

Potassium-Competitive Acid Blocker–Based Triple Therapy versus Proton Pump Inhibitor–Based Triple Therapy for *Helicobacter pylori* Eradication: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Introduction: Gastric acid secretion is strongly and persistently inhibited by potassium competitive acid blocker (P-CAB). The safety and effectiveness of P-CAB-based triple therapy versus conventional proton pump inhibitor (PPI)-based triple therapy for eradication of *Helicobacter pylori* have been examined in a number of studies, however the outcomes are still inconsistent. To assess the safety, treatment compliance/adherence, and effectiveness of P-CAB-based triple therapy in comparison to PPI-based triple therapy for the eradication of *H. pylori*, we have conducted this systematic review and meta-analysis.

Methods: The PRISMA 2020 requirements for systematic review and meta-analysis were adhered to. Randomized controlled trials (RCTs) comparing P-CAB-based triple therapy with PPI-based triple therapy (PTT) for *H. pylori* eradication that were published between February 2015 and February 2026 were found by searching MEDLINE, Embase, and the Cochrane Library. Informations were gathered on treatment compliance/adherence, adverse drug reactions, and the eradication rates (intention-to-treat analysis). Pooled risk ratios (RR) at 95% confidence intervals (CI) were computed using Review Manager.

Results: The analysis includes eight randomized controlled trials (RCTs) with 2378 individuals. Six RCTs evaluated vonoprazan-based triple therapy (VTT), while two RCTs assessed tegoprazan-based triple therapy (TTT). Pooled analysis of six RCTs (1780 patients) evaluating VTT showed significantly higher eradication rate compared with PTT (806/898 vs 695/882; RR:1.13, 95% CI 1.04–1.23; $P = 0.004$), although substantial heterogeneity was observed ($I^2 = 75\%$, $\text{Chi}^2 = 19.50$, $P = 0.002$). TTT was found to be non-inferior to PTT in two studies with 598 participants (214/296 vs. 206/302; RR:1.07; 95% CI 0.98–1.18; $P = 0.14$) with no heterogeneity ($I^2 = 0\%$, $\text{Chi}^2 = 0.24$, $P = 0.62$). In both intervention and control groups across all RCTs, treatment compliance was at least 90%. The common encountered adverse drug reactions by the participants of either group were nausea, diarrhea, abdominal discomfort, headache, and altered taste. These reactions were generally minor and similar in the intervention and control groups.

Conclusion: P-CAB-based triple therapy appears to be an effective and well-tolerated alternative to conventional PPI-based therapy. Although VTT showed better eradication rates than PTT, TTT exhibited non-inferior efficacy. Before validating these results, further large-scale, multi-center, and multi-national trials across diverse populations are required.

Key words: *Helicobacter pylori*, Eradication, potassium competitive acid blocker, P-CAB, proton pump inhibitor

Introduction

Helicobacter pylori is a common chronic bacterial infection, affecting nearly 50 % of the world's population.¹ Its prevalence varies worldwide, with higher rates in developing countries like Nepal.¹ Factors such as poor sanitation, unsafe drinking water, overcrowding, and lower socioeconomic conditions contribute to higher prevalence in these regions.¹ *H. pylori* infection is a major concern of public health, as it is associated with chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma.² Although it typically appears in adulthood, the infection is mainly acquired during childhood.³ It affects both genders equally, though some studies report higher prevalence and complications in males.^{1,4}

After successful elimination of *H. pylori*, improvements in mucosal healing in patients with gastroduodenitis and peptic ulcer disease have been observed.⁵ Additionally, complete eradication

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has been linked to reduction in the risk of gastric carcinoma significantly.⁵ In recent years, particularly in developing countries like Nepal, low eradication rates of *H. pylori* are mainly due to rising anti-microbial resistance, substantial treatment regimens, and CYP2C19 genetic polymorphisms.^{6,7,8,9}

