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REVIEW

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Potassium-competitive acid blockers: rethinking acid suppression for gastroesophageal reflux disease and *Helicobacter pylori*

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ABSTRACT

Gastroesophageal reflux disease (GERD) and *Helicobacter pylori (H. pylori)* infection are different disease states that are united by the core role of acid suppression in their management. In GERD, proton pump inhibitors (PPIs) have long been standard therapy based on abundant positive clinical trial data supporting their efficacy and safety. In *H. pylori*, PPIs are also a critical element of therapy in combination with 1 or more antibiotics to achieve and maintain a pH that maximizes the efficacy of therapy. Despite the considerable clinical success and widespread use of PPIs, room remains for agents with differentiated pharmacokinetic and pharmacodynamic profiles. The potassium-competitive acid blockers (PCABs) are mechanistically distinct from PPIs but are acid-stable and do not require activation of the proton pump by coadministration of food. In pharmacodynamic studies, these agents have shown greater durations of acid suppression above the critical threshold of pH 4 (for GERD) and pH 6 (for *H. pylori*), which have been shown to optimize therapeutic efficacy in these settings. These results have translated in clinical studies to similar and, in some cases, improved outcomes relative to PPIs in these disease states. This review summarizes current knowledge on the physiology of acid secretion, pathophysiology and management of GERD and *H. pylori*, and key characteristics and clinical trial data for PPIs and PCABs.

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Gastroesophageal reflux disease; *Helicobacter pylori*; proton pump inhibitors; potassium competitive acid blockers; clinical trials; patient management; therapy

1. Introduction

Gastroesophageal reflux disease (GERD) and *Helicobacter pylori* infection are common and clinically consequential diseases affecting millions worldwide. These otherwise disparate diseases are united by the fact that gastric pH not only plays a key role in modulating disease severity and progression but is also a key treatment target [1,2].

GERD – a disorder characterized by reflux of gastric contents into the esophagus – is one of the most common gastrointestinal diseases. Based on self-report studies, heartburn and/or acid regurgitation occurs at least weekly in up to 20% of people, many of whom have significant symptoms such as pain and dysphagia [3,4]. GERD is not a single disease; instead, it consists of a spectrum of multiple phenotypes with different underlying mechanisms and treatment considerations [5].

Diseases causally linked to *H. pylori* infection are sources of considerable morbidity and mortality worldwide. Between 40% and 50% of people globally carry *H. pylori* chronically, although regional prevalence varies substantially even within individual countries [6,7] Although histologic gastritis occurs in all people infected with *H. pylori*, the majority never experience overt clinical symptoms. In 10% to 20% of infected patients, chronic gastritis and progressive damage to the gastric mucosa ultimately leads to peptic ulcers [8]. Although perhaps underappreciated as a causative factor for cancer, chronic *H. pylori* infection dramatically increases the risk for gastric adenocarcinoma and marginal zone B-cell lymphoma of MALT type [9]. It has been estimated that between 1% and 3% of people infected with *H. pylori* will develop gastric cancer and <0.1% develop MALT lymphoma [10,11].

Standard therapy for GERD and *H. pylori* includes acid-suppressive treatment [1,2]. The introduction of proton pump inhibitors (PPIs) to US clinical practice in 1989 marked a revolution in the management of these diseases, and they have since become the first-line standard of care for GERD and an integral part of combination therapy, along with antibiotics, for *H. pylori* infection, largely supplanting older drugs such as histamine-2 (H2) receptor antagonists for most patients [1,2]. Since their introduction, advances in acid-suppressive treatment in the US have primarily been related to the introduction of new and reformulated PPIs.

Potassium-competitive acid blockers (PCABs) are a well-established therapy outside of the US, having been first approved in Japan in 2014. However, it was not until 2022 that the PCAB vonoprazan received its first approval in the US [12]. Like PPIs, PCABs exert their acid-suppressive activity via the H+/K+ ATPase of the parietal cell – the ion pump responsible for gastric acid secretion, but they are otherwise distinct from PPIs in terms of mechanism of action, pharmacokinetics, and metabolism [13,14]. They thus offer a potential alternative to PPIs with a markedly different clinical profile [13–16].

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This review contextualizes current knowledge on the pathophysiology and current management paradigm for GERD and *H. pylori* infection, with a focus on understanding the differences between PPIs and PCABs and where vonoprazan may fit in the management of these diseases.

2. Physiology of gastric pH and the parietal cell

The physiology of acid secretion has been well-reviewed elsewhere [17,18]. However, it is important to review the basics of acid secretion as it has implications for the management of both GERD and *H. pylori* infection.

The mucosal surface of the stomach remains intact despite continuous exposure to acidic gastric juice and digestive enzymes. The median pH of the gastric lumen is approximately 1.4, but levels below 1.0 can occur when unbuffered by food [19]. The stomach resists autodigestion through a tripartite mechanism consisting of a thick coating of bicarbonate-rich mucus, tight junctions between the epithelial cells of the mucosa to prevent leakage of gastric juice into the underlying tissue layers, and continuous self-renewal of the epithelial surface via rapid differentiation of underlying stem cells [20]. As a result of its bicarbonate content, the pH of the mucosal surface can be close to neutral when luminal pH is above 2.0; below this threshold, the gradient breaks down, and the luminal surface rapidly acidifies [21,22].

Parietal cells are epithelial cells that reside within oxyntic (acid-secreting) glands of the corpus of the stomach (Figure 1) [17,18]. The apical (lumen-facing) surface of these cells is characterized by the presence of canaliculi lined with microvilli, and the interior of the cell contains membranous structures (tubulovesicles), within which abundant H+/K+ ATPase is inserted [18]. Signals that induce acid secretion result in the relocation of these membranes and the embedded H+/K+ ATPase to the canaliculi surface, where the pump actively exchanges extracellular potassium for intracellular protons using energy donated by ATP [17,18]. Adequate luminal potassium, which is required for exchange by the H+/K+ ATPase, is likely supplied by the KCNQ1-KCNE2 efflux channel, and chloride is supplied via diffusion via a transmembrane channel [14,17,23] The H+/K+ ATPase has a relatively short half-life of about 2.5 days and is replaced at a rate of approximately 20% every 24 hours [14,24]. Given its potent effect on gastric pH, the activity of the H+/K+ ATPase is tightly regulated; in the fasted state, less than 10% of pumps are active; stimulation with food intake increases the proportion of active pumps to 70% [25].

3. Acid suppressive therapies: mechanisms of action

Acid suppression with PPIs is the current primary pharmacologic approach to managing GERD symptoms and is the backbone of therapy for *H. pylori* in combination with antibiotics [1,2] Vonoprazan, the only PCAB available in the United States, was first approved in 2022 as part of *H. pylori* eradication therapeutic regimens and in late 2023 for the healing of all grades of erosive esophagitis, relief of heartburn associated with erosive GERD, and maintenance of healing of all grades of erosive GERD [12]. Vonoprazan has yet to be incorporated into US guideline recommendations for either *H. pylori* or GERD. Tegoprazan, another PCAB, is also currently being evaluated in several ongoing trials in the US (NCT05587322 and NCT05587309) [26,27].

