



Role of Acid Suppression in Acid-related Diseases: Proton Pump Inhibitor and Potassium-competitive Acid Blocker

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Proton pump inhibitors are commonly utilized for the treatment of gastric acid-related diseases, such as gastroesophageal reflux disease, peptic ulcer disease, and *Helicobacter pylori* infection, and for the prevention of low-dose aspirin or nonsteroidal anti-inflammatory drug-induced peptic ulcers. Vonoprazan is a first-in-class potassium-competitive acid blocker, which has distinct advantages compared to other conventional proton pump inhibitors in terms of the efficacy for acid suppression. Due to its strong gastric acid suppression capabilities, vonoprazan serves as an effective drug for the treatment of gastroesophageal reflux disease and *H. pylori* infection.

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Key Words

Gastroesophageal reflux; *Helicobacter pylori*; Peptic ulcer; Potassium; Proton pump inhibitors

Introduction

Gastric acid secretory inhibitors are effective agents in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and *Helicobacter pylori* infection, and in the prevention of low-dose aspirin (LDA) or nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcers.¹⁻⁵ Since the market release of proton pump inhibitors (PPIs) in the late 1980s, the severity of the situation regarding gastric acid-related conditions improved dramatically. Vonoprazan, a first-in-class potassium-competitive acid blocker (P-CAB) made in Japan, appeared on the market in 2015, and exhibited rapid, strong, and continuous gastric acid suppres-

sion.⁶ As new P-CABs are becoming available, the standard treatment for acid-related conditions is changing.

Pharmacology of Proton Pump Inhibitor

PPIs are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production by inhibiting the H⁺/K⁺-ATPase enzyme system on the surface of parietal cells.⁷ PPIs are prodrugs which are activated by acid and bind covalently to the gastric H⁺/K⁺-ATPase via a disulfide bond.⁸ Omeprazole was the first PPI introduced, followed by lansoprazole, pantoprazole, rabeprazole, and esomeprazole. PPIs have stronger inhibitory effect on gastric acid secretion than histamine H₂ receptor antago-

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nists (H2RAs).⁷ PPIs are metabolized and inactivated by a number of cytochrome P450 (CYP) enzymes (CYP2C9, CYP2C8, CYP2C18, CYP2C19, CYP3A4, CYP3A1A2, and CYP3A4), mainly CYP2C19 and CYP3A4.⁹ The distribution of CYP2C19 phenotypes was divided into 4 phenotypes: extensive metabolizers (EM), intermediate metabolizers, ultra-rapid metabolizers, and poor metabolizers.¹⁰ CYP2C19 is responsible for > 80% of the metabolism of omeprazole, lansoprazole, and pantoprazole metabolism.¹¹ Esomeprazole, the S-isomer of omeprazole, is metabolized to a less extent by CYP2C19 than omeprazole.¹² Rabeprazole is mainly metabolized via a non-enzymatic reduction to rabeprazole thioether.⁹ Therefore, the effectiveness of omeprazole and lansoprazole is sometimes insufficient in EM and ultra-rapid metabolizers.¹³ Another issue with PPIs is that the effect on gastric acid secretion is slow and reaches a plateau in 3-5 days because several doses are required to inhibit newly synthesized proton pumps and achieve maximal acid-inhibition.¹⁴⁻¹⁶

Pharmacology of Potassium-competitive Acid Blockers

P-CAB is a class of drug that competitively blocks the potassium-binding site of the gastric H^+/K^+ -ATPase.⁶ The first P-CAB used in clinical practice was revaprazan, which has been available in South Korea and India since 2007. Revaprazan showed an early effect on acid suppression.¹⁷ However, the effect was not superior to conventional PPIs for the treatment of endoscopic submucosal dissection-induced ulcers¹⁸ and there are no reports that revaprazan is more effective than PPIs for the other gastric acid-related conditions. In 2015, vonoprazan became the second P-CAB available in the Japanese market, and it is now available in the Philippines, Singapore, and Thailand. Tegoprazan was approved as a treatment for GERD in South Korea since July 2018. Other P-CABs (YH4808, DWP14012, and KFP-H008) are still in clinical trials.¹⁹⁻²³

