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Research Article

COMPARATIVE EFFICACY OF VONOPRAZAN AND PROTON PUMP INHIBITORS IN *HELICOBACTER PYLORI* ERADICATION BASED ON CLARITHROMYCIN SUSCEPTIBILITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objectives: Due to the rising burden of *Helicobacter pylori*-resistant strains, specifically to clarithromycin (CAM), there is a decline in eradication rates (ERs) with proton-pump inhibitors (PPI) containing regimens. Vonoprazan (VPZ), a first-in-class potassium-competitive acid blocker, has a rapid onset, and longer, more profound acid suppression than PPIs. This systematic review and meta-analysis aims to evaluate the efficacy of VPZ versus PPI-based triple therapy in eradicating *H. pylori* based on clarithromycin susceptibility.

Methods: A systematic search was performed using relevant MeSH terms in PubMed, Cochrane, Web of Science, and Google Scholar databases for studies comparing the efficacy of VPZ and PPI triple therapies in eradicating *H. pylori*, with results stratified by clarithromycin susceptibility. Studies meeting the inclusion criteria were included, and data were extracted. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Random effects model was applied in all analyses.

Results: Eight potentially eligible studies were included. Among patients with clarithromycin-resistant *H. pylori* strains, VPZ-triple therapy showed significant superiority to PPI-triple therapy in both randomized controlled trials (RCT) (pooled ER-75.0% vs. 49.0%; OR-3.28; 95% CI 1.62–6.66; p=0.001) and non-RCT (NRCT) (ER-82.0% vs. 42.0%; OR-4.98; 95% CI, 2.47–10.03; p<0.001) studies. For eradication of clarithromycin susceptible (CAM-S) strains in RCTs, VPZ therapy showed significant superiority over PPI therapies (ER-90.0% vs. 86.0%; OR-1.42; 95% CI, 1.02–1.98; p=0.038); however, there was no significant difference between the therapies seen in NRCTs (ER-89.0% vs. 86.0%; OR-4.30; 95% CI, 0.72–25.85; p=0.111).

Conclusion: VPZ triple therapy is superior to the conventional PPI triple therapy in eradicating CAM-resistant *H. pylori* strains. For CAM-S *H. pylori* infection, VPZ is comparable to PPI triple therapy.

Keywords: *Helicobacter pylori*, Proton-pump inhibitor, Vonoprazan, Clarithromycin resistance, Meta-analysis.

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INTRODUCTION

Helicobacter pylori, a spiral-shaped Gram-negative rod, is one of the most common pathogens that colonize the gastric mucosa and cause several gastrointestinal diseases and chronic gastritis, peptic ulcer, including gastric adenocarcinoma [1]. The estimated prevalence of *H. pylori* infection is approximately 43.1% worldwide. This prevalence, however, varies greatly between countries and geographic areas [2]. Over the last several years, the incidence of antibiotic-resistant *H. pylori* strains has increased, rendering eradication of *H. pylori* burdensome. In areas with low levels of clarithromycin resistance (<15%), the first standard treatment for *H. pylori* eradication is triple therapy, which consists of two antibiotics (clarithromycin and metronidazole) and a proton pump inhibitor (PPI) (rabeprazole, lansoprazole, omeprazole, or esomeprazole). The prevalence of clarithromycin-resistant *H. pylori* has been rising recently, rising by 29.1% between 2015 and 2019 and 36.5% between 2020 and 2023 [3]. This increasing prevalence of clarithromycin (CAM)-resistant strains significantly contributes to the decline in eradication rate (ER) by the standard triple therapy comprising a PPI with amoxicillin and clarithromycin (PAC). Since then, the WHO has designated clarithromycin-resistant (CAM-R) *H. pylori* as a high-priority pathogen for the development of new treatments [4]. The following are other therapeutic options in regions with high prevalence of clarithromycin resistance: Metronidazole and amoxicillin triple therapy, bismuth-containing quadruple therapy, and non-bismuth concurrent quadruple therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole) [5]. However, increasing resistance leads to refractory *H. pylori* infections, the eradication of which is unsuccessful even after one or more courses of standard regimens. *H. pylori* replication is facilitated by maintaining a stomach pH >5, whereas acid suppression increases bacterial susceptibility and antibiotic stability. Therefore, adequate acid suppression is necessary for successful *H. pylori* eradication [6].

