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Vonoprazan: A systematic review of an alternative to proton pump inhibitors

Abstract

Vonoprazan is a novel potassium-competitive acid blocker (P-CAB) that works through a reversible potassium-specific competitive mechanism to inhibit active proton pumps directly. In contrast to standard proton pump inhibitors, vonoprazan does not require acid activation or any time constraints for its administration. As a result of its rapid onset and prolonged action, vonoprazan is a suitable option for PPI. In this study, we compare the efficacy of vonoprazan and PPIs in treating Gastroesophageal Reflux Disease (GERD), *H. pylori,* and post-endoscopic submucosal dissection (ESD) bleeding and ulcers. A PRISMA-guided systematic review was conducted on Pubmed. It included English or Portuguese articles published in the last five years describing adult patients treated with vonoprazan and/or PPI for GERD, *H. pylori,* or post-endoscopic dissection of the gastroesophageal submucosa bleeding and ulcers. There were six articles on GERD. Half suggested vonoprazan was superior to PPIs, while the other half considered it non-inferior or of comparable efficacy. There were 19 articles on *H. pylori* eradication, and vonoprazan outperformed PPI in 68,42% (13/19) of them. Vonoprazan was more effective than PPIs in 8 of the 13 studies chosen for post-ESD and ulcer prevention. As a result, in most studies, vonoprazan is either superior or not inferior to PPIs. However, the racial bias of the results is a significant limitation, as many of these studies were conducted in the Japanese population. More research on greater racial diversity is required. Nonetheless, in the current scenario, vonoprazan is a potential alternative pharmacological treatment for post-ESD bleeding and ulcers, GERD, and *H. pylori.*

Keywords: acid suppression agents, proton pump inhibitor, potassium-competitive acid blocker, vonoprazan

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Abbreviations: P-CAB, potassium-competitive acid blockers; PPI, proton pump inhibitors; GERD, Gastroesophageal Reflux Disease; ESD, endoscopic submucosal dissection; OR, odds ratio; CI, confidence interval; UGET, upper digestive endoscopic treatment; RR, relative risk

Introduction

Since 1990, proton pump inhibitors (PPIs) have been the standard treatment for acid-related diseases such as gastroesophageal reflux disease (GERD), as well as for the prevention of bleeding and ulceration after endoscopic gastroesophageal submucosa dissection (ESD) and the eradication of *Helicobacter pylori*. GERD is one of the most common gastroenterological diseases in the United States and Europe, affecting 20-30% of the global population. Serious complications such as stricture, ulceration, or Barrett's esophagus may develop if treatment is ineffective.[1] Endoscopic gastroesophageal submucosal dissection (ESD) has become a standard treatment for early gastric cancer that has not spread to lymph nodes. However, bleeding from the resection site remains a significant complication, with a 3-5% incidence.[2] *H. pylori* is one of the most common bacterial pathogens in the world, accounting for approximately 50% of the global population, and its treatment is based on PPIs and antibiotics.[2]

Despite PPIs being essential in treating these conditions, critical therapeutic limitations exist. In GERD, approximately two-thirds of symptomatic patients do not have adequate control of their reflux symptoms after the first dose of PPI, and approximately half of them continue to have symptoms even after a few days of starting therapy.[3] Additionally, the standard dose of PPIs cannot always induce acid suppression because of their pharmacological limitations, such as their need to be activated by gastric acid, which delays the onset of its pharmacological effects.[4] PPIs are the preferred therapy for ulcers and post-ESD bleeding, but there is no standard treatment plan, especially concerning the length of time and method of administration.[5] The success of combining PPIs with antibiotics in cases of *H. pylori* has been hampered by rising antimicrobial resistance.[2] Even though PPIs are already a well-established and effective drug therapy for treating these diseases, there is still room for new drugs that may supplement PPI-based treatment.

In this scenario, other acid secretion-suppressing drugs were developed to treat the same conditions as PPIs[6] Vonoprazan, a potassium-competitive acid blocker (P-CAB)[7] developed by Takeda Pharmaceutical Company, can directly inhibit H^+/K^+-ATPase-mediated gastric acid secretion by reversibly competing with potassium ions, bypassing the need for acid activation.[8] Furthermore, vonoprazan has a higher positive charge than other P-CABs, allowing it to accumulate in the canalicular space of parietal gastric cells, enhancing and prolonging its anti-secretory effects. vonoprazan has a rapid release due to its acid resistance, with studies from Japan and the United Kingdom indicating that the maximum plasma concentration is reached 1.5-2.0hours after oral intake on an empty stomach.[9] Excretion occurs after nine hours on average.[10] The most common side effects of vonoprazan are similar to those of PPIs and include diarrhea, nasopharyngitis, dyspepsia, headache, and abdominal pain.[11]

P-CABs have different mechanisms of action and pharmacokinetics that can overcome the limitations of PPIs. Therefore, this review aims to compare the therapeutic efficacy of vonoprazan and PPIs in treating GERD, *H. pylori*, ulcers, and post-ESD bleeding.