Vonoprazan was significantly effective in the treatment of *H. pylori* infection, GERD, and LDA-induced peptic ulcers.^{6,24} There are several advantages to using vonoprazan than conventional PPIs from a pharmacological point of view. It is rapidly absorbed in the small intestine where it accumulated in the canalicular membranes of parietal cells²⁵ and it shows a greater acid-inhibitory effect than those of esomeprazole and rabeprazole, as observed from the first day of administration.²⁶ It also has a longer duration of action. The pH 4 holding time ratios of vonoprazan were significantly longer than those of esomeprazole and rabeprazole.²⁶ It does not require acid activation, whereas PPIs are acid-activated prodrugs that re-

quire acid protection. In addition, vonoprazan has a higher value of alkaline pKa (> 9) than PPIs, and previous P-CABs can be easily protonated and accumulated at high concentrations in the intracellular canaliculi of parietal cells.^{6,8} As such, vonoprazan is more stable in an acidic environment than PPIs.²⁷ In addition, vonoprazan is shown to have consistent acid suppression capabilities irrespective of CYP2C19. It is metabolized to its inactive form mainly by CYP3A4, and partially also by CYP2B6, CYP2C19, CYP2D6, and SULT2A1, whereas most PPIs are mainly metabolized by CYP2C19.²⁸ Therefore, vonoprazan showed quite rapid, strong, and continuous gastric acid suppression when compared to conventional PPIs. Tegoprazan is another potent and highly selective inhibitor of gastric H^+/K^+ -ATPase. Interestingly, tegoprazan evoked a gastric phase III contraction of the migrating motor complex in a canine model.¹⁹ YH4808 had a faster onset than esomeprazole and can maintain an intra-gastric acidity of pH > 4 for a longer time during both day and night in healthy volunteers.²⁰ DWP14012 showed rapid and sustained suppression of gastric acid secretion in healthy volunteers.²² KFP-H008 showed a more effective, potent, and longer-lasting inhibitory action than lansoprazole in a rat model.²³ However, there are no reports about the usefulness of tegoprazan, YH4808, DWP14012, and KFP-H008 in actual clinical practice.

Gastroesophageal Reflux Disease

For most patients with GERD, PPIs are the first choice of treatment.²⁴ A recent Japanese guideline for GERD recommended the use of PPIs as first-line and maintenance treatments (Fig. 1A).²⁹ PPIs were shown to be superior to H2RAs in healing erosive esophagitis and decreasing relapse rates.³⁰⁻³² A randomized study suggested that esomeprazole has a more rapid effect against heartburn and reflux symptoms than omeprazole, lansoprazole, and pantoprazole; however, there was no significant difference in the rate of endoscopic healing of reflux esophagitis at 8 weeks.³³ Despite this, most studies determined that there is no notable difference in effect among PPIs in terms of short-term symptom management.³⁴

Vonoprazan could be the first-line drug in the future. In CYP2C19 EM patients with erosive esophagitis, 90.0% treated with vonoprazan (20 mg/day) achieved mucosal healing at 2 weeks compared with the 79.3% that were treated with lansoprazole ($P < 0.01$).³⁵ Similarly, at 4 and 8 weeks, the proportion of patients with healed erosive esophagitis tended to be higher in the vonoprazan group than in the lansoprazole group (at 4 weeks 96.1% vs 90.9%, $P < 0.05$; at 8 weeks 98.9% vs 94.5%, $P < 0.03$).³⁵ Moreover, vonoprazan was more effective for severe erosive esophagitis (Los