Vonoprazan (VPZ) is an orally active first-in-class potassium-competitive acid blocker (P-CAB). VPZ acts at the last step of gastric acid secretion pathway in gastric parietal cells and causes competitive and reversible inhibition of H+, K+-ATPase, resulting in rapid, stronger, and prolonged acid suppression than PPIs. VPZ is about 350 times more effective than PPIs at inhibiting H+-K+ ATPase. VPZ demonstrates potent inhibition of proton pump even under neutral pH conditions, with Ki values of 3 nM (pH 6.5) and 10 nM (pH 7) [7]. This increase in the intragastric pH by VPZ provides an ideal environment (pH 6.0–8.0) for the growth of *H. pylori*, thereby enhancing its susceptibility to antibiotics that target proteins, such as amoxicillin [8]. In addition, unlike the debatable effect of CYP2C19 polymorphisms in PPIs, the metabolism of VPZ does not involve CYP2C19 [9,10]. VPZ is FDA approved for the treatment of GERD, erosive gastritis, and peptic ulcer disease [11]. Multiple analytical methods have been developed to quantify VPZ-based triple therapy formulations, reflecting their growing pharmaceutical and potential clinical relevance [12,13]. Furthermore, several studies including a meta-analysis have demonstrated that VPZ triple therapy is superior to PPI triple therapy in the eradication of *H. pylori* infection [14,15].

However, only few randomized and non-randomized studies have performed subgroup analysis based on CAM resistance and this aspect is not comprehensively addressed in existing meta-analyses. Thus, this meta-analysis was conducted to evaluate the efficacy of VPZ-based triple therapy (VAC) against PPI-based triple therapy (PAC) in eradicating *H. pylori* infection based on CAM susceptibility.

METHODS

Literature search

This systematic review and meta-analysis adhered to the reporting standards outlined in the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. A comprehensive search of the literature was conducted using databases such as PubMed, Web of Science, Cochrane Library, and Google Scholar, using the keywords and MeSH terms: "VPZ," "vonoprazan," "TAK438," "TAK-438," "takecab," "P-CAB," "potassium-competitive acid blocker") AND ("*Helicobacter pylori* eradication," "*H. pylori* eradication", "*Campylobacter pylori*", "*H. pylori*") until July 2023.

Inclusion criteria and exclusion criteria

All studies, both randomized and non-randomized were included for the analysis, if: VPZ is compared with PPI based triple therapy for a period of 7–14 days, as first-line eradication regimen for *H. pylori*; confirmatory diagnosis of *H. pylori* infection was done before treatment followed by confirmation of eradication after treatment made using one of the methods such as 13C-urea breath test (UBT), rapid urease test, culture, and *H. pylori* stool antigen test; CAM susceptibility test was done for both groups and stratified results of ERs were given for the same. Studies were excluded if they were of low quality, poorly characterized population, duplicate publications, descriptive studies, or review articles. Non-English articles were also excluded due to limitations in translation resources and to maintain consistency in data extraction.

Data extraction

Two authors independently screened the titles and abstracts and once a study meets the inclusion criteria, the following data: first author name, published year, study design, study site, treatment regimens, duration of treatment, and ERs stratified by clarithromycin resistance from the subgroup analysis of each study.

Risk of bias (RoB) assessment

The quality of the included randomized controlled trials (RCTs) was assessed using RoB-2 tool and the Newcastle Ottawa scale was used to assess the quality of Non-RCT (NRCTs) [17,18].