Potassium competitive acid blockers (P-CAB), such as vonoprazan, tegoprazan, reveprazan, linaprazan, and soraprazan, strongly and continuously inhibit gastric acid production.¹⁰ P-CAB reversibly blocks the potassium-binding site of the gastric H⁺/K⁺-ATPase proton pump, thereby inhibiting the terminal pathway of acid generation and total acid output.¹¹ Unlike proton pump inhibitors (PPIs), which require an empty stomach for absorption, P-CAB is meal-independent, reaches plasma concentrations within two hours, and has a plasma half-life of over nine hours.¹¹ Because of these pharmacologic properties, acid inhibition occurs quickly and is maintained for a sustained period of time. CYP2C19 polymorphism does not affect the effectiveness of P-CAB.¹² P-CAB has recently been approved the U.S. Food and Drug Administration for use as dual and triple regimens in order to eliminate *H. pylori*.^{12,13} Variable results have been reported from randomized controlled trials comparing the safety and effectiveness of P-CAB-based triple therapy with conventional PPI-based triple therapy for *H. pylori* eradication. In this systematic review and meta-analysis, we compared eradication efficacy, treatment compliance/adherence, and safety outcomes of P-CAB-based triple therapy to PPI-based triple therapy.

Methods

Search strategy:

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 statement was followed for reporting this article (14) [Supplemental content 1]. For the search approach of each parameter, we established the Population, Intervention, Comparator, Outcomes, and Study design (PICOS) statement [Table 1]. This systematic and meta-analysis's procedure was registered in PROSPERO (CRD420261398890).

Table 1: PICOS statement for systematic review and meta-analysis

S.n.:	PICOS	Description
	Population	Patients of either sex with confirmed diagnosis of <i>Helicobacter pylori</i>
	Intervention/Comparator	Vonoprazan, Tegoprazan, Omeprazole, Lansoprazole, Esomeprazole, Pantoprazole, Rabeprazole
	Outcomes	Primary outcome: Eradication rate (Intention-to-treat Analysis; ITT) at 7 to 14 days Secondary outcome: Compliance/Adherence Adverse drug reactions
	Study design	Randomized controlled trial
	Country	Global
	Language	English

Randomized controlled trials (RCTs) published in peer-reviewed journals between February 2015 to February 2026 were found by searching MEDLINE, Embase, and the Cochrane Library. Further studies were identified by manually scanning Google Scholar and the reference list. The following command was used to search the articles: [("*Helicobacter pylori*" OR "*H. pylori*") AND ("Vonaprazan" OR "Tegoprazan" OR "Reveprazan" OR "Linaprazan" OR "Soraprazan" OR "Potassium-Competitive Acid Blocker" OR "P-CAB") AND ("Triple therapy" OR "Eradication") AND ("Randomized Controlled Trial")].

Selection criteria:

The RCTs published in English language were included. Exclusion criteria comprised observational studies, unpublished trials, case reports, conference papers, and case series.

Outcomes of interest:

The primary outcome included eradication rate in terms of intention-to-treat analysis at 7 to 14 days, and secondary outcomes were compliance/adherence and adverse drug reactions.

Data abstraction:

The articles were obtained from electronic databases on the basis of predetermined inclusion and exclusion criteria, and they were independently reviewed by five reviewers (RRP, RP, BKB, AJ, and RH). Full texts were examined for those articles which fulfilled the eligibility requirements. For data extraction, we utilized Microsoft Excel version 2021 (Microsoft Corp., Redmond, WA, USA). For each eligible study, records were made for author, publication year, research nation, design of research, overall sample size, type of potassium-competitive acid blocker (P-CAB) used, accompanying antibiotics used in therapy, dose and duration of treatment, *Helicobacter pylori* eradication rates (intention-to-treat analysis), treatment compliance/adherence, and reported adverse events. The retrieved data were independently confirmed by other reviewers (TWS, DK, ML, TRB, SP, SA, and SKS). Any disagreements were settled after reaching a consensus following discussion among reviewers.

Risk of assessment of bias:

In order to individually assess the quality of methodology of the included RCTs, the reviewers RRP, RP, BKB, AJ, and RH used the Cochrane Risk of Bias 2 (RoB 2). The assessment of bias was based on five domains i.e.: randomization method, changes from planned interventions, missing outcome data, outcome measurement, and selection of reported results. Individual domain was classified as "low risk," "some concerns," or "high risk" of bias as per RoB 2 guidelines. Other reviewers (TWS, DK, ML, TRB, SP, SA, and SKS) were consulted in order to settle any disputes among the reviewers.