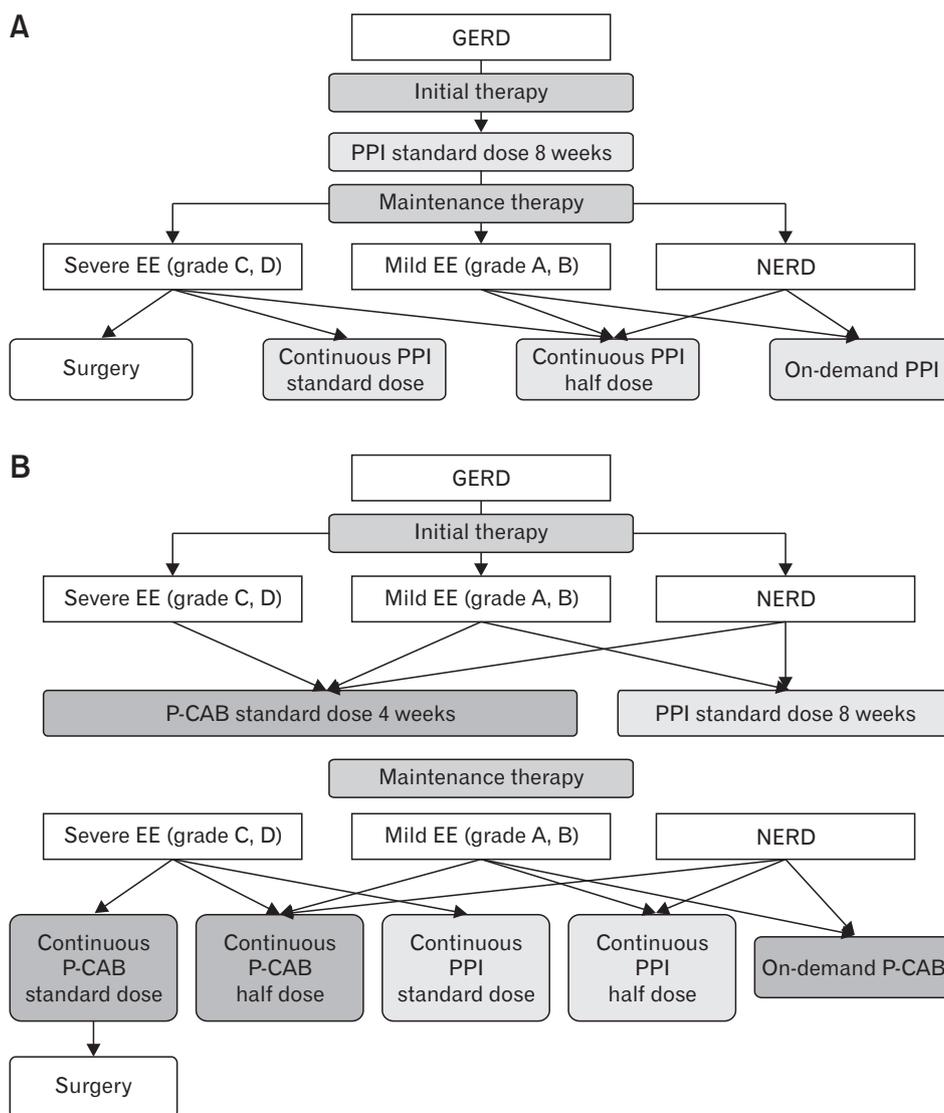


Figure 1. Strategy of gastroesophageal reflux disease (GERD) treatment. (A) Conventional strategy of GERD treatment (an abridged edition of the Evidence-based Clinical Practice Guidelines for GERD 2015 published by the Japanese Society of Gastroenterology).²⁹ Initial treatment is administration of proton pump inhibitor (PPI) standard dose for 8 weeks. Then, maintenance treatment is administration of PPI half dose daily. If incomplete healing occurs, maintenance with continuous PPI standard dose is permissible. On-demand PPI treatment is alternative management strategy. (B) The authors propose a new strategy of GERD treatment considering the effectiveness of potassium-competitive acid blocker (P-CAB). Initial treatment is 4-week treatment with P-CAB standard dose for severe erosive esophagitis. Four-week treatment with P-CAB or 8-week treatment with PPI are recommended as an initial therapy for mild erosive esophagitis or non-erosive reflux disease (NERD). Then, maintenance treatment is administration of P-CAB half dose daily. If incomplete healing, maintenance with continuous P-CAB standard dose is permissible. Continuous PPI standard or half dose daily is one of the options. On-demand P-CAB treatment is a workable alternative management strategy. The severity of reflux esophagitis is classified according to the Los Angeles classification. EE, erosive esophagitis.

Angela classification grades C/D) than lansoprazole (at 8 weeks 98.7% vs 87.5%, $P < 0.01$) and had more rapid effectiveness (at 2 weeks 88.0% vs 63.9%, $P < 0.01$; at 4 weeks 96.0% vs 80.6%, $P < 0.03$).³⁵ Therefore, vonoprazan is highly effective for patients with more severe erosive esophagitis and CYP2C19 EM patients.