Statistical analysis

STATA, version 14.0 (Stata Corp LLC, Texas) software was used to perform all the statistical analyses. Each trial contributed an effect size expressed as a proportion (ER) and pooled odds ratios (ORs) were calculated and represented as standard plots with the confidence intervals (CIs) of 95%. Publication bias was examined using Funnel plot analysis Heterogeneity was tested using the Cochran Q and I-squared statistics with a threshold of I^2<50% or p<0.10. Random effects model was applied in all analyses. Other than heterogeneity, for all other analyses, p<0.05 was considered statistically significant.

RESULTS

Screening flow and search results

During the screening process through database searches, a total of 248 records were identified after eliminating 51 duplicates. All 248 records were then screened, out of which 219 records were excluded after reviewing the titles and abstracts by the authors due to irrelevant topic or treatment regimen, non-clinical/animal studies, non-English language, and review articles. From the 29 remaining articles, 16 articles could not be retrieved due to unavailable full texts or inaccessible sources. The 13 articles that remained were further

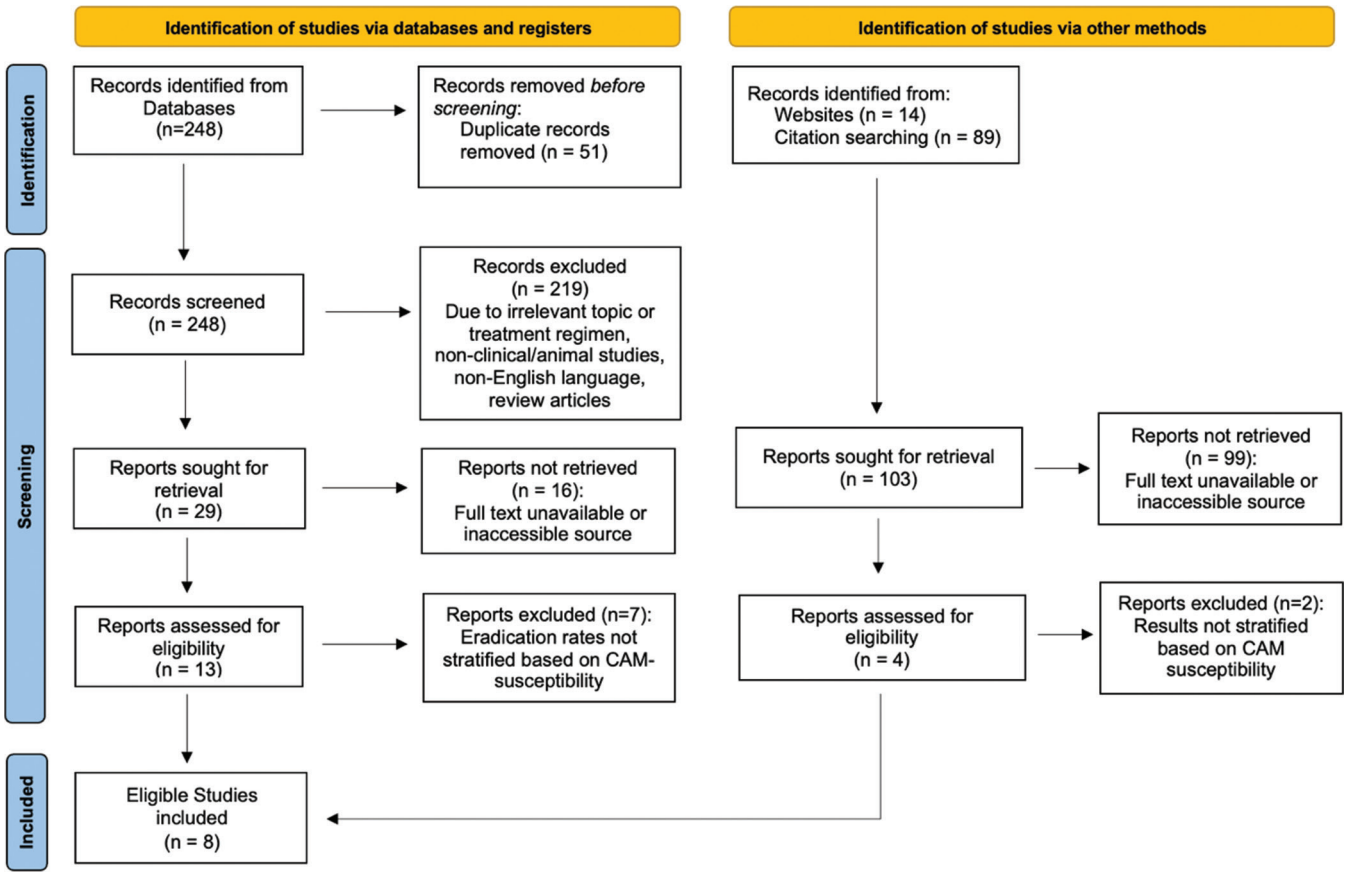

Fig. 1: Screening flow for study identification, inclusion, and exclusion according to PRISMA

assessed for eligibility. Of these, 7 were excluded for not reporting eradication outcomes stratified by CAM susceptibility, resulting in 6 eligible studies. In addition, 103 records were identified through other sources such as websites and citation searching; however, 99 articles could not be retrieved due to unavailability or inaccessible source. Of the remaining 4 articles assessed from this group, 2 were excluded as their results were not stratified based on CAM susceptibility, ultimately contributing 2 more studies. Thus, a total of 8 studies (5RCTs and 3NRCTs) were included for the final analysis [19-26]. The flowchart illustrating the retrieved and included studies for this systematic review and meta-analysis is given in Fig. 1.

Study characteristics

