

Evidence-Based Case Report: Comparison of Potassium Competitive Acid Blocker and Proton Pump Inhibitor as First Line Therapy in Adult Patients with *H. pylori* Infection

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ABSTRACT

Background: Increased eradication of *Helicobacter pylori* decreases the incidence of gastric cancer. Vonoprazan is a potassium-competitive acid blocker (PCAB) with a stronger acid production suppression effect than proton pump inhibitors (PPI). Vonoprazan has been recognized as a therapy for gastric acid reflux disease since 2015 in Japan, but the comparison of the effectiveness of PCAB first-line therapy with PPI for adult patients with *H. pylori* infection is still controversial.

Method: A literature search was carried out on three databases: Pubmed, Cochrane, and Scopus on March 30th 2023, using keywords vonoprazan, potassium competitive acid blocker (PCAB), proton pump inhibitor, and *H. pylori*. There were 7 studies on Pubmed, 26 studies on Cochrane, and 144 studies on Scopus. Critical screening was conducted using the Oxford Centre for Evidence-Based Medicine for systematic reviews and randomized controlled trials.

Results: Based on screening of inclusion and exclusion criteria, one study met the criteria. The intention to treat analysis (ITT) showed eradication of *H. pylori* in the combination of three therapies with PCAB vs PPI of 91.81% vs 75.5% (1,18 [1.08–1.28], $p < 0.0001$), no heterogeneity found ($I^2 = 43\%$). Analysis per protocol showed PCAB versus PPI eradications of 92.99% vs 78.57% (1,13 [1.02–1.26], $p = 0.02$), heterogeneity obtained ($I^2 = 75\%$).

Conclusion: Generally, PCAB has better eradication than PPI as first-line therapy for adult patients with *H. pylori* infection

Keywords: potassium competitive acid blocker, proton pump inhibitors, *helicobacter pylori*

INTRODUCTION

H. pylori infection is a major risk factor that plays a role in the pathogenesis of gastric cancer. According to the US Centers for Disease Control and Prevention, two-thirds of the world's population has been infected with *Helicobacter pylori*, especially in developing countries.¹ The number of new cases of stomach cancer in 2018 is estimated to reach 1.033.700 with the death rate reaching 782.700.^{1,2} Prevalence of oral *H. pylori* did not differ significantly by generation, ranging from 21.4% to 48.3%. Increased eradication of *H. pylori* can affect a decrease in the incidence of gastric cancer.^{2,3} Various gastrointestinal diseases such as chronic asymptomatic gastritis, atrophy of the stomach, and peptic ulcers can also be caused by *H. Pylori* infection.

The combination of three therapies with a proton pump inhibitor (PPI) and four therapy combinations with bismuth is the most widely used first-line therapy to eradicate *H. pylori*.^{2,3} The standard combination of three therapies for 7 days is applied in the healthcare system in Japan, whereas the four-combination therapy for 14 days is widespread in China.^{4,5} Since 2015, vonoprazan has been used in clinical practice in Japan, with the estimated prevalence of *H. pylori* infection around 30%.¹ The most commonly used *H. pylori* eradication regimes in Japan are a combination of three therapies vonoprazan (20 mg), amoxicillin (750 mg), and clarithromycin (200 mg or 400 mg) twice a day, respectively, for 7 days.^{14,18} The *H. Pylori* management guidelines in Japan in the 2016 revised edition state that the standard therapy for

eradicating *H. pylori* in Japan is a combined three-day therapy of 7 days with PPI or PCAB, amoxicillin, and clarithromycin or metronidazole.⁵ Vonoprazan has also been recognized in China as a cure for reflux esophagitis since 2019.¹ However, a comparison of the effectiveness of first-line therapy with PCAB and PPI for adult patients with *H. pylori* infection needs to be further investigated.

This review article aim to compare the effectiveness of potassium competitive acid blockers (PCAB) compared to proton pump inhibitors (PPI) for first-line therapy of adult patients with *H. pylori* infection

METHODS

Using PRISMA method, we searched literature on three databases: Pubmed, Cochrane, and Scopus. The keywords used are potassium competitive acid blocker (PCAB), vonoprazan, proton pump inhibitor, and *H. pylori* from 2013 until 2023. The literature search was carried out on March 30, 2023. From the literature search, seven studies on Pubmed, 26 studies on Cochrane, and 144 studies on Scopus were obtained. The articles found were screened on the basis of inclusion criteria and exclusion criteria.