Statistical analysis:

Review Manager (RevMan) version 5.4 (Cochrane Collaboration, Oxford, UK) was used for the statistical evaluation. The 95% confidence interval (CI) for the risk ratio (RR) was used to express the pooled eradication rates. If $P < 0.05$, the results were considered to be statistically significant. For VTT vs. PTT and TTT

vs. PTT, we conducted independent meta-analyses. To evaluate the heterogeneity Chi-square (Cochran's Q) test was used, and it was quantified using I^2 statistic. For heterogeneity assessment, $I^2 < 25\%$, $25\text{--}50\%$, and $>50\%$ were regarded as low, moderate, and considerable heterogeneity respectively. Random-effects model was applied for significant heterogeneity.

Results

The search technique found 257 records in total. 118 papers were checked for titles and abstracts after duplicates were eliminated. 18 pertinent papers were taken into consideration for full text evaluation after 100 studies were eliminated during abstract screening. This systematic review and meta-analysis comprised eight RCTs that met the eligibility criteria [Figure 1].

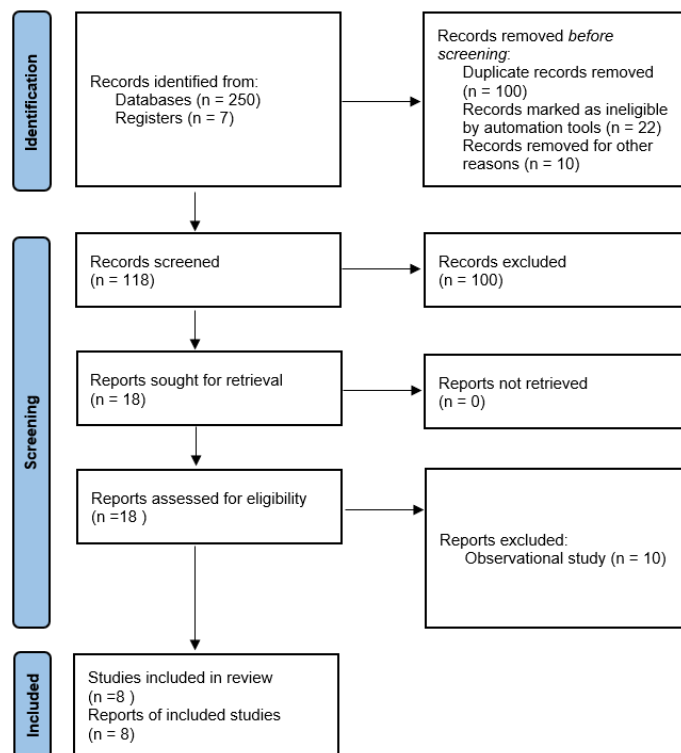


Figure 1: PRISMA diagram detailing identification of study and method of selection

Bias evaluation of trials included:

Figure 2 summarizes the potential risk of bias evaluation of the included research. Two out of eight included RCTs have a low overall risk of bias, four have some concerns, and two have a high risk. In certain trials, open-label study designs led to variations from targeted interventions, which were the primary source of bias. Because successful elimination of *H. pylori* was evaluated using objective diagnostic techniques, such as stool antigen testing or urea breath testing, the majority of trials showed little risk in outcome measurement.

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Murakami et al. 2016	+	+	+	+	-	-
Maruyama et al. 2017	-	-	+	+	-	-
Sue et al. 2018	+	-	+	+	-	-
Bunchorntavakul et al. 2021	-	✗	+	+	-	✗
Chey et al. 2022	+	+	+	+	+	+
Ang et al. 2022	-	✗	+	+	-	✗
Choi et al. 2022	+	+	+	+	+	+
Park et al. 2026	+	-	+	+	-	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
✗ High
- Some concerns
+ Low

Figure 2: Summary of risk of bias of included trials

Vonoprazan-based triple therapy versus PPI-based triple therapy:

The meta-analysis comparing vonoprazan-based triple therapy (VTT) with PPI-based triple therapy (PTT) for *Helicobacter pylori* eradication included six RCTs with 1780 participants.