Characteristics of the included studies for this meta-analysis are tabulated in Table 1. A total of 1838 patients from five randomized and three non-randomized studies were included for analysis. The included studies were published between 2016 and 2022 and were conducted in Japan, Singapore, USA, and Europe, with majority of the studies originating from Japan. This may be attributed to VPZ receiving its first approval and wide usage in Japan before its introduction in other countries. The non-randomized studies comprised two retrospective cohorts and one prospective cohort study. In all the studies, the conventional PPI triple regimen comprising 750 mg or 1 g of amoxicillin, 200 mg or 400 mg of clarithromycin, and a PPI (30 mg lansoprazole, 10 mg or 20 mg rabeprazole, 20 mg esomeprazole) twice daily for a treatment period of 7–14 days was used. In the VPZ-based regimen, PPI was replaced with VPZ 20 mg twice daily. ^{13}C UBT was used to confirm the diagnosis and successful eradication of *H. pylori* in the studies. CAM-susceptibility-based ERs have been reported in all the studies. However, ERs with PPI regimen were reported only for clarithromycin-susceptible strains in two studies, as resistant cases were predominantly treated with VPZ-based regimens. These studies were included to ensure a comprehensive analysis of available subgroup data.

RoB

The RoB assessment based on the ROB-2 tool for five RCTs and the Newcastle Ottawa scale for three NRCTs are given in Fig. 2 and Table 2, respectively. All the RCTs included in the study were regarded to be of good quality with low RoB, and all the NRCTs received high scores of 7 to 8 in the Newcastle Ottawa scale, indicating minimal RoB.

Funnel plot analysis

The funnel was largely symmetrical for large well-powered studies but with a faint suggestion that small, positive studies were over-represented (Fig. 3). Egger's test was performed which reinforced the visual impression, indicating statistically significant small-study effects. Further, trim-and-fill correction suggests that the presence of publication bias is likely but its quantitative influence on the overall effect estimate appears modest.