Inclusion criteria:

1. A meta-analysis or systematic review study of randomized controlled trials (RCT), a primary study of a randomized controlled trial.
2. A study comparing vonoprazane, amoxicillin,

Table 1. literature review

Database	Keywords	Hits	Selected
Pubmed	((potassium competitive acid blocker) OR (vonoprazan)) AND (proton pump inhibitor) AND (helicobacter pylori) AND (amoxicillin) AND (clarithromycin) Filters: Meta-Analysis, Randomized Controlled Trial, Systematic Review, Full Text	7	1
Cochrane	((potassium competitive acid blocker) OR (vonoprazan)) AND (proton pump inhibitor) AND (helicobacter pylori) AND (amoxicillin) AND (clarithromycin)	26	1
Scopus	((potassium competitive acid blocker) OR (vonoprazan)) AND (proton pump inhibitor) AND (helicobacter pylori) AND (amoxicillin) AND (clarithromycin) Filters: Article, Review, English	144	1

and clarithromycin with a proton pump inhibitor, amoxicillin, and clarithromycin in adult patients with *H. pylori* infection in patients who were new to therapy.

3. Study conducted in English.

Exclusion criterias:

1. Full text article not available.

2. Age of the subject < 18 years Critical examination is carried out using the evaluation sheets of the Oxford Centre for Evidence-Based Medicine for systematic reviews and randomized controlled trials.

RESULT

Figure 1 describes the literature search in a systematic review and meta-analysis. The characteristics of the study are shown in table 1.