Both PPIs and PCABs act by inhibiting the final step of acid secretion mediated by the H+/K+ ATPase (Figure 1 and Table 1) [28].

3.1 Proton pump inhibitors

Proton pump inhibitors, such as omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole, are

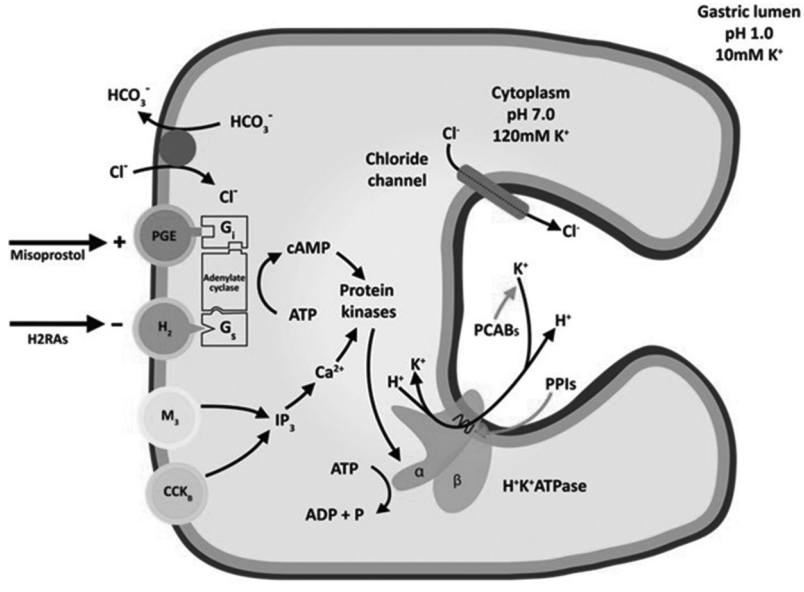

Figure 1. Parietal cell physiology and mechanism of action of acid-suppressive therapies. See text for details [28].

Table 1. Comparison of key characteristics of proton pump inhibitors (PPIs) and vonoprazan.

	PPIs	Vonoprazan[a]
Mechanism	Covalent binding of acid-activated drug to cysteine residues on luminal face of active H+/K+ ATPase [25]	Noncovalent reversible binding to K+ binding site of active and inactive H+/K+ ATPase; does not require acid activation [13,38,39]
Requirement for Food	Yes, to stimulate parietal cell acid production [14]	No, activity is independent of food [30]
Time to maximum effect	Cumulative with repeated dosing; maximum inhibition reached in ≥3 days [14]	~4-5 hours after each dose [40]
Half-life	0.6 to 2 h [25]	7–8 h [43]
Metabolism	CYP2C19 [25]	CYP3A4 [12]

[a]As the only PCAB currently approved in the United States, the characteristics listed here are from studies of vonoprazan.

prodrugs [29]. Because they are weak bases, they accumulate within the acidic environment of stimulated parietal cell canaliculi at levels up to 1000 times higher than in the blood [16]. Within this acidic milieu, the prodrug is activated and forms a covalent, permanent bond with cysteine residues on the luminal face of the active H+/K+ ATPase that inhibits its activity [25].

Because of their requirement for acid activation, the relative timing of dosing and food intake is critical [30]. PPIs are formulated with an enteric coating that protects the prodrug from gastric acid until it reaches the duodenum, where the coating degrades and the drug is absorbed [31]. Maximum plasma concentrations are achieved between 1 and 5 hours after administration [16]. All PPIs require activation of proton pumps by administration of food, and most require that the drug be administered 30 to 60 minutes before a meal to allow for absorption, activation of proton pumps, and acidification of the secretory canaliculi [8]. Once absorbed, PPIs have half-lives ranging from about 0.6 to 2 hours [16]; however, because they bind covalently to the proton pump, their acid-suppressive effect is maintained throughout the lifespan of the pump [25]. The action of PPIs is terminated by the natural and continuous replacement of about 20% of the pumps every 24 hours [25].

The mechanistic profile of PPIs has important implications for their clinical efficacy. As noted previously, food activates approximately 70% of pump enzymes, and only these active pumps are inhibited by the drug [25]. Combined with the turnover of pumps at the luminal surface, it has been estimated that it takes ≥3 days to reach steady-state inhibition of gastric acid secretion, at which time acid suppression peaks at about 66% of maximum output [14].

Proton pump inhibitors are predominantly (>80%) metabolized by the cytochrome (CYP) 450 enzyme CYP2C19 and, to a lesser extent, by CYP3A4 [32]. The pharmacokinetics, acid-suppressive effects, and, ultimately, therapeutic efficacy of PPIs vary depending on *CYP2C19* genotype. In particular, there is a graded relationship between intragastric pH and *CYP2C19* genotype, such that intragastric pHs during PPI treatment are highest in poor metabolizers, intermediate in intermediate metabolizers, and lowest in rapid metabolizers [32,33]. Consistent with the importance of adequate acid suppression, *CYP2C19* genotype has been shown in most, but not all, studies to influence outcomes of GERD and *H. pylori* eradication therapy [32]. Additionally, omeprazole and esomeprazole, but not other PPIs, inhibit CYP2C19 [32]. A risk exists for interaction with other medications metabolized by the enzyme, particularly the antiplatelet medication clopidogrel [1,34].

3.2 Vonoprazan: a potassium-competitive acid blocker

Vonoprazan shares similarities with PPIs in that it also inhibits the H+/K+ ATPase. However, it is not a prodrug, is acid-stable, and does not require activation of the proton pump by coadministration of food [13,35,36]. Upon administration, vonoprazan reaches maximum plasma concentrations in ≤2 hours and maximum acid-suppressive effects ~4 hours after each dose [35,37]. Instead of binding covalently to active pumps, vonoprazan accumulates to high levels (~100,000-fold higher than plasma) in the canaliculi in a pH-independent manner by binding reversibly and noncovalently to the potassium-binding sites of both active and inactive (intracellular) proton pumps [13,38]. This blockade of the potassium-binding site prevents potassium ions from binding, inhibiting exchange and suppressing basal and stimulated gastric acid secretion [38,39]. Although the binding is noncovalent, vonoprazan dissociates slowly from the H+/K+ ATPase; coupled with a half-life of ~7-8 hours, it results in an increased duration of acid suppression relative to PPIs [35,40].