Even in whole patients, vonoprazan is more effective than lansoprazole at each time point (at 2 weeks 90.7% vs 81.9%, $P < 0.01$; at 4 weeks 96.6% vs 92.5%, $P < 0.01$; at 8 weeks 99.0% vs 95.5%, $P < 0.01$). On the other contrary, no data showed that P-CAB was effective to relieve the symptoms of mild esophagitis and NERD.

A non-randomized, controlled trial reported that 4-week treatment with vonoprazan (20 mg/day) was effective to relieve symptoms in 66.7% of NERD patients and 53.8% of PPI-resistant NERD patients.³⁶ In summary, 4-week treatment with vonoprazan (20 mg/day) was effective as an initial therapy for severe erosive esophagitis (Fig. 1B), and 4-week treatment with vonoprazan and 8-week treatment with a PPI were recommended as initial therapies for mild erosive esophagitis and NERD (Fig. 1B). Conventionally, double dose PPI therapy, combination therapy of PPI and H2RA and the addition of a prokinetic agent to PPI were used for PPI-resistant reflux esophagitis (Fig. 2A).³⁷⁻⁴⁰ Vonoprazan seems to be effective for PPI-resistant reflux esophagitis.⁴¹ Twenty-four PPI-resistant reflux esophagitis patients were enrolled in this study and 58.3% had severe erosive esophagitis. In total, 87.5% of the whole patients and 85.7% of severe erosive esophagitis patients achieved endoscopic healing of erosive esophagitis at 4 weeks after drug change from PPI to vonoprazan (20 mg/day).⁴¹ In addition, the symptoms of GERD were significantly improved from the day after drug change.⁴¹ Vonoprazan (40 mg/day) rescue therapy may also be useful for PPI-resistant reflux esophagitis.⁴² Shinozaki et al⁴³ reported that vonoprazan (10 mg/day; maintenance dose) treatment is also effective for PPI-resistant reflux esophagitis. Thus, we believe that the first choice for the treatment of PPI-resistant reflux esophagitis will be vonoprazan in the near future (Fig. 2B). There is no evidence of P-CAB plus prokinetic combination treatment for PPI-resistant reflux esophagitis until now. Further study is needed to additional effect of prokinetics on P-CAB based treatment.

Continuous administration of vonoprazan (10 mg/day or 20 mg/day) is more efficacious than that of lansoprazole (15 mg/day) in maintaining healed erosive esophagitis.⁴⁴ Therefore, at present, the optimal maintenance strategy for erosive esophagitis is continuous administration of vonoprazan at 10 mg/day (Fig. 1B). In addition, on-demand PPI therapy is an attractive option for long-term management of GERD. However, because of the slow onset of action of PPIs, their efficacy is sometimes insufficient.⁴⁵ Umezawa et al⁴⁶ showed that on-demand therapy using vonoprazan is more effective than continuous PPI treatment as an alternative maintenance therapy for patients with mild erosive esophagitis. These data could change the strategy of GERD treatment around the world (Fig. 1B). Comparative clinical studies are being conducted on an every-other-day administration of vonoprazan (20 mg/day) and lansoprazole (15 mg/day) as maintenance treatments for erosive esophagitis.⁴⁷ There is little evidence on other P-CABs being used to successfully treat GERD. A phase-III clinical trial on reflux esophagitis is currently being conducted in Korea to compare the