Methods

The present review followed PRISMA PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009

guidelines. An article search was conducted in Pubmed starting on April 27th, 2022. The following search terms were used: "vonoprazan + PPI," "vonoprazan + GERD," "vonoprazan + UGIB," "vonoprazan + bleeding," "vonoprazan + *H. pylori* eradication," and "PCAB + PPI."In total, 316 articles were found.

Inclusion criteria were studies written in English or Portuguese that compared the efficacy of the PPI versus vonoprazan-based therapeutic regimen in GERD, H. Pylori eradication, and prevention of bleeding and ulceration after ESD in adult patients (>18years old)Articles that did not compare vonoprazan to PPI-based treatment were excluded. According to the PRISMA diagram (Figure 1), 175 studies were excluded after reading the titles and abstracts and 63 after reading the full article, leaving 38 studies to be analyzed in this systematic review. Data extraction was carried out by four independent reviewers and checked by a senior reviewer.

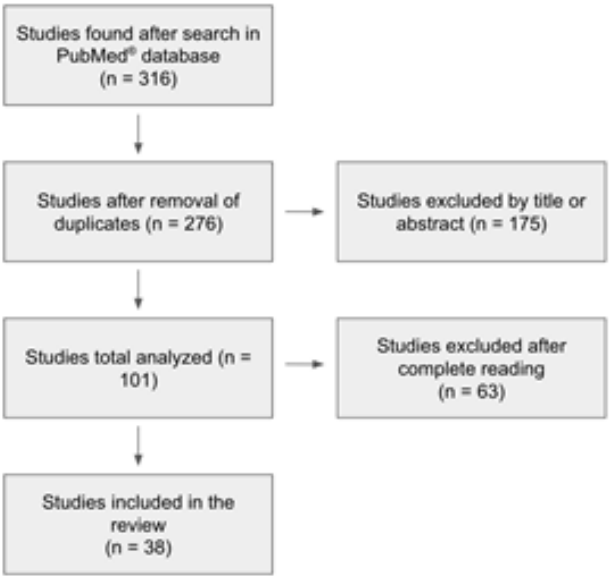

Figure 1 PRISMA diagram.

Results

The articles were divided into three categories. The first category was GERD treatment. Six articles were selected, out of which three were systematic reviews and meta-analyses: one was a randomized control study, one was a comparative study, and one was a prospective cohort study. Moreover, four of these studies were Japanese, one was Chinese-Japanese, and one was exclusively Chinese.

The second category was *H. Pylori* eradication. There were 19 studies, ten meta-analyses, one systematic review, three randomized controlled trials, one observational study, two randomized controlled trials, and two retrospective studies. Eleven of these studies were from Japan, five from China, one from South Korea, one from Thailand, one from Indonesia, and one from multiple countries, including the USA, Israel, Italy, France, and Spain.

Finally, the third category was the prevention of post-ESD bleeding and ulcers, which included 13 articles: 2 retrospective cohort studies, six meta-analyses, four prospective studies, and one case-control randomized study. Among these studies, nine were Japanese, one was from the USA and Thailand, one was from South Korea, and one was from China.

Prevention of post-ESD bleeding and ulcers (Table 1)

Table 1 Studies on the use of vonoprazan or proton pump inhibitors to treat post-ESD ulcer and prevent late bleeding

Study type	Country	Number of articles revised	Number of patients	Goal	Intervention	Results	Is vonoprazan better than PPI?	Ref
Systematic review and Meta-analysis	South Korea	12	1265	To compare vonoprazan and PPIs in treating post-ESD ulcers and preventing bleeding	Vonoprazan (20mg/day) or PPIs like lansoprazole, rabeprazole, omeprazole or esomeprazole	Scar tissue formation post-endoscopy was higher after four weeks of vonoprazan. However, after eight weeks, PIIs had better ulcer healing	Yes, after four weeks of treatment	[47]

Table Continued...