The relative effects of once daily vonoprazan 20 mg and lansoprazole 30 mg on gastric pH were evaluated in an open-label crossover trial conducted in 44 *H. pylori*-negative healthy adults aged 18 to 55 [40]. Treatments were administered in the morning after an overnight fast, and food was provided at 4, 9, and 12 hours after each dose, and intragastric pH was recorded for 24 hours before administration of the medications and during the first and seventh days of each 7-day treatment period. On both days 1 and 4, the percentage of time above the pH thresholds of 4 and 6 was significantly greater with vonoprazan than with lansoprazole (Figure 2). Mean 24-hour intragastric pH was higher with vonoprazan than with lansoprazole on day 1 (4.6 vs 2.8, respectively) and day 7 (5.9 vs 3.8). Similarly, nocturnal (12–24 h) intragastric pH was higher with vonoprazan vs lansoprazole on both days 1 and 7. Additional pharmacodynamic studies conducted in healthy Japanese adults showed similar results vs lansoprazole, rabeprazole, and esomeprazole [41,42].

Vonoprazan is metabolized predominantly by CYP3A4 and is thus not subject to interindividual variability related to *CYP2C19* polymorphisms. Pharmacokinetic studies have demonstrated no relationship between *CYP2C19* genotype and drug exposure [43]. As a CYP3A4 substrate, coadministration with strong or moderate CYP3A inducers may reduce exposure to the drug [12]. Vonoprazan is also a weak CYP3A4 and CYP2C19 inhibitor and may increase exposure to substrates of these enzymes [12].

4. Gastroesophageal reflux disease and the role of vonoprazan

Gastroesophageal reflux disease is characterized by typical symptoms, such as heartburn and regurgitation, and a range of atypical symptoms, including, but not limited to, hoarseness, chronic cough, throat clearing, laryngitis, pharyngitis, and pulmonary fibrosis [1]. If left untreated or inadequately managed, serious complications can occur, including esophageal ulcers and bleeding, scarring leading to peptic stricture, Barrett's esophagus, and esophageal adenocarcinoma [44]. Guidelines define GERD clinically as 'a condition in which the reflux of gastric contents into the esophagus results in symptoms and/or complications' and objectively as 'the presence of characteristic mucosal injury seen at endoscopy and/or abnormal acid exposure demonstrated on a reflux monitoring study' [1].

The pathogenesis of GERD is multifactorial and may include dysfunction of the antireflux barrier at the esophagogastric junction, reduced esophageal clearance, compromised esophageal mucosal integrity, and inflammation at the site of injury [1]. As a multifactorial disease, GERD exists on a clinical spectrum ranging from nonerosive reflux disease (NERD; also referred to as nonerosive GERD), a condition in which patients experience the symptoms of GERD but have no evidence of macroscopic tissue injury, to overtly erosive esophagitis (EE; also referred to as erosive GERD), a condition in which patients suffer from inflammation or injury to the esophageal mucosa [5]. Seventy percent of patients with GERD have the nonerosive phenotype, with the remainder having erosive disease of varying severity [45].

Gastric pH and hold time at pH >4.0 predict benefit in GERD [46]. Well-established data show that the amount of time intragastric pH <4 correlates strongly with the frequency of symptoms (Figure 3(a)) [47]. Among patients with EE, time above this critical threshold is predictive of both optimal healing of esophageal tissue (Figure 3(b)) and long-term maintenance of healing [48]. Acid suppression with PPIs has thus become the foundation of therapy for GERD. Clinically, these agents have consistently demonstrated superior acid suppression and higher rates of EE healing than H2RAs; for example, in one randomized trial, EE remission, as determined endoscopically, was observed in approximately twice as many patients who received omeprazole (80.2%) as compared to those who received ranitidine 150 mg (39.4%) [49]. These results, along with abundant data from many short- and long-term studies, have led to guidelines to recommend these agents as the first-line treatment for patients with known or suspected GERD [1]. Key guideline recommendations regarding the use of PPIs in GERD are summarized in Table 2.

While PPIs are effective in the management of GERD, concerns have arisen regarding overprescription and long-term use, particularly regarding potentially increased risks for cardiovascular events, chronic kidney disease, and enteric infections, including *C. difficile*, among other concerns [1]. However, the guidelines acknowledge that many of these studies are methodologically flawed and do not establish a definitive causal relationship between PPIs and these adverse conditions, aside from intestinal infections [1].

4.1 Clinical efficacy and safety of vonoprazan in GERD

The clinical efficacy of vonoprazan for healing and maintenance of healing in EE was evaluated in US and European populations in the pHalcon-EE trial (NCT04124926) [37]. This double-blind, active-controlled, multicenter trial randomly assigned 1027 patients to vonoprazan 20 mg or lansoprazole 30 mg once daily for up to 8 weeks; those with healing (n = 878) were rerandomized to maintenance therapy with vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg once daily for an additional 24 weeks of treatment. The coprimary endpoints were the percentage of subjects with healing by Week 8 and the percentage who maintained healing at 24 weeks.

At the end of the 8-week healing phase, vonoprazan was noninferior to lansoprazole for the primary endpoint of

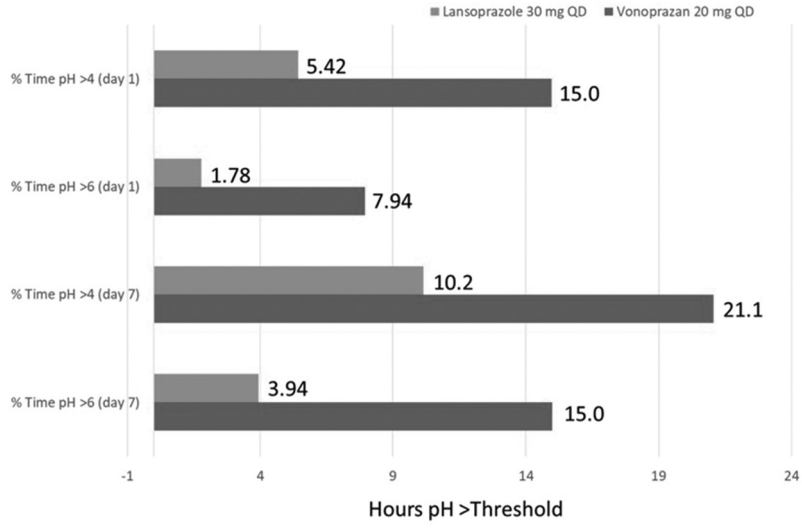

Figure 2. Hours and percentage of time per 24-hour period above pH thresholds of 4 and 6 for lansoprazole 30 mg QD and vonoprazan 20 mg QD in a randomized 7-day crossover trial in healthy US adults (N = 40). Trial drugs were administered to fasted patients and followed by meals 4 h, 9 h, and 12 h later. $P < 0.001$ for all comparisons [40].

Table 2. Key recommendations and concept statements related to proton pump inhibitor use from the 2022 American College of Gastroenterology Clinical Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. Refer to the complete guideline for a comprehensive summary of recommendations [1].