Study characteristics vonoprazan-based triple therapy versus PPI-based triple therapy:

Table 1 displays the study's characteristics of included trials. Only one study was carried out in the United States and Europe, whereas the majority of the studies were carried out in Japan. Vonoprazan 20 mg plus amoxicillin 750/1000 mg and clarithromycin 200/400/500 mg, given two times in a day, comprised the intervention regimen in each study. Amoxicillin 750/1000 mg, clarithromycin 200/400 mg, and a proton pump inhibitor (lansoprazole 30 mg/rabeprazole 10–20 mg/omeprazole 20 mg) were administered two times in a day as part of the control regimen. The majority of studies used a 7-day course, but the treatment period varied from 7 to 14 days.

Table 1: Study characteristics of vonoprazan-based triple therapy versus PPI-based triple therapy

Author	Year	Country	Study Design	Sample Size	Vonoprazan Triple Therapy	PPI Triple Therapy	Treatment Duration
Murakami et al. (15)	2016	Japan	Phase III multicenter double-blind RCT	650	Vonoprazan 20 mg BID + Amoxicillin 750 mg BID + Clarithromycin 200/400 mg BID	Lansoprazole 30 mg BID + Amoxicillin 750 mg BID + Clarithromycin 200/400 mg BID	7 days
Maruyama et al. (16)	2017	Japan	Randomized controlled trial	141	Vonoprazan 20 mg BID + Amoxicillin 750 mg BID + Clarithromycin 200/400 mg BID	Lansoprazole 30 mg BID + Amoxicillin 750 mg BID + Clarithromycin 200/400 mg BID	7 days
Sue et al. (17)	2017	Japan	Randomized open-label trial	147	Vonoprazan 20 mg BID + Amoxicillin 750 mg BID + Clarithromycin 200/400 mg BID	Lansoprazole 30 mg/ Rabeprazole 10 mg/ Esomeprazole 20 mg BID + Amoxicillin 750 mg BID + Clarithromycin 200/400 mg BID	7 days
Bunchorntavakul et al. (18)	2021	Thailand	Randomized controlled trial	122	Vonoprazan 20 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	Omeprazole 20 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	7 days in Vonoprazan group, and 14 days in Omeprazole group
Chey et al. (13)	2022	USA and Europe	Multicenter double-blind RCT	1046	Vonoprazan 20 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	Lansoprazole 30 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	14 days
Ang et al. (19)	2022	Singapore	Randomized controlled trial	244	Vonoprazan 20 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	Omeprazole 20 mg/ Esomeprazole 20 mg/ Rabeprazole 20 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	7 days in Vonoprazan group/14 days in PPI-group

RCT: Randomized controlled trial

USA: United States of America

BID: Twice in a day

PPI: Proton pump inhibitor

Diagnosis and confirmation of *Helicobacter pylori* eradication:

The majority of the trials used both invasive as well as non-invasive methods to make sure the *H. pylori* diagnosis, ensuring the accuracy of test. Urea breath test (UBT) was the most commonly used method for confirming eradication. In accordance with normal guidelines, eradication was checked at least four to six weeks following the end of therapy to prevent false-negative results brought on by acid suppression or recent antibiotic usage [Table 2].

Compliance and adverse events:

Adherence rates exceeded 90% in both arms of all included studies, and treatment compliance was comparable between VTT and PTT groups. In both groups, adverse effects were often minor. Diarrhea, headache, nausea, discomfort in the abdomen, and dysgeusia were the most common adverse drug reactions [Table 2].