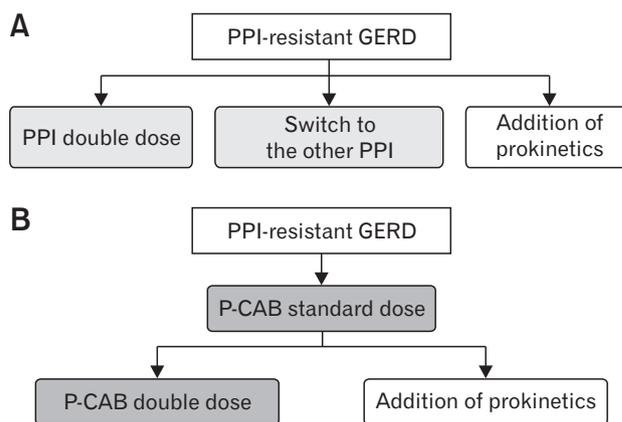


Figure 2. Strategy of proton pump inhibitor (PPI)-resistant gastroesophageal reflux disease (GERD) treatment. (A) Conventional strategy of PPI-resistant GERD treatment (an abridged edition of the Evidence-based Clinical Practice Guidelines for GERD 2015 published by the Japanese Society of Gastroenterology).²⁹ First choice is double dose PPI therapy. Switching to the other PPI is an option. Addition of prokinetics to PPI is effective in some cases. (B) The authors propose a new strategy of PPI-resistant GERD treatment. First choice is administration of potassium-competitive acid blocker (P-CAB) standard dose. Addition of prokinetics to P-CAB may have an additional effect.

safety and efficacy of a new P-CAB, tegoprazan (50 mg and 100 mg), with those of esomeprazole 40 mg.⁶

Helicobacter pylori Eradication

Induction of a strong acid inhibition stimulates growth of *H. pylori* and increases the bactericidal effect of amoxicillin, hence, PPIs are important for *H. pylori* eradication.⁴⁸ A meta-analysis revealed that high-dose PPIs are more effective than standard-dose for curing an *H. pylori* infection.⁴⁹ CYP2C19 polymorphisms are associated with the efficacy of PPI-based *H. pylori* eradication therapy. The eradication rates of triple omeprazole and lansoprazole therapies were lower in EM than in the other groups.^{50,51} Eradication regimens involving esomeprazole, rabeprazole, and new generation PPIs showed better overall *H. pylori* eradication rates (especially those in CYP2C19 EM patients) than those involving omeprazole, lansoprazole, and pantoprazole.⁵²

Vonoprazan-amoxicillin-clarithromycin triple regimen dramatically improved the eradication rate of first-line *H. pylori* treatment. The eradication rate was 92.6% with vonoprazan-based triple therapy versus 75.9% with lansoprazole-based triple therapy.⁵³ The eradication rate was significantly higher with vonoprazan compared with lansoprazole in those patients infected with clarithromycin-

resistant strains (82.0% vs 40.0%, $P < 0.01$).⁵³ In CYP2C19 EM patients, the eradication rate of vonoprazan-based triple therapy was significantly higher than that of lansoprazole-based triple therapy (92.9% vs 75.0%, $P < 0.01$).⁵³ In CYP2C19 PM patients, there was no significant difference, but the rate of vonoprazan-based triple therapy was high compared with the rate of lansoprazole-based triple therapy (90.9% vs 81.3%, $P = \text{NS}$). Conversely, the rate of the second-line metronidazole and amoxicillin-based triple therapy did not differ significantly between the PPI and vonoprazan groups (96.8% vs 90.5%, $P = \text{NS}$).⁵⁴ A meta-analysis showed that vonoprazan- and conventional PPI-based therapies are similarly effective in eradicating clarithromycin-susceptible *H. pylori* strains (95.4% vs 92.8%, $P = 0.230$), and that vonoprazan-based triple therapy was significantly superior to PPI-based therapy in treating patients infected with clarithromycin-resistant *H. pylori* strains (82.0% vs 40.0%, $P < 0.01$).⁵⁵ Ono et al⁵⁶ showed that a clarithromycin-metronidazole-vonoprazan regimen had greater efficacy than clarithromycin-metronidazole-PPI regimen for penicillin allergy patients (92.9% vs 54.6%, $P < 0.01$). There is geographic distribution of resistance to clarithromycin and metronidazole in *H. pylori*. High resistance to clarithromycin and low resistance to metronidazole are found in Japan.⁵⁷ Further studies are needed to evaluate the efficacy of vonoprazan-based therapy because vonoprazan has been approved only in Japan, Philippines, Singapore, and Thailand at this time. The Maastricht V/Florence Consensus Report recommended that the optimal regimen should be selected with the prevalence of antibiotic resistance rates (Fig. 3A).⁵⁸ Amoxicillin-clarithromycin-PPI triple therapy without prior susceptibility testing should be abandoned when the clarithromycin resistance rate in the region is more than 15%.⁵⁸ In the area with high resistance to clarithromycin and low resistance to metronidazole, amoxicillin-metronidazole-PPI triple regimen is recommended.⁵⁸ In the area with dual resistance to clarithromycin and metronidazole, bismuth quadruple therapy is recommended. As a rescue treatment, bismuth quadruple therapy or quinolone-containing therapy is recommended.⁵⁸ In the area with low resistance to clarithromycin, we recommend the amoxicillin-clarithromycin-vonoprazan triple regimen. If antimicrobial susceptibility testing is available, amoxicillin-clarithromycin-PPI triple regimen can be an alternative choice. In the area with high resistance to clarithromycin and low resistance to metronidazole, amoxicillin-metronidazole-vonoprazan or PPI triple regimen is recommended because there is no evidence of the amoxicillin-metronidazole-vonoprazan triple regimen being more effective than the amoxicillin-metronidazole-PPI triple regimen. Little has been reported on bismuth quadruple therapy, quinolone-containing therapy, and vo-