Study type	Country	Number of articles revised	Number of patients	Goal	Intervention	Results	Is vonoprazan better than PPI?	Ref
Systematic review and Meta-analysis	China	7	548	To compare vonoprazan's and PPI's efficiency and safety doses in treating	Vonoprazan (20mg/day) or PPIs like lansoprazole, rabeprazole or omeprazole for 4 to 8 weeks post-ESD	No difference	Similar	[19]
Systematic review and Meta-analysis	Several	6	461	To compare vonoprazan's and PPI's efficacy in scar formation in post-ESD ulcers	Vonoprazan or PPI for 4 to 8weeks post-ESD	Greater scar formation and less late bleeding in post-ESD ulcers following vonoprazan therapy	Yes	[48]
Prospective observational study	Japan	-	621	To compare vonoprazan's and PPI's efficacy in preventing post-ESD bleeding	Vonoprazan (20mg/day) or esomeprazole (20mg/day), rabeprazole (40mg/day), or lansoprazole (30mg/day)	No difference in ulcer scaring. Vonoprazan was better in reducing bleeding post-ESD	Yes	[26]
Retrospective cohort	Japan	-	1715	To compare the effect of vonoprazan and PPIs in post-ESD bleeding	Omeprazole (20mg/day) for 2days, then vonoprazan (20 mg/day) or lansoprazole (dose?) for 12days	Vonoprazan was more effective in reducing ulcers and forming granulation tissue	Yes	[18]
Retrospective cohort study	Japan	-	115	To compare the effect of vonoprazan and lansoprazole in ulcer scaring formation related to ESD in the two first weeks post-intervention	Omeprazole (20mg/day) in the first two days, then vonoprazan (20mg/day) or lansoprazole (30mg/day) for 12days	Vonoprazan reduced ulcer size and granulation tissue more significantly than lansoprazole. Bleeding post-surgery was not observed in any of the groups	Yes	[49]
Retrospective cohort study	Japan		124,422	To compare the effect of vonoprazan and PPIs in preventing post-ESD bleeding	Vonoprazan dose was categorized into standard/high dose (>20mg/day) and low dose (<20mg/day). Regarding PPIs, the standard daily dose in Japan is 30, 10, 20 and 20mg in lansoprazole, rabeprazole, esomeprazole, and omeprazole, respectively. Hence, the PPI dose in this study was categorized into two groups: standard/high-dose PPI and low dose, which included the dose under the standard dose of each PPI.	Vonoprazan was associated with a lower risk of late bleeding	Yes	[11]

Table Continued...

Study type	Country	Number of articles revised	Number of patients	Goal	Intervention	Results	Is vonoprazan better than PPI?	Ref
Meta-analysis	Japan	13	1214	To discuss vonoprazan and PPIs' efficacy in preventing ESD-induced bleeding	10mg vonoprazan, 20mg vonoprazan, and 20mg vonoprazan combined with 300mg rebamipide. Control arm (PPI) studies included 30mg lansoprazole, 20mg lansoprazole plus 300mg rebamipide, 20mg esomeprazole, 30mg lansoprazole, 20mg omeprazole, 10mg rabeprazole, and 20mg rabeprazole	No difference	Similar	[50]
Randomized clinical studies	Japan	-	168	Evaluate how vonoprazan helps in ulcer healing post-ESD	20mg/day of vonoprazan and 3 mg/day of lansoprazole for 8weeks	No difference	Similar	[29]
Meta-analysis	China	14	1328	Evaluate the efficacy and safety of vonoprazan in healing ulcers and preventing post-ESD bleeding		Vonoprazan reduced the risk of bleeding post-ESD	Yes	[51]
Prospective randomized study	Japan	-	80	To compare the effect of vonoprazan and PPIs in preventing post-ESD bleeding	Vonoprazan (20mg/day) or esomeprazole (20mg/day) for 8weeks	No significant difference between vonoprazan and PPIs	Similar	[52]
Prospective randomized study	Japan	-	33	To compare the effect of vonoprazan and PPIs in preventing post-ESD bleeding	Vonoprazan (20mg/day) or rabeprazole (10mg/day) for four weeks, starting one day before ESD.	Vonoprazan was better than PPIs in preventing late bleeding	Yes	[53]

Abbreviations: PPI, proton pump inhibitors; ESD, endoscopic submucosal dissection.

In the study by Abe et al.[11] 124,422 upper digestive endoscopic treatment (UGET) patients were analyzed between 2014 and 2019, with 34,822 and 89,600 prescribed vonoprazan and PPIs, respectively. The risk of late bleeding was lower in the vonoprazan group than in the PPI group. vonoprazan was significantly beneficial in endoscopic esophageal submucosal dissection (E-ESD) (OR, 0.71; 95% CI, 0.54-0.94) and endoscopic gastroduodenal submucosal dissection (GD-ESD) subgroup analyses of seven UGET procedures (OR, 0.70; 95% CI, 0.65-0.75).

PPIs were administered two days before the procedure in Shiratori et al.[18] carried out in nine hospitals with a total of 1715 patients. After ESD, patients were randomly assigned to treatment with vonoprazan or PPIs. The Post-ESD bleeding rates were significantly lower in the vonoprazan group than in the PPI group (overall, 11.9% vs. 17.2%, P=0.008; bleeding between days 2 and 30, 7.8% vs. 11.8%, P =0.015). In addition, the vonoprazan group had a lower readmission rate for post-ESD bleeding (2.4% vs. 4.1%, P=0.081).