Table 2: Outcomes of vonoprazan-based triple therapy versus PPI-based triple therapy

Author	Results	Compliance	Adverse events	Diagnosis of H. pylori	Confirmation of eradication	Timing of confirmation
Murakami et al. (15)	641 of the 650 patients who were randomly assigned to first-line triple therapy finished first-line treatment, while 50 finished second-line therapy. The vonoprazan group's first-line eradication rate (primary endpoint) was 92.6% (95% CI: 89.2%–95.2%) while the lansoprazole group's was 75.9% (95% CI: 70.9%–80.5%) [$p < 0.0001$]. The second-line eradication rate (secondary endpoint) was also high at 98.0% (95% CI: 89.4%–99.9%).	>98%	Diarrhea, dysgeusia, abdominal discomfort	Urea breath test, rapid urease test, histology	Urea breath test	At least 4 weeks after therapy
Maruyama et al. (16)	When comparing the VPZ group to the PPI group, the eradication rate was noticeably higher. Eradication rates were 95.8% versus 69.6% in the intention-to-treat analysis ($P = 0.00003$; 95% CI: 88.3–99.1% vs. 57.3–80.1%). Rates were 95.7% versus 71.4% in the per-protocol analysis ($P = 0.0002$; 95% CI: 88.0–99.1% vs. 58.7–82.1%).	VTT:95.7% PTT: 92.9%	Diarrhea, nausea, abdominal pain	Rapid urease test, histology	Urea breath test	At least 4 weeks after therapy
Sue et al. (17)	The Vonoprazan group's intention-to-treat and per-protocol eradication rates for patients with clarithromycin-susceptible H. pylori were 87.3% (95% CI: 75.5%–94.7%) and 88.9% (95% CI: 77.4%–95.8%), respectively. The equivalent eradication rates for the PPI group were 86.7% (95% CI: 73.2%–94.9%) and 76.5% (95% CI: 62.5%–87.2%). Neither the intention-to-treat ($P = 0.21$) nor the per-protocol ($P = 0.77$) analysis revealed a statistically significant difference between the Vonoprazan and PPI groups. Vonoprazan-based triple therapy had an intention-to-treat and per-protocol eradication rate of 82.9% (95% CI: 67.9%–92.8%) in patients who were resistant to clarithromycin.	VTT: 97.3% PTT: 95.9%	Dysgeusia, diarrhea	Urea breath test, stool antigen test	Urea breath test	At least 4 weeks after therapy
Bunchorntavakul et al. (18)	By intention-to-treat analysis, the H. pylori eradication rates for the Vonoprazan and Omeprazole groups were 96.7% and 88.5% ($P = 0.083$), respectively; by per-protocol analysis, they were 98.3% and 93.1% ($P = 0.159$).	VTT: 98.3% PTT: 96.7%	Diarrhea, nausea	Urea breath test, rapid urease test	Urea breath test	6 weeks after therapy
Chey et al. (13)	H. pylori was eliminated in 84.7% (222 of 262) of patients with vonoprazan triple therapy compared to 78.8% (201 of 255) with lansoprazole triple therapy (difference 5.9%; 95% CI, -0.8 to 12.6; noninferiority $P < 0.001$).	VTT: 98.3% PTT: 96.7%	Diarrhea, headache, taste disturbance	Urea breath test, stool antigen test	Urea breath test or stool antigen test	At least 4 weeks after therapy
Ang et al. (19)	By intention-to-treat analysis, the eradication rates were 87.4% for triple therapy based on vonoprazan and 88.0% for triple therapy based on PPI. 96.3% for vonoprazan-based triple therapy and 94.0% for PPI-based triple therapy, according to protocol analysis. The efficacy of one-week vonoprazan-based triple therapy was similar to that of two-week PPI-based triple therapy, and it was well tolerated.	VTT: 96.3% PTT: 94%	Nausea, diarrhea	Urea breath test, rapid urease test	Urea breath test	6 weeks after therapy

CI: Confidence interval

PPI: Proton pump inhibitor

VTT: Vonoprazan-based triple therapy

PTT: PPI-based triple therapy

Eradication rates:

A total of 898 patients received VTT, and 882 patients received PTT. The pooled analysis demonstrated that VTT achieved a significantly higher eradication rate compared with PTT (806/898 vs 695/882). The combined effect estimate showed a risk ratio (RR) of 1.13 (95% CI 1.04–1.23; $P = 0.004$) using a random-effects model. However, substantial heterogeneity was observed among the included studies ($I^2 = 75\%$, $\text{Chi}^2 = 19.50$, $P = 0.002$), suggesting variability in treatment effects across trials [Figure 3].

