model in the meta-analysis still showed that the eradication rate of VBCQ was significantly higher than that of PBCQ ($P < 0.05$), consistent with the results from the fixed-effect model. In the PP analysis, the meta-analysis results remained consistent after switching to the random-effects model ($P < 0.05$). For the safety analysis, the results from the random-effects model also showed no significant difference, indicating that the findings are relatively stable.

2.6 Publication Bias

A funnel plot for studies comparing the eradication of *H. pylori* by VBCQ and PBCQ was generated using RevMan 5.4 software. The funnel plot indicated minimal publication bias, as the included studies were relatively symmetrically distributed on both sides of the plot (Figure 6).

Figure 6. Funnel plot of the efficacy of VBCQ versus PBCQ for *H. pylori* eradication (ITT analysis)



3. Discussion

The intragastric acid environment is a key factor influencing the eradication of *Helicobacter pylori* (Hp). Increasing gastric pH can enhance the bacterium's susceptibility to antibiotics^[14]. Compared with proton pump inhibitors (PPIs), vonoprazan (VPZ) exhibits a faster and more potent acid-suppressing effect. VPZ is primarily metabolized by cytochrome P450 enzyme CYP3A4^[15], and is thus less affected by CYP2C19 gene polymorphisms, which commonly influence the efficacy of PPIs. Studies have shown that VPZ suppresses gastric acidity more rapidly and effectively than lansoprazole^[16]. In recent years, the issue of antibiotic resistance in *H. pylori* has become increasingly severe, with resistance rates for metronidazole, clarithromycin, and levofloxacin rising significantly^[17–18], potentially reducing the effectiveness of eradication therapies. The introduction of potassium-competitive acid blockers (P-CABs) like VPZ may bring a paradigm shift in *H. pylori* eradication regimens. International consensus guidelines have also recommended the use of P-CABs for *H. pylori* eradication^[19–20]. Currently, the PPI-based bismuth-containing quadruple therapy (PBCQ) is the most widely used *H. pylori* eradication regimen in China. Compared with PBCQ, the widespread use of P-CAB-based therapies may improve eradication rates. As a representative P-CAB, VPZ has been the focus of a growing body of research, both domestically and internationally. In China, VPZ-based eradication regimens primarily include dual and quadruple therapies. Our research team has previously conducted a meta-analysis comparing a VPZ-amoxicillin dual therapy with the traditional PPI-based bismuth quadruple regimen, showing that the dual therapy was not inferior^[21]. However, whether VPZ-based bismuth quadruple therapy (VBCQ) can further improve eradication rates remains a subject of debate.

This meta-analysis included 10 randomized controlled trials, with low heterogeneity and minimal bias among the studies, indicating relatively stable results. Both ITT and PP analyses demonstrated that the eradication rate of VBCQ was higher than that of PBCQ. In terms of safety, there was no significant difference in adverse event rates between the two regimens. Compared with PBCQ, VBCQ increased eradication rates by 3.9% in ITT analysis and 4.0% in PP analysis. These findings support that VBCQ offers a higher eradication rate with acceptable tolerability.

Limitations: This study included only publications in Chinese and English, and the number of included studies was limited, with some having small sample sizes, potentially introducing bias. The safety analysis only assessed the overall incidence of adverse events and did not examine specific adverse reactions. Additionally, other types of P-CAB-based bismuth quadruple therapies were not included. Since all study populations were East Asian, the generalizability of the findings to other regions remains to be confirmed.

In conclusion, the results of this study suggest that VBCQ provides a higher eradication rate than PPI-based bismuth quadruple therapy, with comparable tolerability. VBCQ is recommended for the treatment of *H. pylori* infection. Further in-depth research is warranted to confirm these findings, and the potential of other P-CAB-based bismuth quadruple therapies in *H. pylori* eradication should also be explored.

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no

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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