Two studies compared the effects of vonoprazan and PPIs in treating ESD-induced artificial ulcers and preventing late bleeding. Following ESD, patients were given vonoprazan 20mg or PPIs (Lansoprazole, Omeprazole, Rabeprazole) for four or eight weeks. In He et al.[19] the success rates of vonoprazan-based and PPI-based therapy were equivalent. The combined relative risk (RR) for vonoprazan compared to PPI treatment for ESD was 0.64 (95% CI, 0.33-1.22) for the four-week study group and 0.98 (95% CI, 0.84-1.15) for the eight-week study group. The RR for adverse events was 0.65 (95% CI, 0.31-1.38) (p>0.05). However, in Kang et al.[20] the vonoprazan group recovered significantly faster than the PPI group four weeks after the endoscopy. In the same study, the PPI group had a significantly higher healing rate than the vonoprazan group at eight weeks post-endoscopy. All patients in Horikawa et al.[20] received an intravenous infusion of omeprazole during the first two days. Following the ESD procedure, patients were randomly assigned to either 20mg vonoprazan (P-CAB group) or 30mg lansoprazole (PPI group) treatment. All treatments were given orally for 12days. When comparing the PPI and P-CAB regimens, ulcers were smaller (median [range], 80.6% [67.6%–94.5%] vs. 62.7% [33.4%–85.2%]; p<0.0001) and granulation was faster (median [range], 84.1% [67.7%–95.3%] vs. 61.9% [12.1%–90.1%]; p<0.0001) in the P-CAB group. Moreover, postoperative bleeding was not observed in any of the groups.

Jaruvongvanich et al.[21] analyzed six studies (three cohort studies and three randomized studies) involving 461 patients (215 in the vonoprazan group and 246 in the PPI group) that compared

vonoprazan-based and PPI-based treatment for four or eight weeks after mucosectomy. Upper digestive tract endoscopy was used to simultaneously measure and report post-ESD bleeding and complete ulcer healing rates in both groups. Patients who received vonoprazan had a significantly higher chance of having their ESD ulcers healed four-eight weeks after the procedure, with a combined odds ratio (OR) of 2.27 (95% CI: 1.38-3.73) than those who received PPIs. In addition, the four-week and eight-week subgroups had significantly higher rates of fully healed ulcers, with pooled ORs of 2.21 (95% CI: 1.19-4.08; I^2=0%) and 2.40 (95% CI: 1.04-5.55; I^2=0%), respectively. The risk of developing late post-ESD bleeding was lower among those who received vonoprazan, with a pooled OR of 0.79, although the result did not reach statistical significance (95% CI: 0.18–3.49).

In their meta-analysis, Martin et al.[22] included only randomized controlled trials and observational monotherapy studies with vonoprazan or those that combined vonoprazan with a mucosa-protective agent. The overall OR for late bleeding was 0.66 (P=0.26) with a (95% CI: 0.32-1.35). After excluding drug combination studies, the overall ORs for vonoprazan and PPIs to promote ulcer healing and prevent late bleeding were 1.44 and 0.76, respectively. Vonoprazan was thus comparable to PPIs for preventing delayed bleeding after ESD, as the differences between the two drug classes were not statistically significant.

In their meta-analysis, Liu et al.[23] included fourteen articles with 1,328 patients. Vonoprazan outperformed PPIs regarding ulcer reduction rate (mean difference 0.56, 95% CI: 0.18-0.93). Additionally, with vonoprazan, there was more scar formation (OR 1.58, 95 % CI 1.00-2.47) and lower bleeding risk post-ESD (OR 0.69) compared to PPIs, although there was no statistically significant difference.

In Yang et al.[24] five studies evaluated the effectiveness of vonoprazan in post-ESD ulcers. Two of the five studies yielded favorable results for vonoprazan, two yielded favorable results for PPIs, and one yielded no difference in results between vonoprazan and PPIs. As a result, it is unclear whether vonoprazan is superior to PPIs in healing ulcers after ESD. More research into PPI-based unified administration is needed.

Hirai et al.[25] performed a prospective randomized controlled trial with 149 patients to compare the effects of vonoprazan and lansoprazole in treating ESD-induced ulcers and preventing bleeding. Patients received 40 mg of intravenous omeprazole for the first two days post-ESD and 20 mg of vonoprazan or 30mg of lansoprazole daily for eight weeks. There was no significant difference in ulcer resolution or prevention of late bleeding between the two groups.

Ishida et al.[26] treated post-endoscopy gastric cancer patients (≥20years old) with PPI (n=398) or vonoprazan (n=223) patients. One day before the endoscopy, the PPI group received oral esomeprazole (20mg/day), rabeprazole (40 mg/day), or lansoprazole (30 mg/day), followed by intravenous omeprazole (40mg/day), lansoprazole (60mg/day), and rebamipide (300mg/day). Succeeding that, oral medication was continued. PPI treatment was continued for at least eight weeks after endoscopy, and esophagogastroduodenoscopy was performed eight weeks later. In the other group, oral vonoprazan (20mg/day) was started one day before surgery and continued for six weeks, followed by esophagogastroduodenoscopy. Ulcers were scarred in 68.3% of patients after six weeks of vonoprazan and 74.6% after eight weeks of PPI.