noprazan (or other P-CABs)-based concomitant therapy; therefore, studies on this regard are expected (Fig. 3B). Currently, a phase III clinical trial for *H. pylori* eradication is being conducted in Korea to compare tegoprazan-amoxicillin-clarithromycin triple regimen with lansoprazole-amoxicillin-clarithromycin triple regimen.

Low-dose Aspirin or Nonsteroidal Anti-inflammatory Drug-induced Peptic Ulcers

The use of LDA in the prevention of atherothrombosis is frequently associated with a development of erosions or ulcerations in the upper gastrointestinal tract. Compared to controls, PPIs reduced the risk of LDA-induced peptic ulcers but did not increase the risk of mortality.^{59,60} Another meta-analysis showed that PPIs were superior to H2RAs for prevention of LDA-induced peptic ulcers.⁵ PPIs are also effective and safe in preventing NSAID-induced peptic ulcers when compared to placebos and H2RAs.^{61,62} Recently, vonoprazan showed an equivalent efficacy to that of lansoprazole in preventing LDA-induced ulcer recurrence (Farrington and Manning test: margin 8.7%, significance level 2.5%). At the same time, peptic ulcer recurrence rates were significantly lower with vonoprazan 10 mg than with lansoprazole 15 mg, as shown by the results of the *post hoc* analyses of the extension study (log-rank test, $P = 0.039$).⁶³ The 24-week peptic ulcer recurrence rate was 2.8% and 0.5% in the lansoprazole (15 mg) and vonoprazan (10 mg) groups, respectively. With regard to NSAID-induced peptic ulcers, vonoprazan showed better efficacy.⁶⁴ The proportion of patients with endoscopically confirmed recurrent NSAID-induced peptic ulcers within 24 weeks was 3.3%, 3.4%, and 5.5%, for vonoprazan (10 mg, 20 mg) and lansoprazole (15 mg), respectively.⁶⁴

Complications

The long-term use of PPIs could cause the development of fundic gland polyps, carcinoid tumors, increase the risk of community acquired pneumonia, iron and vitamin B12 deficiencies, *Clostridium difficile*-associated diarrhea, dementia, and chronic kidney disease.^{25,65-72} Clinical trials evaluating the safety and tolerability of vonoprazan revealed that most of treatment-emergent adverse events with vonoprazan were mild in intensity and there was no obvious trend towards an increase in incidence over time up to 52 weeks of treatment.^{35,63} In these trials, hepatotoxicity was rarely observed. One differential characteristic of vonoprazan is that it is a pyrrole derivative, whereas previous P-CABs are imidazole-pyridine