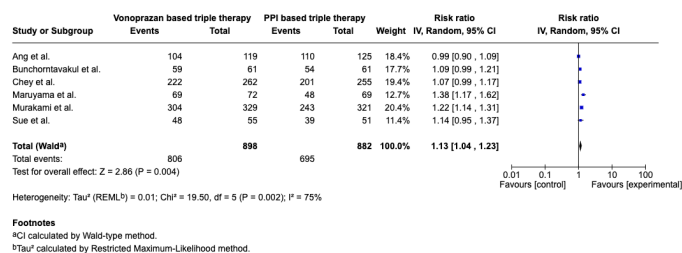


Figure 3: Eradication rates of vonoprazan-based triple therapy versus PPI-based triple therapy

Tegoprazan-based triple therapy versus PPI-based triple therapy:

Two randomized controlled trials involving 598 patients were included in the meta-analysis comparing tegoprazan-based triple therapy (TTT) with PPI-based triple therapy (PTT) for *Helicobacter pylori* eradication.

Table 3: Study characteristics of tegoprazan-based triple therapy versus PPI-based triple therapy

Author	Year	Country	Study design	Total sample size	Tegoprazan triple therapy	PPI triple therapy	Treatment duration
Choi et al. (20)	2022	South Korea	Multicenter randomized controlled trial	350	Tegoprazan 50 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	Lansoprazole 30 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	7 days
Park et al. (21)	2026	South Korea	Multicenter randomized controlled trial	382	Tegoprazan 50 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	Lansoprazole 30 mg BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	14 days

BID: Twice in a day, PPI: Proton pump inhibitor

Study characteristics:

Both the studies were conducted in South Korea. Tegoprazan 50 mg, amoxicillin 1000 mg, and clarithromycin 500 mg were given twice daily as part of the intervention regimen in both studies. The control regimen included lansoprazole 30 mg together with amoxicillin 1000 mg and clarithromycin 500 mg given twice daily. The treatment durations were 7 days and 14 days. For the studies of Choi et al. (20) and Park et al. (21), the treatment periods were seven days and fourteen days respectively [Table 3].

Diagnosis and confirmation of *Helicobacter pylori* eradication:

Both RCTs employed both invasive and non-invasive techniques

to confirm the *H. pylori* diagnosis. At least four weeks after treatment, the eradication was confirmed by a urea breath test/stool antigen test [Table 4].

Compliance and adverse events:

The adherence rates were 85.7%, and 95% in both arms in study of Choi et al. (20) and Park et al. (21) respectively. In both groups, adverse effects were often minor. Diarrhea, headache, nausea, dyspepsia, and abdominal discomfort were commonly reported incidents [Table 4].

Table 4: Outcomes of tegoprazan-based triple therapy versus PPI-based triple therapy

First Author	Results	Compliance	Adverse drug reactions	Diagnosis of <i>H. pylori</i>	Confirmation of Eradication	Timing of Confirmation
Choi et al. (20)	In an intention-to-treat analysis, the <i>H. pylori</i> eradication rates were 62.86% (110/175) and 60.57% (106/175) for the Tegoprazan group and 69.33% (104/150) and 67.33% (101/150) for the Lansoprazole group (non-inferiority test, $P=0.009$ and $P=0.013$). Subgroup studies based on CYP2C19 or MICs did not reveal notable variations in the eradication rate.	85.7% in both groups	Diarrhea, nausea, dyspepsia, headache	Urea breath test, rapid urease test, histology	Urea breath test or stool antigen test	4-6 weeks after therapy
Park et al. (21)	In modified intention to treat analysis eradication rates were 86.0%, and 78.7% for Tegoprazan and Lansoprazole groups, respectively. Among clarithromycin-resistant infections, the eradication rates were higher for Tegoprazan group (47.8%) compared with Lansoprazole group (35.5%).	>95% in both groups	Diarrhea, abdominal discomfort, nausea	Urea breath test, rapid urease test	Urea breath test	6 weeks after therapy

MICs: Minimal inhibitory concentrations

Eradication rates:

A total of 296 patients received TTT, and 302 patients received PTT. On intention-to-treat (ITT) analysis, the eradication rates were 214 and 206 in TTT, and PTT groups respectively. The pooled analysis demonstrated that TTT is non-inferior to PTT (RR:1.07 ;95% CI 0.98–1.18; P = 0.14). No heterogeneity was observed among the included studies ($I^2 = 0\%$, $\text{Chi}^2 = 0.24$, $P = 0.62$) [Figure 4].