Tsuchiya et al.[27] looked at 92 gastric cancer patients who had ESD and were given vonoprazan (20mg/day) or esomeprazole (20mg/day) for eight weeks. The ulcer healing rate was better for vonoprazan than esomeprazole (94.9% [37/39] vs. 78.0% [32/41], respectively; P=0.049). However, in a multivariate analysis, only vonoprazan was correlated with ulcer healing (OR 6.33; 95% CI: 1.21-33.20; P=0.029).

Komori et al.[28] looked at 40 gastric cancer patients who had ESD and were given vonoprazan (20mg/day) or rabeprazole (10mg/day), starting one day before ESD and continuing for four weeks. Ulcer size was measured before ESD and after four weeks of treatment. The mean ulcer reduction rate was lower in the vonoprazan (93.3%) than in the rabeprazole group (96.6%). In addition, post-ESD bleeding (n=2) and drug-induced liver injury (n=1) were observed in the rabeprazole group.

Kawai et al.[29] randomly assigned 168 gastric cancer patients to receive intravenous lansoprazole (30mg) twice daily before ESD and vonoprazan (20mg/day) or lansoprazole (30mg/day) post-ESD. Esophagogastroduodenoscopy was also performed between four and eight weeks after ESD. There was no significant difference in ulcer healing between the two groups. Additionally, there was no postoperative bleeding, and only one patient presented late perforation two days after ESD.

Vonoprazan was more effective in preventing bleeding and ulcer reduction in eight (8/13-61.5%) of the 13 studies that compared the effect of vonoprazan and PPIs on bleeding and ulcer prevention after ESD. Another three studies (3/13-23%) found that vonoprazan and PPIs were equally effective in preventing ulcers and bleeding. However, in one of these studies, when patients were analyzed four or eight weeks after ESD, vonoprazan performed better in the first four weeks, while PPIs performed better at eight weeks. As a result, vonoprazan has an excellent therapeutic effect in preventing ESD-induced bleeding and artificial ulcers, with results comparable to or better than PPI therapy. However, most of these studies were conducted in Asian countries. Therefore, further research in other countries must determine vonoprazan's global effectiveness.

Gastroesophageal reflux disease treatment (Table 2)

Table 2 Studies on the treatment of gastroesophageal reflux disease with vonoprazan or proton pump inhibitors

Study type	Country	Number of articles revised	Number of patients	Goal	Intervention	Results for GERD symptom resolution	Is vonoprazan better than PPI?	Ref
Meta-analysis and systematic review	China and Japan	6	-	To compare PPI and vonoprazan efficiency in treating DRGE	Vonoprazan (20mg/day) or esomeprazole ou lansoprazole (15 to 30 mg/day)	Vonoprazan was superior in treating erosive esophagitis than PPIs.	Similar	[12]

Citation: Silva GAV, Figueiredo JS, Gonçalves RJB, et al. Vonoprazan: A systematic review of an alternative to proton pump inhibitors. *Gastroenterol Hepatol Open Access.* 2022;13(6):221–231. DOI: 10.15406/ghoa.2022.13.00527

Table Continued...

Study type	Country	Number of articles revised	Number of patients	Goal	Intervention	Results for GERD symptom resolution	Is vonoprazan better than PPI?	Ref
Randomized clinical trial	Japan	-	60	To compare esomeprazole and vonoprazan in reducing GERD symptoms	Vonoprazan (20 mg/day) or esomeprazole (20 mg/day)	No difference	Similar	[13]
Comparative studies	Japan	-	12,069	To compare the adverse effects of vonoprazan and PPIs		No difference	Similar	[14]
Systematic review with network meta-analysis	Japan	23	-	To compare the efficacy of vonoprazan and PPIs	Vonoprazan (10 mg/day), esomeprazole (10 mg/day) and omeprazole (10 mg/day)	Vonoprazan was better than esomeprazole and omeprazole in reducing GERD symptoms; however, it was not better than other PPIs	Yes	[15]
Prospective cohort	Japan	-	124	To analyze the use of vonoprazan in GERD patients not responding to PPIs	Omeprazole (20 mg/day), lansoprazole (30 mg/day), rabeprazole (10 or 20 mg/day) or esomeprazole (20 mg/day) and then vonoprazan (20 mg/day) was given for 8 weeks.	Vonoprazan reduced GAET (41.1%; p = 0.01), suppressed esophageal acid exposure in 46% (p=0.005), and improved reflux (p<0.01) and esophagitis (p=0.01) symptoms.	Yes	[16]
Meta-analysis	China	-	18	To compare the effect of vonoprazan and PPIs in treating GERD and *H. pylori*		Vonoprazan improved symptoms in patients resistant to PPIs and helped post-ESD ulcer healing. It was also a better drug for first-line *H. pylori* therapy.	Yes	[17]

Abbreviations: PPI, proton pump inhibitors; GERD, gastroesophageal reflux disease; ESD, endoscopic submucosal dissection

Cheng et al.[44] and Miwa et al.[45] compared vonoprazan and PPIs as first-line and maintenance GERD treatments, respectively. Vonoprazan (10 mg/day) showed a better response than esomeprazole (10mg/day) or omeprazole (10 mg/day), but it was not better than other PPIs prescribed in Japan. On the other hand, Yang et al.[46] demonstrated that vonoprazan was as effective as PPIs in treating erosive esophagitis and was an excellent option for GERD patients who no longer responded to PPIs.