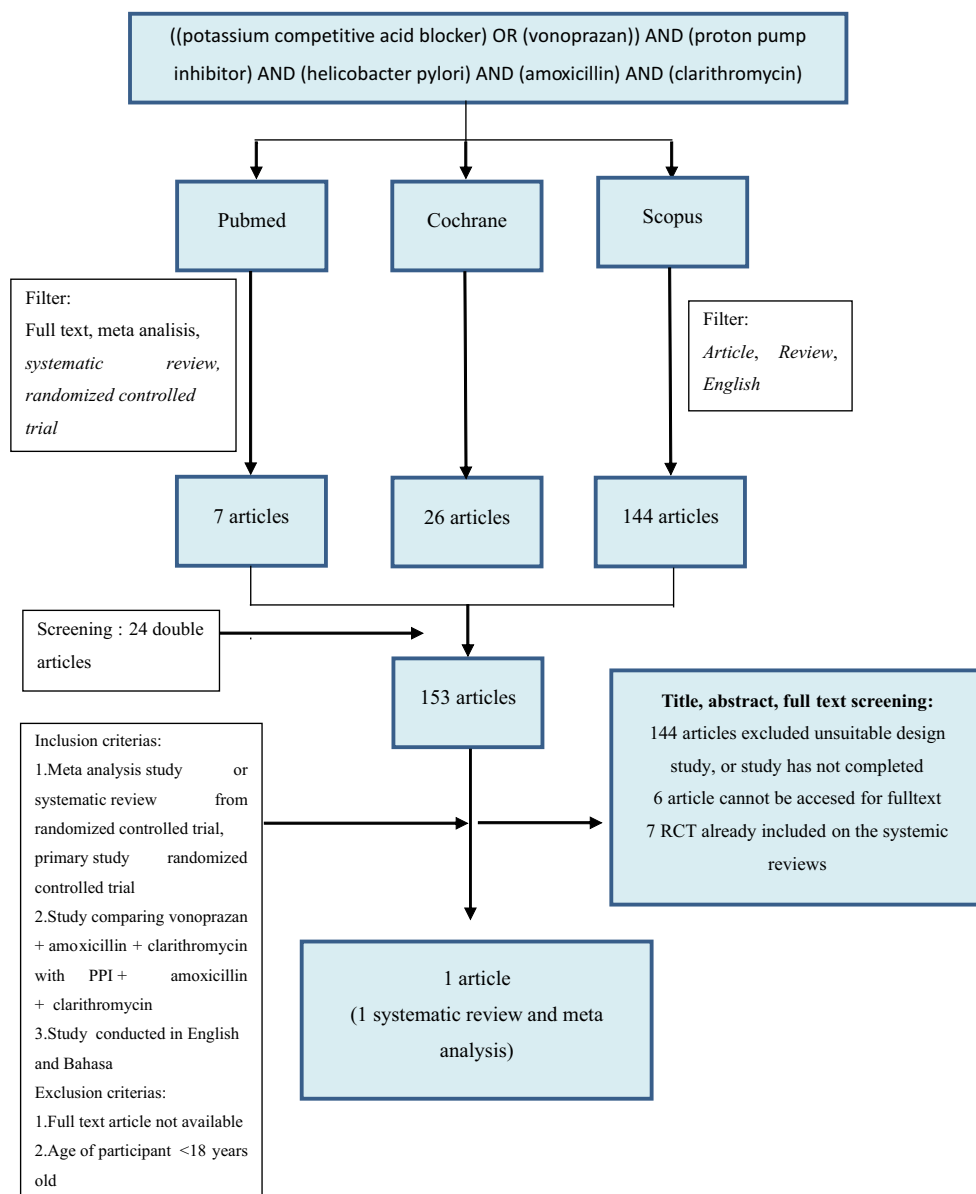


Figure 1. Algorithm of literature search

Table 1. Characteristic of the study

No	Author	Year Published and Country	Study Design	Population	Summary
1	Mengran Zhang et al ²	2022 Country: Japan (3 RCT), Korea (1 RCT), and Thailand (1 RCT)	Systematic review and meta analysis	5 RCT studies, 1059 participant (537 participant on PCAB group and 522 participant in PPI group)	A total of 4 RCT studies using vonoprazan PCAB (517 subjects) and 1 RCT study using YH4808 PCAB (20 subjects). The meta-analysis of five RCT studies covering first-line therapy in adult patients with <i>H. pylori</i> infection. The eradication rate of <i>H. pylori</i> was compared between a combination of three therapies using PCAB and a combined three therapy using PPI. The dosage of vonoprazan used is 2x20 mg once daily for 7 days. The dose of YH4808 used was 2x200 mg once daily for 7 days. The PPI used included omeprazole 2x20 mg for 14 days, esomeprazole 2x20 mg for 7 days, lansoprazole 3x30 mg for 7 days, rabeprazole 2x20mg for 7 days, or rabeprazole 2x10 mg for 7 days. <i>H. pylori</i> eradication after therapy are performed at least 4 weeks after the therapy is completed using the urea breath test. Significant differences were found in <i>H. pylori</i> eradication rates between the two therapeutic groups. Using intention to treat analysis (ITT), <i>H. pylori</i> eradication in PCAB, amoxicillin, and clarithromycin group was 91,81%. Eradication in PPI, amoxicillin, and clarithromycin group was 76.45%. RR [95% IK] = 1,18 [1.10–1.28], $p < 0,0001$. No heterogeneity found ($I^2 = 39\%$). Analysis per protocol (PP) showed that the eradication rate of <i>H. pylori</i> in the PCAB group was 92.99% and in the PPI group 78.57%. RR [95% IK] = 1.13 [1,02–1,26], $p = 0.02$. Heterogeneity ($I^2 = 75\%$)

DISCUSSION

In recent years, the prevalence of *H. pylori* resistance to clarithromycin antibiotics has increased.⁴ This has contributed to a decrease in the success rate of eradicating *H. Pylori*.⁵ Previous studies have a reduction in the eradication rate with the use of a combination of three PPI-based therapies to less than 80% in Europe and the United States, mainly because of clarithromycin resistance.^{3,6,7} The effectiveness of antibiotics in eradicating *H. pylori* depends on the intragastric pH. Previous studies suggested that amoxicillin and clarithromycin are more stable at a more basal gastric pH.⁸ The acid retention effect of PPI is influenced by the dietary pattern and polymorphism of the CYP2C19 gene. In addition, PPI has a long onset and a short half-life.⁹ Vonoprazan is a potassium competitive acid blocker (PCAB) that has a stronger and longer-lasting acid production suppression effect compared to PPI.^{10,11} The mechanisms of action of vonoprazan are not affected by the diets and the polymorphism of the gen.^{12,13}