Subgroup analysis

Relevant subgroups based on clarithromycin susceptibility were included from each study to compare the ERs of PPI and VPZ-containing triple therapies as first-line eradication regimens for *H. pylori*. In the included six RCTs, the pooled ERs of clarithromycin susceptible (CAM-S) strains, VPZ-based therapy showed a modest but statistically significant superiority over PPI therapy 90.0% versus 86.0% (OR-1.42; 95% CI, 1.02–1.98; p=0.038). For CAM-R strains, the ERs were significantly higher with VPZ-based triple therapy compared to PPI triple therapy 75.0% versus 49.0% (OR-3.28; 95% CI 1.62–6.66; p=0.001). Forest plot comparing the two therapies in the eradication of CAM-S and CAM-R strains in RCT studies is given in Figs. 4 and 5, respectively.

Table 1: Baseline characteristics of included studies

Study and year	Study design	Country	VPZ-based regimen	PPI-based regimen	VPZ eradication rates		PPI eradication rates	
					CAM-S	CAM-R	CAM-S	CAM-R
Chey *et al*. (2022)	RCT	USA Europe	VPZ 20 mg bid AMX 1000 mg bid CAM 500 mg bid-14 days	LPZ 30 mg bid AMX 1000 mg bid CAM 500 mg bid-14 days	84.7%	65.8%	78.8%	31.9%
Ang *et al*. (2022)	RCT	Singapore	VPZ 20 mg bid AMX 1000 mg bid CAM 500 mg bid-14 days	OPZ/ESO/RPZ 20 mg bid AMX 1000 mg bid CAM 500 mg bid-14 days	90%	71.4%	89.5%	76.5%
Tamaki *et al*. (2019)	RCT	Japan	VPZ 20 mg bid AMX 750 mg bid CAM 200 mg bid-7 days	ESO 20 mg AMX 750 mg bid CAM 200 mg bid-7 days	87.5%	74.6%	84.6%	56.1%
Sue *et al*. (2017)	RCT	Japan	VPZ 20 mg bid AMX 750 mg bid CAM 200 mg or 400 mg bid-7 days	LPZ 30 mg/RPZ 10 mg/ESO 20 mg bid AMX 750 mg bid CAM 200 mg or 400 mg bid-7 days	87.3%	82.9%	76.5%	
Murakami *et al*. (2016)	RCT	Japan	VPZ 20 mg bid AMX 750 mg bid CAM 200 mg/400 mg bid-7 days	LPZ 30 mg bid AMX 750 mg bid CAM 200 mg/400 mg bid-7 days	97.6%	82%	97.3%	40%
Sue *et al*. (2017)	PCS	Japan	VPZ 20 mg bid AMX 750 mg bid CAM 200 mg or 400 mg bid-7 days	LPZ 30 mg/RPZ 10 mg/ESO 20 mg bid AMX 750 mg bid CAM 200 mg or 400 mg bid-7 days	88.9%	73.2%		
Matsumoto *et al*. (2016)	RCS	Japan	VPZ 20 mg bid AMX 750 mg bid CAM 200 mg or 400 mg bid-7 days	LPZ 30 mg/RPZ 10 mg/ESO 20 mg bid AMX 750 mg bid CAM 200 mg or 400 mg bid-7 days	100%	76.1%	87.8%	40.2%
Noda *et al*. (2016)	RCS	Japan	VPZ 20 mg bid AMX 750 mg bid CAM 200 mg or 400 mg bid-7 days	LPZ 30 mg/RPZ 10 mg/ESO 20 mg bid AMX 750 mg bid CAM 200 mg or 400 mg bid-7 days	100%	87.5%	88%	53.8%

AMX: Amoxicillin, CAM: Clarithromycin, CAM-S: Clarithromycin-susceptible strains, CAM-R: Clarithromycin-resistant strains, ESO: Esomeprazole, LPZ: Lansoprazole, OPZ: Omeprazole, PCS: Prospective cohort study, RCS: Retrospective cohort study, RCT: Randomized controlled trial, RPZ: Rabeprazole