Diagnosis of GERD
- For patients with classic GERD symptoms of heartburn and regurgitation who have no alarm symptoms, an 8-week trial of empiric PPIs once daily before a meal is recommended
- An attempt should be made to discontinue PPIs in patients with classic GERD whose symptoms respond to an 8-week empiric trial of these agents

GERD Management
- In patients with NERD, on-demand or intermittent PPI therapy for heartburn symptom relief is recommended
- Indefinite PPI maintenance therapy (or antireflux surgery) is recommended for patients with Los Angeles Grade C or D esophagitis
- For patients who require PPI maintenance therapy, the lowest PPIs dose that effectively controls GERD symptoms and maintains healing of reflux esophagitis should be used
- For patients with extra-esophageal and typical GERD symptoms, a trial of twice daily PPI therapy is suggested before additional testing
- Switching PPIs can be considered for patients who experience minor PPI side effects, including headache, abdominal pain, nausea, vomiting, diarrhea, constipation, and flatulence

Refractory GERD
- Optimization of PPI therapy is the first step in the management of refractory GERD
- There is conceptual rationale for a trial of switching PPIs for patients who have not responded to one PPI. For patients who have not responded to one PPI, more than one switch to another PPI cannot be supported

Safety
- Some studies suggest an association between long-term PPI use and the development of adverse events such as intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, kidney disease, vitamin and mineral deficiencies, heart attacks, strokes, dementia, and early death; these studies are not considered definitive and do not establish a cause-and-effect relationship. High-quality studies suggest that PPIs do not significantly increase the risk of any of these conditions except intestinal infections
- Patients should be advised on the potential risks of PPIs while acknowledging that the 'well-established benefits of PPIs far outweigh their potential risks'

GERD, gastroesophageal reflux disease; NERD, nonerosive gastroesophageal reflux disease; PPI, proton pump inhibitor.

healing by week 8 (92.9% and 84.6%, respectively; noninferiority $P < 0.0001$) and superior to lansoprazole ($P < 0.0001$) in a predefined exploratory analysis conducted after establishing noninferiority for the primary endpoint [37]. Noninferiority was also demonstrated for the first secondary endpoint, the percentage of 24-hour heartburn-free days. The percentage of patients with sustained resolution of heartburn by day 3, the third secondary endpoint, was similar in the 2 groups (34.4% vs 32.0%). Vonoprazan 10 and 20 mg were noninferior to lansoprazole for maintenance of healing at Week 24 (80.7%, 79.2%, and 72.0% for vonoprazan 20 mg, vonoprazan 10 mg, and lansoprazole 15 mg, respectively) and superior in a secondary analysis of this endpoint.

Patients with Los Angeles Grade C and D EE have the lowest healing rate with PPIs and frequently relapse after treatment. In this subgroup, which comprised 34.3% of patients in the healing phase and 32.2% of those in the maintenance phase, rates of healing at week 2 were 70.2% and 52.6% in the vonoprazan and lansoprazole groups, respectively (superiority $P = 0.0008$) [37]. Although hypothesis testing was not performed because the prior endpoint (onset of sustained resolution of heartburn by day 3 in the total patient population) did not show superiority, healing rates at Week 8 were higher with vonoprazan 20 mg (91.7%) than with lansoprazole (72.0%) in this group. Healing was maintained at Week 24 in Los Angeles Grade C and D patients in 77.2% (with vonoprazan 20 mg) and 74.7% (with vonoprazan 10 mg) compared with 61.5% with lansoprazole 15 mg ($P = 0.020$ and $P = 0.049$, respectively).

The frequency and spectrum of adverse events were similar in the 2 groups [37]. Serum gastrin levels were relatively elevated with vonoprazan; however, there were no significant changes in gastric mucosal atrophy or neuroendocrine cell proliferation. Serum gastrin fell to similar levels in all 3 groups at a measurement conducted 4 weeks after the end of maintenance therapy.

The time course of relief of heartburn with vonoprazan was compared directly with lansoprazole in a small (N = 32) study conducted in Japan [51]. The study enrolled patients with EE and heartburn symptoms at least once weekly who were randomly allocated to double-blind treatment with vonoprazan 20 mg or lansoprazole 30 mg; daytime and nighttime symptoms were assessed on a 5-point scale. Complete relief of heartburn on day 1 was seen in 31.3% of patients who received vonoprazan vs 12.5% of those who received lansoprazole ($P < 0.05$) and heartburn relief was sustained from days 2 to 7 in more patients who received vonoprazan than those who received lansoprazole (hazard ratio [HR] 3.58; 95% CI 1.16–11.08; $P < 0.05$). Of note, from day 1, numerically more patients who received vonoprazan than lansoprazole experienced complete relief of daytime heartburn (37.5% vs 18.8%; $P = 0.07$) and significantly more experienced complete relief of nighttime heartburn (33.3% vs 9.1%; $P < 0.01$) for seven consecutive days.

The safety and efficacy of vonoprazan vs placebo for the as-needed treatment of symptomatic NERD were assessed in a phase 2, double-blind, placebo-controlled trial (NCT04799158) [52]. Following a 4-week run-in period in which all patients received once daily vonoprazan 20 mg, patients were randomized to vonoprazan dosages of 10, 20, or 40 mg or to placebo and instructed to take no more than 1 dose of study drug for 24 hours after a heartburn episode and to take no rescue antacids ≤3 hours after taking the study drug. Of the 407 patients who entered the run-in period, 207 had no heartburn episodes during the last 7 days of the run-in period and were randomized to treatment. Vonoprazan resulted in complete and sustained relief of heartburn episodes within 3 hours in 56.0% to 70.0% of patients, with a clear dose-response vs 27.3% for placebo patients ($P < 0.0001$ for all comparisons). Fewer patients in the vonoprazan groups (16.3% to 18.4%) reported treatment-emergent adverse events compared with placebo (21.3%).