Sakurai et al.[13] administered vonoprazan or esomeprazole once daily for four weeks to two groups of 30 GERD patients. Symptoms' improvement was assessed through a questionnaire to track the clinical improvement. There was no significant difference in GERD symptom relief between vonoprazan and esomeprazole.

Kambara et al.[14] compared patient-reported adverse effects of vonoprazan and PPIs from 2004-2017 using the Japanese database "Adverse Drug Event Repo." The adverse effects of both treatments were similar.

Akiyama et al.[16] analyzed chronic GERD patients that did not respond to PPI therapy. Out of 124 patients undergoing multichannel intraluminal impedance-pH monitoring, 13 patients were monitored during PPI therapy and after introducing vonoprazan therapy. Median gastric acid exposure times associated with vonoprazan treatment (23.8%) were lower than for PPI treatment (41.1%; p=0.01), including daytime and nighttime measurements. In addition, vonoprazan resulted in lower esophageal acid exposure time (4.5%) than PPIs (10.6%) during the 24-hour monitoring period (p=0.055). Additionally, vonoprazan reduced gastric acid secretion in 46% of esophageal acid-exposed patients (p=0.005), improved reflux symptoms (p=0.01), and decreased erosive esophagitis (p=0.01).

GERD is a highly prevalent disease worldwide, mainly due to changes in lifestyle, diet, and obesity. Although GERD has been classically treated with PPIs, many patients have been unresponsive. Therefore, looking for new treatment options is critical to close this gap and improving quality of life. Here we examined six studies comparing vonoprazan to PPIs in the first-line and maintenance treatment of GERD patients. In three of these studies (50%), vonoprazan was considered superior to PPIs, and in the other three (50%), vonoprazan was similar to PPIs in treating GERD. Vonoprazan appears to be a promising first-line and maintenance GERD treatment. However, the small number of studies and lack of research outside of the Japanese population continue to be barriers to accepting this new drug as a replacement for PPIs.

H. Pylori eradication (Table 3)

Table 3 Studies on *Helicobacter pylori* eradication using vonoprazan or proton pump inhibitors

Study type	Country	Number of articles revised	Number of patients	Goal	Intervention	Results for *H. pylori* eradication	Is vonoprazan better than PPI?	Ref
Meta-analysis	Spain, Israel, Italy, USA, France	68	22,975	To compare first-line treatments to eradicate *H. pylori*	Comparison between vono-triple therapy, non bismuth quadruple therapy, r-hybrid therapy, levo-therapy, sequential therapy, amox-dual therapy and bismuth quadruple therapy	90% remission in vonoprazan-based therapy	Yes	[30]
Systematic review with meta-analysis	South Korea	10	10,644	To compare vonoprazan and PPI	Vonoprazan (20mg/day) for 7 days or lansoprazole (30mg/day), rabeprazole (10mg/day), esomeprazole (20mg/day) for 7days	87.9% remission in vonoprazan-based treatment; 72.8% remission in PPI-based treatment	Yes	[31]
Meta-analysis	China	8	2012	To analyze vonoprazan's efficacy and safety concerning other drugs	Vonoprazan (20mg/day) or PPI in association with amoxicillin (750mg/day) and clarithromycin 200mg or 400mg/day)	Equal or superior remission with vonoprazan-based treatment	Yes*	[32]
Systematic review	Japan	12	-	To compare sitafloxacin-based third-line therapies with others	Sitafloxacin, amoxicillin, and vonoprazan or PPI	Superior remission of vonoprazan-based treatments	Yes	[33]
Randomized clinical trial	Thailand	-	122	To compare seven days of vonoprazan with 14 days of omeprazole	Group 1: Vonoprazan (20mg/day), amoxicillin (1000mg/day), and clarithromycin 500 (mg/day). Group 2: Omeprazole (20mg/day), amoxicillin (1000mg/day), clarithromycin (500mg/day)	Similar remission for vonoprazan (97%) and omeprazole (93%)	Yes	[34]
Observational	Japan	-	1355	To determine if vonoprazan is a treatment alternative	Lansoprazole (30 mg twice daily) or rabeprazole (10 mg twice daily) or esomeprazole (2 mg twice daily) or vonoprazan (20mg twice daily), amoxicillin (750mg twice daily), and clarithromycin (200-400mg twice daily) for seven days.	Similar remission for vonoprazan and PPIs	Yes*	[35]
Randomized clinical trial	Japan, China, South Korea, and Taiwan	-	531	To compare vonoprazan's and lansoprazole's efficacy and safety	Vonoprazan (20mg, twice daily), lansoprazole (30mg twice daily), bismuth salt (600mg twice daily), amoxicillin (1g twice daily), and clarithromycin (500mg twice daily) for two weeks.	Similar remission and safety for both drugs. 0% *H. pylori* emission with vonoprazan	Yes	[36]
Randomized clinical trial	Japan	-	87	To compare vonoprazan and rabeprazole	Vonoprazan (40mg/dia) or rabeprazole (20mg/day), amoxicillin (1500mg/day), metronidazole (500mg/day)	Similar remission	Same	[37]