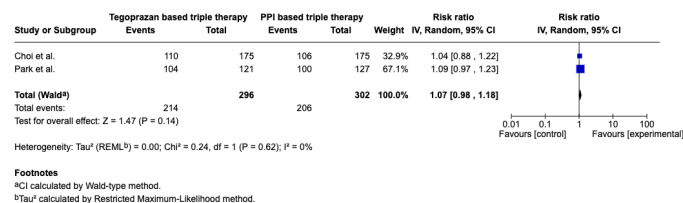


Figure 4: Eradication rates of tegoprazan-based triple therapy versus PPI-based triple therapy

Discussion

We assessed the safety and effectiveness of P-CAB-based triple therapy in comparison to PPI-based triple therapy in the eradication of *H. pylori* in our systematic review and meta-analysis. Eight RCTs ($n=2,378$) that satisfied the inclusion criteria were found in the literature review. The pooled primary outcome of eight RCTs shows that P-CAB-based triple therapy is either superior or comparable to PPI-based triple therapy. In every study, the secondary results were similar for both groups.

The pooled analysis of six trials involving 1780 patients shows that VTT is superior to PTT in *H. pylori* eradication (RR:1.13, 95% CI 1.04–1.23) [Figure 3]. Vonoprazan has this advantage over PPI because it inhibits gastric acid output more quickly, strongly, and persistently (9) a potassium-competitive acid blocker, offers potent and sustained acid inhibition and potentially improves eradication efficacy. Aim This study aimed to evaluate the efficacy and safety of tegoprazan-based triple therapy with two dosing regimens compared with that of lansoprazole-based therapy for first-line *Helicobacter pylori* eradication. Methods This randomized, double-blind, active-controlled, multicenter trial was conducted at 19 referral hospitals in South Korea (February 2023–April 2024). PPI requires acid for activation, and is influenced by CYP2C19 polymorphism (23) U. focusing on: PROTON pump inhibitors; INTESTINAL diseases; PHENOTYPES; METABOLISM; GASTROESOPHAGEAL reflux; HELICOBACTER pylori Abstract: Proton pump inhibitors (e.g. omeprazole/esomeprazole, lansoprazole, pantoprazole, rabeprazole. Whereas, vonoprazan acts by competitively and reversibly inhibiting the potassium-binding site of H^+/K^+ -ATPase pump, and thereby more sustained intragastric pH control (22) at 20 and 10 mg once daily for the treatment and secondary prevention of reflux esophagitis, respectively, at 10 mg once daily for the secondary prevention of low-dose aspirin- or non-steroidal anti-inflammatory drug-induced peptic ulcer, and at 20 mg twice daily in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori*. It inhibits H^+/K^+ -ATPase activities in a reversible and potassium-competitive manner with a potency of inhibition approximately 350 times higher than the proton pump inhibitor, lansoprazole. Vonoprazan is absorbed rapidly and reaches maximum plasma concentration at 1.5–2.0 h

after oral administration. Food has minimal effect on its intestinal absorption. Oral bioavailability in humans remains unknown. The plasma protein binding of vonoprazan is 80 % in healthy subjects. It distributes extensively into tissues with a mean apparent volume of distribution of 1050 L. Being a base with pKa of 9.6 and with acid-resistant properties, vonoprazan is highly concentrated in the acidic canaliculi of the gastric parietal cells and elicited an acid suppression effect for longer than 24 h after the administration of 20 mg. The mean apparent terminal half-life of the drug is approximately 7.7 h in healthy adults. Vonoprazan is metabolized to inactive metabolites mainly by cytochrome P450 (CYP. At higher intragastric pH, the stability, and antibacterial activity of clarithromycin and amoxicillin are maintained, thereby improving the eradication rate.²⁴

The rising clarithromycin resistance and failure of PTT to eradicate *H. pylori* is of particular importance in developing nations like Nepal.^{25,26} The superior eradication rate of VTT is relevant in the era of rising clarithromycin resistance. Potent and sustained acid suppression may overcome the resistance by optimizing antibiotic exposure in gastric mucosa.²⁴ Studies of Murakami et al.¹⁵ and Sue et al.¹⁷ reported improved outcomes with VTT in clarithromycin-resistant strains [Table 2]. Though, this effect is not uniform across all RCTs. Further multi-center, multinational large RCT incorporating antibiotic susceptibility is required to confirm this finding.