Table 2: Newcastle Ottawa scale

Study	Representative of the exposed cohort	Selection of external control	Ascertainment of exposure	Outcome of interest not present at the start of the study	Main factor	Additional factor	Assessment of outcomes	Sufficient follow-up time	Adequacy of follow-up	Total (9/9)
Sue *et al*. 2017	1	1	0	1	1	1	1	1	1	8
Matsumoto *et al*. 2016	1	1	0	1	1	1	1	1	0	7
Noda *et al*. 2016	1	1	0	1	1	0	1	1	1	7

Star ratings are represented as numbers

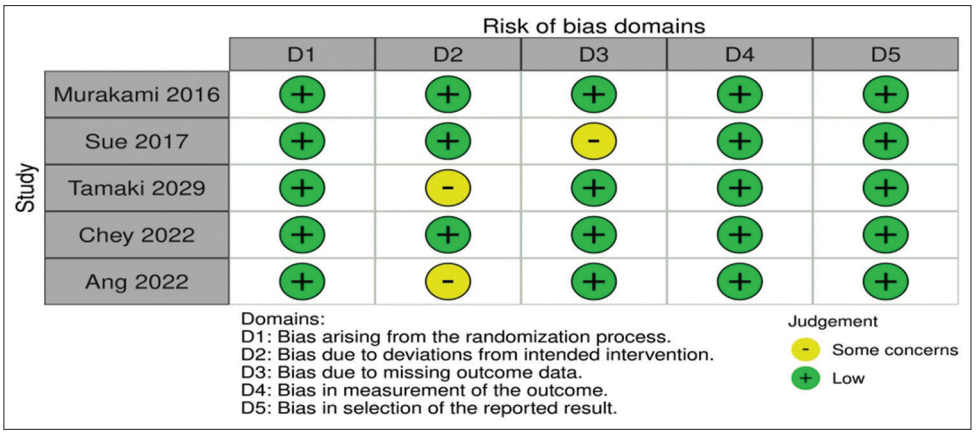

Fig. 2: Cochrane ROB-2 scale

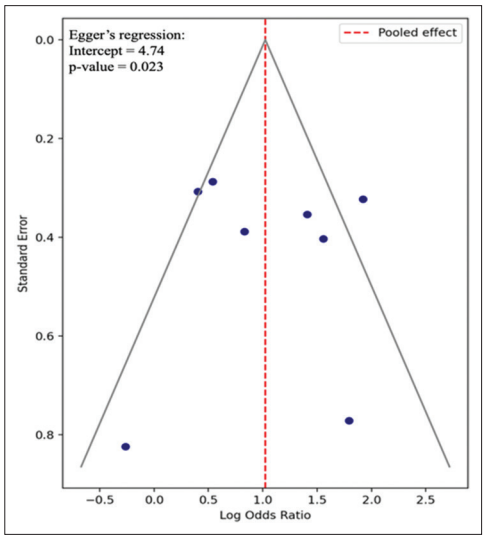

Fig. 3: Funnel plot for publication bias

Similarly, in NRCT studies, VPZ therapy demonstrated superior efficacy for CAM-R strains with a pooled ER of 82.0% versus 42.0% in PPI therapy (OR-4.98; 95% CI, 2.47–10.03; p<0.001). However, for CAM-S strains, although the ER was higher with VPZ (89.0% vs. 86.0%), this difference did not reach statistical significance (OR-4.30; 95% CI, 0.72–25.85; p=0.111). The forest plot comparing the two therapies in the eradication of CAM-S and CAM-R strains in NRCT studies is given in Figs. 6 and 7, respectively.