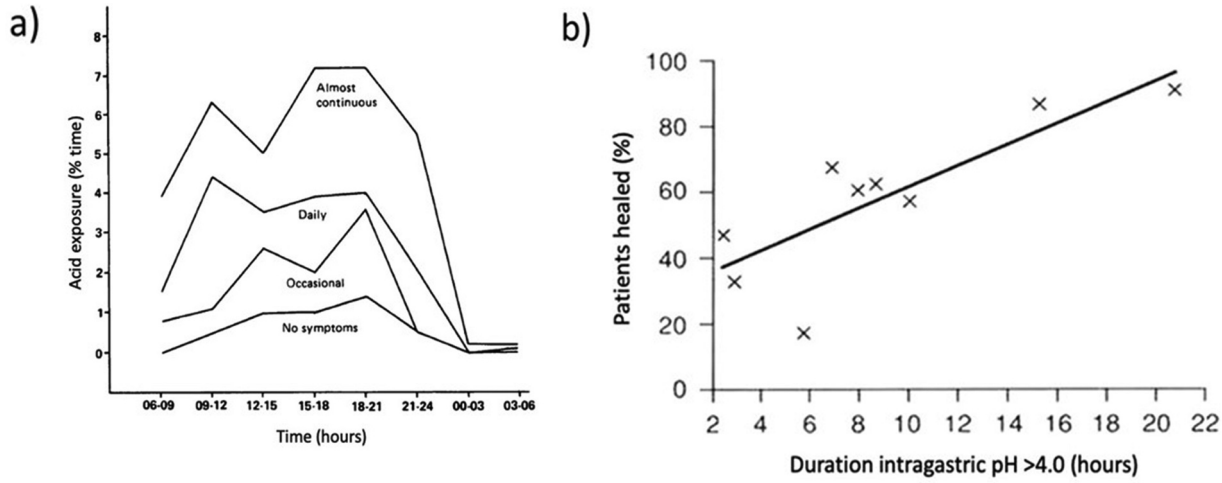

Figure 3. (a) Relationship between esophageal acid exposure (median percentage time spent with pH <4.0) and symptom severity in gastroesophageal reflux disease; (b) Relationship between erosive esophagitis healing at 8 weeks and duration (hours) of intragastic pH is >4.0. Adapted with permission from Joelsson 1989 and S. Karger AG, Basel, Bell 1992 [47,50].

Table 3. First-line treatment strategies for *Helicobacter pylori* infection, per the 2017 American College of Gastroenterology guidelines [1].

- Triple therapy (PPI, clarithromycin, amoxicillin or metronidazole [in regions where *H. pylori* clarithromycin resistance is <15% and in patients with no prior exposure to macrolides]) for 14 days
- Quadruple therapy (PPI, bismuth, tetracycline, and a nitroimidazole) for 10 to 14 days
- Concomitant therapy with a PPI, clarithromycin, amoxicillin, and a nitroimidazole for 10 to 14 days
- Sequential therapy with a PPI and amoxicillin for 5–7 days followed by a PPI, clarithromycin, and a nitroimidazole
- Hybrid therapy with a PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin, and a nitroimidazole for 7 days
- Triple therapy with a PPI, levofloxacin, and amoxicillin for 10–14 days
- Sequential therapy with a PPI and amoxicillin for 5–7 days followed by a PPI, fluroquinolone, and nitroimidazole for 5–7 days

PPI, proton pump inhibitor.

5. *Helicobacter pylori* infection and the role of vonoprazan

H. pylori, a Gram-negative, spiral, microaerophilic bacteria, is widely recognized as one of the few microorganisms that can survive the harsh acidic environment of the stomach [9,53]. The bacterium, which colonizes the gastric epithelium, can survive a pH as low as 2; however, it can only replicate at pH 6 to 8 – close to neutral [19,54]. It has several adaptations that allow it to survive in acidic conditions [9]. Among these is the activity of urease, which raises the pH of the periplasmic space to approximately 6.1, at which the bacterium can replicate [54]. Survival is compromised when mucosal pH drops to a point that cannot be compensated for by urease activity.

Chronic *H. pylori* infection has both gastric and extragastric manifestations, including, but not limited to, gastric and duodenal ulcer disease gastric cancer, and iron deficiency anemia [55–58]. The factors that drive the transition from chronic colonization to overt disease remain unknown. However, specific genetic polymorphisms in genes coding for cytokines and growth factors and environmental factors, including smoking, a low-iron or high-salt diet, and diets low in fresh fruits and vegetables have been implicated [9]. In vulnerable individuals, *H. pylori* incites an inflammatory response that can lead to tissue degeneration and injury, reduced stomach acid levels, dysbiosis, and ultimately progression to gastric cancer [9].

Because the antibiotics used to treat *H. pylori* are ineffective on quiescent cells, treatment of *H. pylori* relies on encouraging the bacteria to replicate. Acid suppression therapy is thus required for *H. pylori* eradication to raise intragastric pH to at least 6, which – as discussed above – is a level that enhances bacterial replication and allows growth-dependent antibiotics to exert their effects [54]. As in GERD, achieving an appropriate gastric pH and hold times above this pH are equally important determinants of therapeutic efficacy.

Guideline-recommended standard therapy for *H. pylori* is thus a PPI combined with antibiotics and, in some cases, bismuth [2]. At present, recommended strategies include, but are not limited to, triple therapy – a combination of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days; quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10 to 14 days; and concomitant therapy including a PPI, clarithromycin, amoxicillin, and a nitroimidazole for 10 to 14 days (Table 3) [2]. Regardless of whether double, triple, or bismuth-based quadruple therapy is used, prolonged acid inhibition pH >6 is critical for eradication therapy to be effective [21,59,60].

It is important to recognize that, like most bacterial pathogens, *H. pylori* can rapidly acquire antibiotic resistance under selective pressure [61]. The initial introduction of 7-day triple therapy regimens was associated with eradication rates of over 90% [62]. However, treatment failures have become more frequent over time even with the currently standard 14-day regimens owing largely to the development of resistance [9,61]. Because eradication rates have fallen substantially with triple therapy with clarithromycin and amoxicillin or metronidazole, guidelines indicate that it should be used

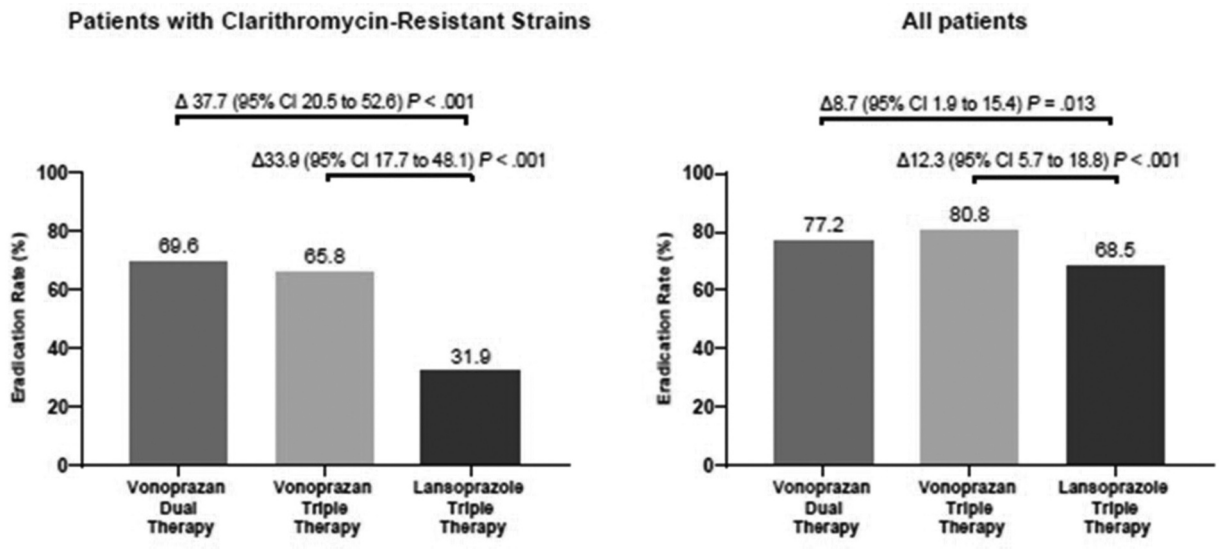

Figure 4. Eradication rates in a phase 3 trial of 14 days of vonoprazan double (amoxicillin) and triple (amoxicillin + clarithromycin) therapy vs lansoprazole triple (amoxicillin + clarithromycin) therapy. See text for details. Adapted from Chey 2022 [63].

only in regions where clarithromycin resistance is low (<15%) and in patients with no history of exposure to macrolides for any reason [1]. Ensuring eradication with the first line of therapy has thus become a priority, both because of the clinical need of the individual patient and from the broader perspective of antibiotic stewardship.