Antibiotic resistance is still a main problem in the therapy of adult patients with *H. pylori* infection. In a 2016 study by Miftah et al conducted on 11 islands in Indonesia with a total of 849 patients and 77 strain cultures, 9.1% were found to have clarithromycin resistance. A low prevalence of resistance was found in amoxicillin (5.2%) and tetracycline (2.6%). By contrast, resistance has been found to be quite high in metronidazole (46.7%), and levofloxacin (31.2%).¹⁹ Another antibiotic resistance study conducted by Kumala and Rani in 2006 in Jakarta with 126 patients and 72 strain cultures, the highest resistance (100.0%), followed by clarithromycin (27.8%), amoxicillin (19.4%), and levofloxacin (1.4%).²⁰

Miftah et al found that the highest resistance to amoxicillin was found in Papua (14.3%). No resistance was found to the strain taken from Bali, Java, and Kalimantan. The highest resistance to levofloxacin and clarithromycin was found in strains taken from the island of Java, at 50% and 21.4%, respectively. Metronidazole resistance was highest in Sumatra (88.9%) and lowest in Kalimantan (20.0%). Some ethnic groups have a fairly high prevalence of *H. pylori*; they are most commonly found in Papua (42.9%), Batak (40.0%), and Bugis (36.7%).¹⁹

Antibiotic resistance decreases the eradication rate of *H. pylori*. Based on a systematic review study by Zou et al, the eradication rate of *H. pylori* in the

clarithromycin-resistant group was lower than in the Clarithromycine-sensitive group (RR: 0.682; 95% CI: 0.636–0.731). The metronidazole-resistant group also had a lower eradication rate for *H. Pylori* compared to the sensitive group of Metronidazol (0.843; 95% CI: 0.810–0.877).

Stronger acid suppression is linked to the success rate of eradication of *H. pylori* with a combination of three therapies.¹⁶ Based on a meta-analysis by Lyu et al, a three-therapy combination with vonoprazan is better compared to a triple therapy association with PPI to eradicate *H. Pylori* on the first line.¹⁷ The *H.pylori* eradication rate in the vonoprazan group reached 91.4% whereas in the PPI group, the eradication rate was 74.8%. In addition, the side effects of a combination of three therapies with vonoprazan were lower compared to PPI.¹⁷

Based on our literature search, one meta analysis met the inclusion and exclusion criteria. From the systematic review and meta analysis we used, obtained 5 RCT studies with 1059 research subjects. Bias assessment uses the Cochrane Risk of Bias Assessment Tool, which includes assessment of random allocation, concealment, participant blinding, external assessment blinds, measured external data bias attrition, selective reporting, and other potential bias. A critical review of the meta-analysis was also carried out by two independent reviewers so that the critical evaluation results were more objective. In the analysis of the intention to treat, an absolute difference in the number of eradication of *H. pylori* was found of 15.37% while in the analysis per protocol, an absolutely difference in eradication of 14.42%.

Aside from the eradication number, Vonoprazan had been proven to be a better choice for healthcare expenses. A study in 2023 showed that in the 12 months following the start of treatment, vonoprazan-based therapy had lower overall healthcare expenses than PPI-based therapy. *H. pylori* eradication rates is better with vonoprazan-based regimens based on prescription data for successive treatments, which is consistent with the findings of comparative clinical studies from Japan and other Asian countries.³

In terms of applicability, the patient's characteristics in the study do not differ far from those of the patient in the clinical scenario of adult Asian ethnic patients with *H. pylori* infection. PCAB vonoprazan is already available in Indonesia, but it is not widely used in

health facilities, especially in primary and secondary services. In terms of effectiveness, PCAB has been shown to have significantly higher eradication rates than PPI.

CONCLUSION

Based on the critical analysis of the meta-analysis, the results obtained in general eradication of PCAB had better results than PPI for first-line therapy of adult patients with *H. pylori* infection. This is statistically proven by significant differences in eradication numbers and 95% confidence intervals between groups. Based on the forest plot graph, the intention to treat analysis shows $p < 0.0001$ with a 39% heterogeneity, while the analysis per protocol shows $p = 0.003$ with a 75% heterogeneity. From the critical analysis, it can be concluded that the eradication of *H. pylori* with a combination of three therapies using PCAB has better effectiveness than PPI as the first line. Further study with bigger subjects, especially in Indonesia, are encouraged for better understanding.

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