DISCUSSION

This updated and comprehensive systematic review and meta-analysis includes 5 RCT and 3 NRCT studies that systematically compare the efficacy of VPZ and PPI-based triple therapies in eradicating *H. pylori* by stratifying results based on clarithromycin susceptibility. Several studies have evaluated the efficacy of VPZ-based triple therapies against PPI therapies as the first-line *H. pylori* eradication regimen. Globally, resistance to antibiotics, especially clarithromycin, has increased in recent years [3]. VPZ's profound and sustained reduction of gastric acid is the fundamental contributing factor to its greater efficacy against *H. pylori*, especially against strains that are resistant to CAM [27,28]. The underlying mechanism of clarithromycin in *H. pylori* is the mutations in 23S rRNA variable region genes, notably A2142G and A2143G. This mutation reduces the affinity of the CAM binding site by causing ribosomal allostery. *H. pylori* eradication therapies are seriously compromised by this increasing resistance [29]. Dual or triple regimens comprising clarithromycin are 60–95% successful against susceptible infections but frequently have <40% efficacy against resistant strains [30]. Since this decrease in efficacy adds to the persistence of *H. pylori* infections worldwide, the WHO has made research on clarithromycin-resistant *H. pylori* a top priority. Empirical elimination of *H. pylori* is classified into first-line, second-line, and rescue therapies, with the goal to prevent excess use of antibiotics. Owing to the increasing burden of antibiotic resistance, these regimens should be tailored based on the local antibiotic resistance profile [31,32]. However, not many studies have evaluated and compared their ERs based on antibiotic susceptibility. A study by Kang *et al*., demonstrated that ERs with susceptibility-guided therapy were significantly higher (85.1% vs. 56.6%, p<0.01) than those with empirical therapy. Furthermore, the authors observed that these reduced ERs were a result of the high rate of clarithromycin resistance (41.6%) in their empirical therapy group, which was caused by growing regional resistance [33].

The results of this meta-analysis reveal that, for the eradication of CAM-R *H. pylori* infection, VPZ-containing triple therapy showed significant superiority over PPI-based triple therapy in all the studies. Similarly, in the eradication of CAM-S *H. pylori* infection, VPZ was significantly superior to PPI triple therapy in RCT studies but did not achieve a significant difference in NRCT studies. Aligning with previous reports, the results suggest that CAM resistance could serve as a potential confounding variable that may significantly affect the therapeutic efficacy of *H. pylori* eradication regimens [34]. These

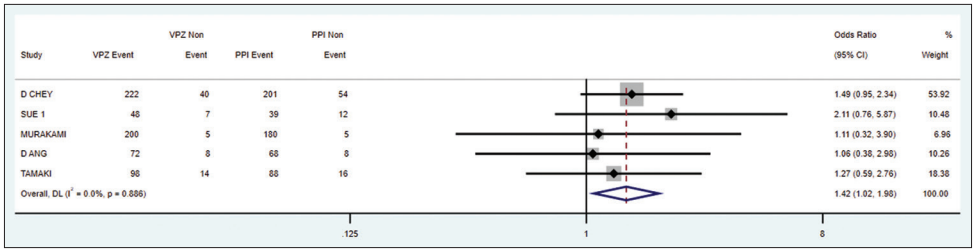

Fig. 4: Forest plot for meta-analysis of randomized controlled trial data comparing VAC and PAC eradication therapy for *Helicobacter pylori* in clarithromycin-susceptible patients using a random effects model

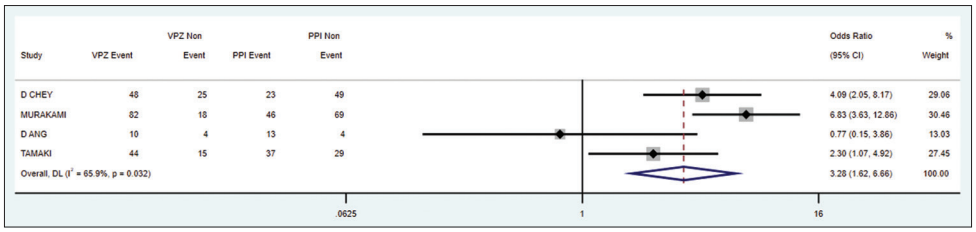

Fig. 5: Forest plot for meta-analysis of randomized controlled trial data comparing VAC and PAC eradication therapy for *Helicobacter pylori* in clarithromycin-resistant patients using random effects model.