5.1 Clinical efficacy and safety of vonoprazan for H. pylori *eradication*

The efficacy of vonoprazan triple and dual therapy for *H. pylori* infection was evaluated in the randomized, controlled, phase 3 pHalcon-HP trial (NCT04167670) [63]. The trial randomized previously untreated adults with symptomatic, proven *H. pylori* infection (N = 1046) to 14 days of treatment with open-label vonoprazan dual therapy (20 mg vonoprazan twice daily, 1 g amoxicillin 3 times daily) or double-blind triple therapy twice daily (vonoprazan 20 mg or lansoprazole 30 mg in combination with amoxicillin 1 g and clarithromycin 500 mg). The primary endpoint was noninferiority for eradication rates in the population without clarithromycin- and amoxicillin-resistant strains.

Eradication rates in patients without clarithromycin- and amoxicillin-resistant strains were 78.5%, 84.7%, and 78.8% for vonoprazan dual therapy, vonoprazan triple therapy, and lansoprazole triple therapy, respectively; both vonoprazan regimens showed similar eradication rates to lansoprazole-based therapy (noninferiority $P < 0.001$) [63]. For the secondary endpoint of efficacy in clarithromycin-resistant infections, the corresponding values were 69.6%, 65.8%, and 31.9%, with both vonoprazan regimens demonstrating superiority over lansoprazole ($P < 0.001$ for both comparisons) (Figure 4). Across all patients, regardless of resistance status, vonoprazan dual and triple therapy were superior to lansoprazole-based triple therapy (77.2% [$P < 0.013$] and 80.8% [$P < 0.001$] vs 68.5%). All regimens were relatively well tolerated, with adverse events dominated by those commonly seen with antibiotic therapy. Serious treatment-emergent adverse events were infrequent, occurring in 1.4%, 1.7%, and 0.9% of the vonoprazan dual therapy, vonoprazan triple therapy, and lansoprazole triple therapy groups; corresponding discontinuation rates were 0.9%, 2.3%, and 1.2%.

A network meta-analysis was conducted assess the efficacy of first-line vonoprazan-containing therapies vs other *H. pylori* eradication regimens. The analysis included 12,773 patients enrolled in 42 trials using 23 distinct regimens [64]. In pairwise comparisons between PPI-based triple therapy and vonoprazan-based triple therapy, vonoprazan dual therapy, PPI plus high-dose amoxicillin, rifabutin-based triple delayed release therapy, and bismuth quadruple therapy, the highest relative efficacy was seen for vonoprazan-based triple therapy (odds ratio [OR], 2.73; 95% credible interval [CrI] 2.11–3.54), with a 72.1% probability of being the best of the regimens evaluated. When the analysis was restricted to trials conducted in North America, vonoprazan triple therapy continued to have the highest relative efficacy (OR 1.95; 95% CrI 1.36–2.79), with a 63.3% probability of being the best. A meta-analysis of vonoprazan- vs PPI-based eradication therapy also showed superiority of vonoprazan over PPI-based regimens in the second-line setting (OR 1.51; 95% confidence interval [CI] 1.27–1.81, $P < 0.001$) [65].

6. Conclusions

Abundant data have led to the first-line use of PPIs in GERD and *H. pylori* infection. Although these agents have been used for decades with success, it is clear that room remains for agents with different mechanistic, pharmacokinetic, and clinical profiles that may address the clinical needs of patients who do not achieve adequate results with PPIs. Vonoprazan, compared with PPIs, is associated with a more rapid onset of adequate acid suppression, increased hours above the critical

pH thresholds of 4 and 6, and the ability to dose independently of a meal, which may translate in the clinic to improved outcomes in terms of healing and maintenance of healing of GERD as well as *H. pylori* eradication.

The PPIs were an important clinical landmark in the management of acid-related disorders and will continue to be a critical element of therapy in both GERD and *H. pylori*. However, these agents are not universally effective. For the first time in several decades, the PCABs offer a differentiated clinical profile that may address areas of remaining unmet need, such as patients with uncontrolled nocturnal symptoms and those who are unable or unwilling to adhere to dosing recommendations for PPIs with regards to meals. Vonoprazan has demonstrated superiority over PPIs in the management of moderate-to-severe erosive GERD (Los Angeles Class C and D), a group that has proved challenging to treat with current agents. Vonoprazan may also offer a viable alternative to PPIs in patients who have failed to respond adequately to these drugs.

In *H. pylori*, it is likely that the improved acid suppression afforded by vonoprazan is responsible for the higher eradication rates seen in patients who received vonoprazan-based therapy relative to other commonly used eradication regimens, including PPI-based triple therapy, a potentially important consideration not only for patients but also for the broader concern of slowing the emergence *H. pylori* antibiotic resistance [61].

As discussed above, concerns have been raised regarding the risks of PPI treatment based on studies of generally poor methodologic quality [1]. Some subset of these concerns – particularly those linked to acid suppression as opposed to off-target effects – could also apply to PCABs. At present, the adverse event profile of the 2 drug classes appears similar. Vonoprazan has a well-established safety profile, with over 90 million patients having been exposed to the drug since its initial approval. However, idiosyncratic, PCAB-specific adverse events may emerge as vonoprazan enters broad clinical use in the United States.