Table Continued...

Study type	Country	Number of articles revised	Number of patients	Goal	Intervention	Results for *H. pylori* eradication	Is vonoprazan better than PPI?	Ref
Randomized clinical trial	Japan	-	63	To compare vonoprazan or PPI after the failure of first- and second-line therapy	Vonoprazan (20mg twice daily), amoxicillin (750mg twice daily), sitafloxacin (100mg twice daily), esomeprazole (20mg twice daily), or rabeprazole (10mg twice daily), or lansoprazole (30mg twice daily) or sitafloxacin (100 mg twice daily) for seven days	Vonoprazan was superior to PPI as a third-line treatment	Yes	[38]
Meta-analysis	Japan	18	-	To analyze vonoprazan's efficacy	Vonoprazan (20 mg/day) or PPI in association with amoxicillin (750mg/day) and clarithromycin 200mg or 400mg/day)	Superior remission with vonoprazan	Yes	[39]
Meta-analysis	China	14	14,636	To analyze vonoprazan's efficacy and safety compared to PPIs	Vonoprazan (20 mg/day) or PPI in association with amoxicillin (750mg/day) and clarithromycin 200mg or 400 mg/day)	92.6% remission with vonoprazan and 74.6% remission with PPI-based therapies	Yes	[40]
Meta-analysis	Indonesia	16	-	To analyze vonoprazan's efficacy	Vonoprazan (20 mg/day) or PPI in association with amoxicillin (750mg/day) and clarithromycin 200mg or 400mg/day)	Superior remission with vonoprazan	Yes	[41]
Meta-analysis	China	18	-	To compare vonoprazan and PPI in *H. pylori*, ulcer and GERD	Vonoprazan (20mg/day) or PPI in association with amoxicillin (750mg/day) and clarithromycin 200mg or 400mg/day)	Superior *H. pylori* remission with vonoprazan	Yes	[42]
Meta-analysis	China	3	897	To compare vonoprazan and PPI's efficacy and safety	Vonoprazan (20mg/day), amoxicillin (750mg/day), and clarithromycin (200-400mg twice daily)	Superior *H. pylori* remission and inferior adverse effects with vonoprazan	Yes	[43]

Abbreviations: PPI, proton pump inhibitors; GERD, gastroesophageal reflux disease

Primary-line treatment

Rokkas et al.[30] selected 68 randomized trials with a total of 22.975 patients, comparing eight different first-line treatments and triple therapy with vonoprazan showing the highest SUCRA (surface under the cumulative ranking curve) value (92.4%).

Six of the seven meta-analysis reviews[31, 40–42, 4] found that vonoprazan-based triple therapy was more effective than PPIs. However, in Yang et al.[46] vonoprazan outperformed lansoprazole and rabeprazole but did not differ significantly from esomeprazole. Furthermore, Liu et al.[23] demonstrated that vonoprazan could treat clarithromycin-resistant *H. pylori*.

Yang et al.[55] looked at eight trials with a total of 2012 patients and found that vonoprazan was significantly more effective than PPIs in first-line treatment, both in intention-to-treat patients (RR, 1.14; 95% CI: 1.06-1.23; p=0.0006) and in per-protocol patients (RR, 1.12; 95% CI: 1.04-1.20; p=0.003).

Bunchorntavakul et al.[34] included 122 patients on first-line vonoprazan and PPIs in randomized clinical trials. Vonoprazan was similar to PPIs (7-VAC and 14-OAC groups: 96.7% and 88.5%, p=0.083, respectively) in the analysis with the intention-to-treat and 98.3% and 93.1%, p=0.159, respectively, in the per protocol). Hou et al.[36] included 415 patients with *H. Pylori,* with vonoprazan eradicating 91.5% (193/211) for vonoprazan and 86.6% (177/204) for lansoprazole.

Tanabe et al.[35] studied 1355 patients treated for *H. pylori*, of which 1143 received vonoprazan or PPIs. Vonoprazan was significantly more effective ($p < 0.001$) in eliminating *H. pylori* and was equally effective to PPI in treating clarithromycin susceptibility.