Several significant clinical and methodological variations among the included studies may be responsible for the significant heterogeneity seen in the vonoprazan-based triple treatment (VTT) study ($I^2 = 75\%$). First, as the investigations were carried out in several nations, including the United States, Japan, Thailand, and Singapore, where patterns of antibiotic resistance, especially clarithromycin resistance, range greatly, regional variation probably played a major role. Second, the length of therapy varied amongst trials; some used 7-day regimens, while others used 14-day regimens, which could have an impact on eradication results. Different PPIs (i.e.: lansoprazole, omeprazole, esomeprazole, and rabeprazole) used across the control group in RCTs have variable acid suppression capabilities, that might have impacted the pooled estimates. Besides, we found that the dose of clarithromycin used in the studies varied from 200 mg to 500 mg, leading to possible variation in efficacy outcomes. While vonoprazan is less impacted by CYP2C19 genotype, host genetic factors including CYP2C19 polymorphisms are another possible source of heterogeneity because PPI metabolism varies between populations, especially between Asian and Western populations. Additionally, variation in trial design (open-label versus double-blind trial), criteria used for compliance/adherence and method of eradication confirmation may explain for significant heterogeneity. Inconsistently reported baseline characteristics of the participants such as: smoking status, prior antibiotic exposure, bacterial load, and prevalence of antimicrobial resistance across the studies might have limited confounding factor adjustment leading to increased heterogeneity in the pooled analysis.

No difference in pooled eradication rate of TTT compared with PTT was observed [Figure 4]. This observation shows that TTT is non-inferior to PTT, and could be used as alternative to traditional PTT. We observed that the evidence for tegoprazan compared with vonoprazan remains limited. However, published RCTs

postulated the promising efficacy of tegoprazan when used in appropriate dose with adequate treatment duration [Table 4].

We observed excellent adherence (>90%) in both intervention as well as control groups across all the studies. The finding suggests the feasibility and tolerability of P-CAB-based regimens in real world practice. The reported short term adverse events were mild, and comparable in either group without any major safety concern.

This study has multiple methodological strengths that support the reliability of the findings. Only RCTs were included. Separate meta-analysis for VTT vs PTT and TTT vs PTT were conducted with special focused on eradication rate, compliance, and adverse events. Besides, pooled report from multi-center international trials can be generalized in real world population.

While interpreting the pooled results of our systematic review and meta-analysis, several limitations should be acknowledged. Performance bias may have been induced by the open-label designs utilized in the included RCTs. Differences in allocation concealment and selective reporting between trials may also have impacted the primary and secondary outcomes [Figure 2]. We couldn't perform the sub-group analysis of the different trials due to the limited number of eligible studies within each subgroup, which remain one of the limitations of our meta-analysis. The majority of vonoprazan-based studies are conducted in East Asia, and both the studies of tegoprazan-based studies are conducted in South Korea [Table 1 and 3], it is therefore, the results should be generalized with caution to South Asian, African or Latin American populations.

Conclusion

In conclusion, our systematic review and meta-analysis has shown that VTT is superior to PTT and TTT is non-inferior to PTT in terms of eradication rates of *H. pylori*. Both P-CAB-based and PPI-based triple therapies are equally safe and well tolerated by the patients. We recommend a large multinational, multicenter RCTs especially including South Asian regions like Nepal to be conducted to validate these findings, and determine the optimal first-line eradication therapy in diverse population. Furthermore, we recommend the studies to be conducted for long term safety profile P-CAB.

Disclosure

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Conflict of interest

The authors declare that they have no conflict of interest.

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