Abbreviations

ATP	adenosine triphosphate
CYP	cytochrome
EE	erosive esophagitis
GERD	gastroesophageal reflux disease
KCNQ1	potassium voltage-gated channel subfamily Q member 1
NERD	non-erosive reflux disease
PCAB	potassium-competitive acid blocker
PPI	proton pump inhibitor

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References

1. Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2022 Jan 1; 117(1):27–56. doi: 10.14309/ajg.0000000000001538
2. Chey WD, Leontiadis GI, Howden CW, et al. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017 Feb;112(2):212–239.
3. Locke GR 3rd, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterol. 1997 May;112(5):1448–1456. doi: 10.1016/S0016-5085(97)70025-8
4. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005 May;54(5):710–717.
5. Katzka DA, Pandolfino JE, Kahrilas PJ. Phenotypes of gastroesophageal reflux disease: where rome, lyon, and montreal meet. Clin Gastroenterol Hepatol. 2020 Apr;18(4):767–776.
6. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. Gastroenterology. 2017 Aug;153(2):420–429. doi: 10.1053/j.gastro.2017.04.022
7. Shah SC, Halvorson AE, Lee D, et al. *Helicobacter pylori* Burden in the United States according to individual demographics and geography: a nationwide analysis of the veterans healthcare system. Clin Gastroenterol Hepatol. 2024 Jan;22(1):42–50 e26. doi: 10.1016/j.cgh.2023.05.016
8. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of *Helicobacter pylori* infection. Clin Microbiol Rev. 2006 Jul;19(3):449–490.
9. Malfertheiner P, Camargo MC, El-Omar E et al. *Helicobacter pylori* infection. Nat Rev Dis Primers. 2023 Apr 20;9(1):19. doi: 10.1038/s41572-023-00431-8
10. Wroblewski LE, Peek RM Jr, Wilson KT. *Helicobacter pylori* and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev. 2010 Oct;23(4):713–739.

11. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med. 2001 Sep 13;345(11):784–789. doi: 10.1056/NEJMoa001999
12. Vonquenza (vonoprazan) [prescribing information]. Buffalo Grove (IL): Phathom Pharmaceuticals, Inc; 2022.
13. Shibli F, Kitayama Y, Fass R. Novel therapies for gastroesophageal reflux disease: beyond proton pump inhibitors.Curr Gastroenterol Rep. 2020 Mar 17;22(4):16. doi: 10.1007/s11894-020-0753-y
14. Shin JM, Munson K, Vagin O, et al. The gastric HK-ATPase: structure, function, and inhibition. Pflugers Arch. 2009 Jan;457(3):609–622.
15. Beil W, Hackbarth I, Sewing KF. Mechanism of gastric antisecretory effect of SCH 28080. Br J Pharmacol. 1986 May;88(1):19–23.
16. Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil. 2013 Jan;19(1):25–35.
17. Engevik AC, Kaji I, Goldenring JR. The Physiology of the Gastric Parietal Cell.Physiol Rev. 2020 Apr 1;100(2):573–602. doi: 10.1152/physrev.00016.2019
18. Yao X, Forte JG. Cell biology of acid secretion by the parietal cell. Annu Rev Physiol. 2003;65(1):103–131.
19. Scott D, Weeks D, Melchers K, et al. The life and death of *Helicobacter pylori*. Gut. 1998 Jul;43(Suppl 1):S56–S60.
20. Marieb EN, Brady PM, Mallatt JB. Human anatomy. New Jersey: Pearson; 2019.
21. Sjostedt S, Sagar M, Lindberg G, et al. Prolonged and profound acid inhibition is crucial in *Helicobacter pylori* treatment with a proton pump inhibitor combined with amoxicillin. Scand J Gastroenterol. 1998 Jan;33(1):39–43. doi: 10.1080/00365529850166185
22. Schade C, Flemstrom G, Holm L. Hydrogen ion concentration in the mucus layer on top of acid-stimulated and -inhibited rat gastric mucosa. Gastroenterology. 1994 Jul;107(1):180–188.
23. Lambrecht NW, Yakubov I, Scott D, et al. Identification of the K efflux channel coupled to the gastric H-K-ATPase during acid secretion.Physiol Genomics. 2005 Mar 21;21(1):81–91. doi: 10.1152/physiolgenomics.00212.2004
24. Gedda K, Scott D, Besancon M, et al. Turnover of the gastric H+,K(+)-adenosine triphosphatase alpha subunit and its effect on inhibition of rat gastric acid secretion. Gastroenterology. 1995 Oct;109(4):1134–1141. doi: 10.1016/0016-5085(95)90571-5
25. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep. 2008 Dec;10(6):528–534.
26. ClinicalTrials.gov. A study to evaluate the efficacy and safety of BLI5100 in patients with non-erosive reflux disease. [cited 2023 Sept 3]. Available from: https://classic.clinicaltrials.gov/study/NCT05587322.2023
27. ClinicalTrials.gov. A study to evaluate the efficacy and safety of BLI5100 in patients with erosive esophagitis. [cited 2023 Sept 1]. Available from: https://classic.clinicaltrials.gov/study/NCT05587309. 2023.
28. Abdel-Aziz Y, Metz DC, Howden CW. Review article: potassium-competitive acid blockers for the treatment of acid-related disorders. Aliment Pharmacol Ther. 2021 Apr;53(7):794–809.
29. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2006 Jun;23 Suppl 2(s2):2–8.
30. Wiesner A, Zwolinska-Wcislo M, Pasko P. Effect of food and dosing regimen on safety and efficacy of proton pump inhibitors therapy-a literature review.Int J Environ Res Public Health. 2021 Mar 29;18(7):3527. doi: 10.3390/ijerph18073527
31. Srebro J, Brniak W, Mendyk A. Formulation of dosage forms with proton pump inhibitors: state of the art, challenges and future perspectives.Pharmaceutics. 2022 Sep 25 14(10):2043. doi: 10.3390/pharmaceutics14102043
32. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. Expert Opin Drug Metab Toxicol. 2018 Apr;14(4):447–460.
33. Furuta T, Shirai N, Sugimoto M, et al. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. Drug Metab Pharmacokinet. 2005 Jun;20(3):153–167. doi: 10.2133/dmpk.20.153
34. Bundhun PK, Teeluck AR, Bhurtu A et al. Is the concomitant use of clopidogrel and proton pump inhibitors still associated with increased adverse cardiovascular outcomes following coronary angioplasty?: a systematic review and meta-analysis of recently published studies (2012 - 2016).BMC Cardiovasc Disord. 2017 Jan 5;17(1):3. doi: 10.1186/s12872-016-0453-6
35. Jenkins H, Sakurai Y, Nishimura A, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther. 2015 Apr;41(7):636–648. doi: 10.1111/apt.13121
36. Echizen H. the first-in-class potassium-competitive acid blocker, vonoprazan fumarate: pharmacokinetic and pharmacodynamic considerations. Clin Pharmacokinet. 2016 Apr;55(4):409–418.
37. Laine L, DeVault K, Katz P, et al. Vonoprazan versus lansoprazole for healing and maintenance of healing of erosive esophagitis: a randomized trial. Gastroenterology. 2023 Jan;164(1):61–71. doi: 10.1053/j.gastro.2022.09.041
38. Scott DR, Munson KB, Marcus EA, et al. The binding selectivity of vonoprazan (TAK-438) to the gastric H+K+-ATPase. Aliment Pharmacol Ther. 2015 Dec;42(11–12):1315–1326. doi: 10.1111/apt.13414
39. Hori Y, Imanishi A, Matsukawa J, et al. 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (TAK-438), a novel and potent potassium-competitive acid blocker for the treatment of acid-related diseases. J Pharmacol Exp Ther. 2010 Oct;335(1):231–238. doi: 10.1124/jpet.110.170274
40. Laine L, Sharma P, Mulford DJ, et al. Pharmacodynamics and pharmacokinetics of the potassium-competitive acid blocker vonoprazan and the proton pump inhibitor lansoprazole in US subjects. Am J Gastroenterol. 2022 Jul 1;117(7):1158–1161. doi: 10.14309/ajg.0000000000001735
41. Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects–a randomised open-label cross-over study. Aliment Pharmacol Ther. 2015 Sep;42(6):719–730. doi: 10.1111/apt.13325
42. Takeuchi T, Furuta T, Fujiwara Y, et al. Randomised trial of acid inhibition by vonoprazan 10/20 mg once daily vs rabeprazole 10/20 mg twice daily in healthy Japanese volunteers (SAMURAI pH study). Aliment Pharmacol Ther. 2020 Mar;51(5):534–543. doi: 10.1111/apt.15641
43. Sakurai Y, Nishimura A, Kennedy G, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising TAK-438 (Vonoprazan) doses in healthy male Japanese/non-Japanese Subjects. Clin Transl Gastroenterol. 2015 Jun 25;6(6):e94. doi: 10.1038/ctg.2015.18
44. Bansal A, Kahrilas PJ. Treatment of GERD complications (Barrett's, peptic stricture) and extra-oesophageal syndromes. Best Pract Res Clin Gastroenterol. 2010 Dec;24(6):961–968.
45. Savarino E, Zentilin P, Savarino V. NERD: an umbrella term including heterogeneous subpopulations. Nat Rev Gastroenterol Hepatol. 2013 Jun;10(6):371–380.
46. Armstrong D. Review article: gastric pH – the most relevant predictor of benefit in reflux disease? Aliment Pharmacol Ther. 2004 Oct;20(Suppl 5):19–26.discussion 38-9
47. Joelsson B, Johnsson F. Heartburn–the acid test. Gut. 1989 Nov;30(11):1523–1525.
48. Johnson DA, Katz PO, Levine D, et al. Prevention of relapse of healed reflux esophagitis is related to the duration of intragastric pH > 4. J Clin Gastroenterol. 2010 Aug;44(7):475–478. doi: 10.1097/MCG.0b013e3181dd9c5b
49. Carlsson R, Galmiche JP, Dent J, et al. Prognostic factors influencing relapse of oesophagitis during maintenance therapy with antisecretory drugs: a meta-analysis of long-term omeprazole trials. Aliment Pharmacol Ther. 1997 Jun;11(3):473–482. doi: 10.1046/j.1365-2036.1997.00167.x
50. Bell NJV, Burger D, Howden CW. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. Digestion. 1992;51(1):59–67.