In Kusunoki et al.[56] 1172 patients received first-line treatment. *H. pylori* elimination was 86.9% (1,019/1,172) when given triple therapy, and 92.5% (384/415) with only vonoprazan. First-line eradication therapy worked significantly better for vonoprazan than for PPI-based therapy (OR 2.36; 95% CI: 1.55 to 3.56).

Sue et al.[57] looked at 147 patients with *H. pylori,* from which 106 patients were susceptible to clarithromycin. *H. pylori* eradication rates in patients receiving vonoprazan with intent-to-treat and per protocol were 87.3% (95% CI=75.5%-94.7%; 48/55) and 88.9% (95% CI=77.4%-95.8%; 48/54), respectively. The same rates of PPI patients were 76.5% (95% CI: 62.5%-87.2%; 39/51) and 86.7% (95% CI: =73.2%- 94.9%, 39/45).

Second-line treatment

Dong et al.[40] revised 14 studies with 14,636 patients comparing vonoprazan with PPIs as a second-line triple therapy in which clarithromycin was replaced by metronidazole. The power of vonoprazan to eradicate *H. pylori* was not significantly different from PPIs (83.4% vs. 81.2%, P=0.79, OR 1.04; 95% CI: 0.77-1.42). Furthermore, the results of the per-protocol analysis were comparable to those of the intention-to-treat analysis (89.3% vs. 90.1%, P=0.06).

In Yang et al.[46] five studies analyzing *H. pylori* second-line treatment indicated an eradication rate of over 90. However, this eradication rate was not significantly different from the use of PPIs.

Shinozaki et al.[43] analyzed six observational studies totaling 6,664 patients treated with three drugs: amoxicillin (750 mg), metronidazole (250mg), and an acid blocker (vonoprazan 20mg, esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20mg, or rabeprazole 10mg) twice daily for seven days. *H. pylori* was eradicated in 91% of cases when vonoprazan was included in the regimen, compared to 88% when PPIs were used. Therefore, the authors considered vonoprazan-based therapy more effective than PPI-based regimens in treating *H. pylori* (OR 1.51; 95% CI: 1.27-1.81; p <0.001) with no heterogeneity (I2=0%).

Kusunoki et al.[58] used 1329 patients with *H. pylori* for second-line therapy containing PPI or vonoprazan, amoxicillin, and metronidazole. The PPIs included esomeprazole (20mg), lansoprazole (30mg) and rabeprazole (10mg). The vonoprazan-based regimen was not superior to the PPI-based regimen for second-line eradication therapy. Nabeta et al.[59] established a regimen containing metronidazole 250mg, amoxicillin 750mg, and an acid-suppressing drug (vonoprazan 20mg, lansoprazole 30mg, or rabeprazole 10mg) twice daily for seven days for *H. pylori* eradication. Vonoprazan-based regimen had a higher *H. pylori* elimination rate than PPI (90% vs. 85%, p=0.045;). Furthermore, in the per-protocol analysis, patients treated with vonoprazan had a higher success rate in eradicating H. pylori than patients under PPI (96 vs. 91%, p=0.008;).

Third-line treatment

In Nishizawa et al.[33] twelve studies were analyzed and concluded that vonoprazan-sitafloxacin-amoxicillin treatment was significantly superior to PPI-sitafloxacin-amoxicillin (OR 6.00; 95% CI: 2.25-15.98; p <0.001).

Sue et al.[60] analyzed 58 patients treated with vonoprazan and PPI. However, no significant differences were observed in the intention-to-treat analysis (p=0.071).

In the 19 studies considered in this systematic review, vonoprazan was equally or more effective (68.4%; 13/19) than PPIs in the first-, second-, and third-line treatment for *H. pylori* eradication. However, most studies were conducted in Asia, mainly in Japan, which may impose a regional bias in the results. It is known that the Japanese ethnicity has a higher incidence of gastrointestinal *H. pylori*-related cancer. In addition, Vonoprazan has been developed and used in Japan longer than in other countries, which may explain the various studies with the Japanese population. Thus, there is a need for new studies comparing vonoprazan and PPIs in non-Asian populations. Furthermore, vonoprazan and PPIs showed similar adverse effects, but no study directly compared their cost-effectiveness.

Conclusion

The literature shows divergent results regarding the treatment with vonoprazan for preventing bleeding and ulcers after ESD, GERD, and *H. pylori* eradication. Vonoprazan had a superior or equal result as PPIs in preventing bleeding and treating post-ESD ulcers. Moreover, in GERD, vonoprazan was a better treatment choice than PPIs in half of the studies, while the other half considered them equally effective. Finally, vonoprazan was more efficient in eradicating *H. pylori* than PPIs in 68.42% of the studies, showing vonoprazan's potential as an alternative to the current therapy. Lastly, it is worth emphasizing the need for multicenter studies to avoid implicit bias in the sample population.

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Conflicts of interest

The authors declare no conflict of interest.

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