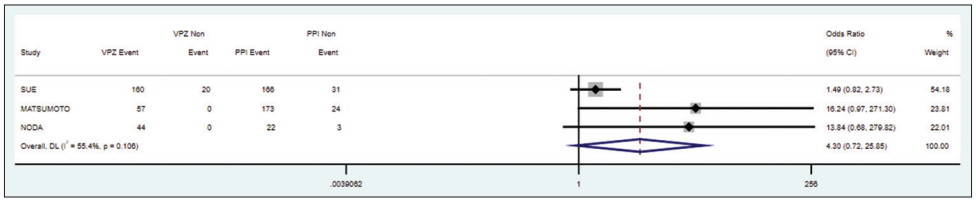

Fig. 6: Forest plot for meta-analysis of non-randomized controlled trial data comparing VAC and PAC eradication therapy for *Helicobacter pylori* in clarithromycin-susceptible patients using random effects model

Fig. 7: Forest plot for meta-analysis of non-randomized controlled trial data comparing VAC and PAC eradication therapy for *Helicobacter pylori* in clarithromycin-resistant patients using random effects model

results are consistent with a meta-analysis by Dong *et al*. in the subgroup analysis and Li *et al*., 2018, who found that VPZ-triple therapy demonstrated higher OR for *H. pylori* eradication in patients with clarithromycin-resistant strains than with clarithromycin-susceptible strains (OR: 5.92 vs. 2.02 and OR: 6.38 vs. 1.63, respectively) [35,36]. Our findings also imply that clarithromycin susceptibility may have a significant impact on the effectiveness of VPZ-based triple therapies, as evidenced by data from recently published studies, both randomized and non-randomized comparing triple therapies containing PPIs and VPZ for *H. pylori* eradication.

Notable drawbacks of earlier meta-analyses, such as not including recent RCTs and insufficient subgroup analyses according to clarithromycin susceptibility, which is a significant factor affecting eradication results. While subgroup analyses were conducted by Jung *et al*. and Dong *et al*., most of the included studies were retrospective. Moreover, all these studies mostly focused on Japanese populations, limiting generalizability [35-37].

This meta-analysis updates the current evidence by including recently published randomized and non-randomized studies, both prospective and retrospective, with subgroup analyses based on clarithromycin susceptibility and studies from countries beyond Japan, to improve the generalizability and relevance of the findings. However, there are some limitations in this study. Consistent with prior studies, rather than the full study population, only subgroup data were analyzed, preventing the assessment of safety outcomes. Relevant RCTs are not abundant due to the lack of antibiotic sensitivity testing. Among the included studies, only two were conducted outside Japan, so the results may not be generalizable to other populations; heterogeneity was observed in two forest plot analyses, which could be due to difference in the sample sizes, regional antibiotic resistance patterns and the treatment duration was only 7 days in most of the included studies, which is shorter than the recommended 14 days treatment in most of the consensus reports. These limitations underscore the need for more randomized studies with robust data based on clarithromycin susceptibility and larger populations for generalizability.

CONCLUSION

VPZ-based triple therapy (VAC) demonstrates superior efficacy over conventional PPI-triple therapy (PAC) in the eradication of CAM-R *H. pylori* strains. In the eradication of CAM-S *H. pylori* infection, VPZ triple therapy is comparable to PPI triple therapy. Although the

conclusions are drawn from a limited number of studies due to a lack of antibiotic susceptibility testing in many studies, our findings support the consideration of VPZ triple therapy as an effective eradication regimen over the conventional PPI-based triple therapy, especially in regions with high CAM-resistant *H. pylori* infection. More RCTs in different geographical areas with optimal treatment duration and antibiotic susceptibility testing are warranted.

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CONTRIBUTION OF AUTHORS

Dr. Sheethal and Dr. Karthik designed the study and conducted the systematic review. Dr. Sheethal and Dr. Sowmya were involved in statistical analysis and manuscript writing. Dr. Kavitha, Dr. Karthik and Dr. Sowmya contributed to the study design, final screening of articles, and reviewed the manuscript. All authors revised and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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Nil.

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