51. Oshima T, Arai E, Taki M, et al. Randomised clinical trial: vonoprazan versus lansoprazole for the initial relief of heartburn in patients with erosive oesophagitis. Aliment Pharmacol Ther. 2019 Jan;49 (2):140–146. doi: 10.1111/apt.15062
52. Fass R, Vaezi M, Sharma P, et al. Randomised clinical trial: efficacy and safety of on-demand vonoprazan versus placebo for non-erosive reflux disease. Aliment Pharmacol Ther. 2023 Sep 26;58 (10):1016–1027. doi: 10.1111/apt.17728
53. Scott DR, Marcus EA, Wen Y, et al. Gene expression in vivo shows that *Helicobacter pylori* colonizes an acidic niche on the gastric surface. Proc Natl Acad Sci USA. 2007 Apr 24;104(17):7235–7240. doi: 10.1073/pnas.0702300104
54. Scott DR, Sachs G, Marcus EA. The role of acid inhibition in *Helicobacter pylori* eradication. F1000Res. 2016;5:1747.
55. Sipponen P, Varis K, Fraki O, et al. Cumulative 10-year risk of symptomatic duodenal and gastric ulcer in patients with or without chronic gastritis. A clinical follow-up study of 454 outpatients. Scand J Gastroenterol. 1990 Oct;25(10):966–973. doi: 10.3109/00365529008997621
56. Yamagata H, Kiyohara Y, Aoyagi K, et al. Impact of *Helicobacter pylori* infection on gastric cancer incidence in a general Japanese population: the Hisayama study. Arch Intern Med. 2000 Jul 10;160 (13):1962–1968. doi: 10.1001/archinte.160.13.1962
57. Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med. 1991 Oct 17;325(16):1127–1131. doi: 10.1056/NEJM199110173251603
58. Wong F, Rayner-Hartley E, Byrne MF. Extraintestinal manifestations of *Helicobacter pylori*: a concise review.World J Gastroenterol. 2014 Sep 14;20(34):11950–11961. doi: 10.3748/wjg.v20.i34.11950
59. Sugimoto M, Furuta T, Shirai N, et al. Evidence that the degree and duration of acid suppression are related to *Helicobacter pylori* eradication by triple therapy. Helicobacter. 2007 Aug;12(4):317–323. doi: 10.1111/j.1523-5378.2007.00508.x
60. Ke H, Li J, Lu B, et al. The appropriate cutoff gastric pH value for *Helicobacter pylori* eradication with bismuth-based quadruple therapy. Helicobacter. 2021 Feb;26(1):e12768. doi: 10.1111/hel.12768
61. Moss SF, Chey WD, Daniele P, et al. Brief communication: global temporal trends in the efficacy of clarithromycin-based regimens for the treatment of *Helicobacter pylori* infection. Therap Adv Gastroenterol. 2023;16:17562848231167284.
62. Lind T, Megraud F, Unge P, et al. The MACH2 study: role of omeprazole in eradication of *Helicobacter pylori* with 1-week triple therapies. Gastroenterology. 1999 Feb;116(2):248–253. doi: 10.1016/S0016-5085(99)70119-8
63. Chey WD, Megraud F, Laine L, et al. Vonoprazan triple and dual therapy for *Helicobacter pylori* infection in the United States and Europe: randomized clinical trial. Gastroenterology. 2022 Sep;163 (3):608–619. doi: 10.1053/j.gastro.2022.05.055
64. Malfertheiner P, Moss SF, Daniele P, et al. Potassium-Competitive Acid Blocker and Proton Pump Inhibitor–Based Regimens for First-Line *Helicobacter pylori* Eradication: a Network Meta-Analysis. Gastro Hep Advances. 2022;1(5):824–834.
65. Shinozaki S, Kobayashi Y, Osawa H, et al. Effectiveness and safety of vonoprazan versus proton pump inhibitors for second-line *helicobacter pylori* eradication therapy: systematic review and meta-analysis. Digestion. 2021;102(3):319–325. doi: 10.1159/000504939