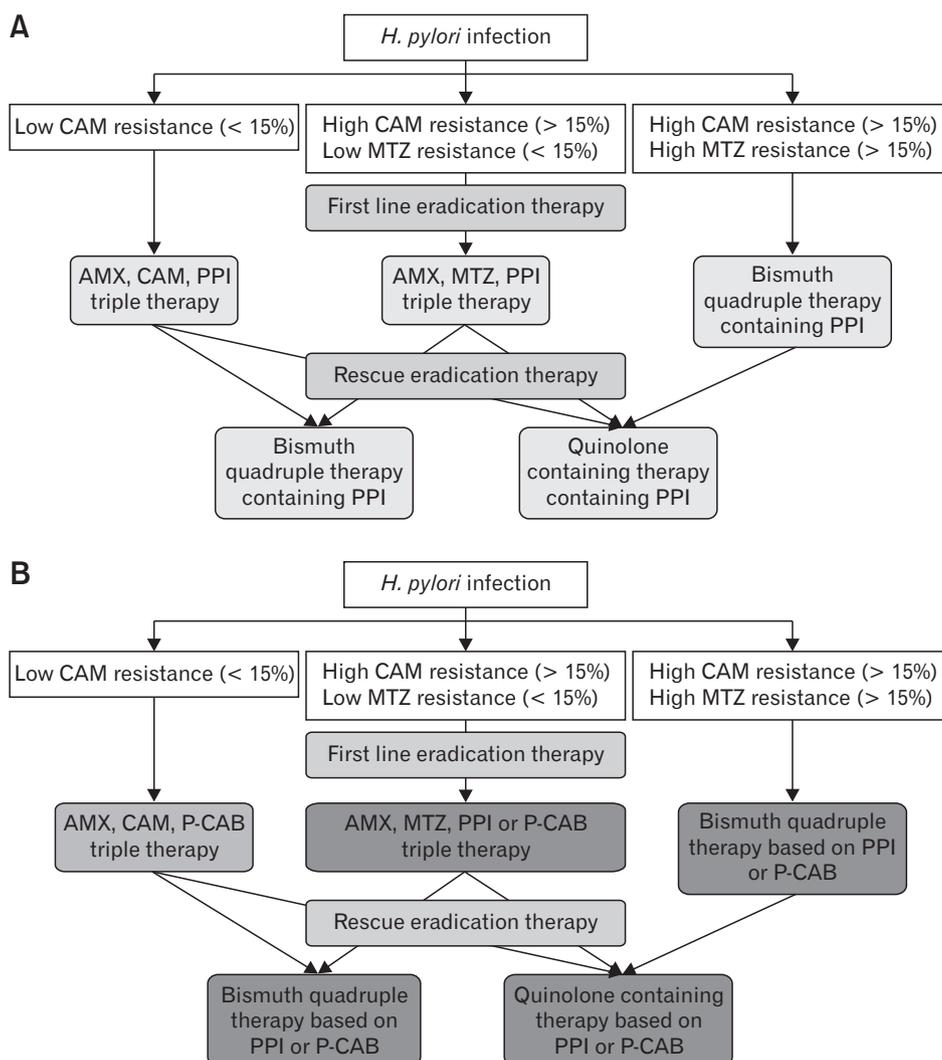


Figure 3. Strategy of proton pump inhibitor (PPI)-resistant *Helicobacter pylori* (*H. pylori*) eradication treatment. (A) Conventional strategy of *H. pylori* eradication treatment (an abridged edition of Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report published by the European Helicobacter and Microbiota Study Group).⁵⁸ In areas of low clarithromycin (CAM) resistance (< 15%), amoxicillin (AMX), CAM, and PPI triple therapy is the recommended first-line treatment. In areas of high CAM resistance (> 15%) and low metronidazole (MTZ) resistance (< 15%), AMX, MTZ, and PPI triple therapy is recommended. In areas of dual resistance, bismuth quadruple therapy is recommended. Quinolone containing therapy and bismuth quadruple therapy are recommended as rescue therapy. (B) The authors propose a new strategy of *H. pylori* eradication treatment. AMX, CAM, and potassium-competitive acid blocker (P-CAB) triple therapy is sufficient treatment even for CAM resistant strains. AMX, MTZ, P-CAB, or PPI triple therapy, quinolone containing therapy and bismuth quadruple therapy may be recommended as rescue therapy.

derivates, which might cause the hepatotoxicity of previous P-CABs (SCH 28080 and AZD 0865) and subsequent termination of their clinical development.^{73,74} Serum gastrin levels tended to be higher in the vonoprazan group than in the PPI group.^{75,76} Although there is no evidence that hypergastrinemia induced by PPIs or P-CABs causes neuroendocrine tumors in humans, P-CAB-induced stimulation of enterochromaffin cells and increased risk of neuroen-

docrine tumors remained. Bone fracture, hypomagnesemia, pneumonia, and *C. difficile*-associated diarrhea may also be caused by strong inhibition of gastric acid by continuous P-CABs treatment.⁶ In addition, parietal cell protrusion and dilated oxyntic glands can be observed after vonoprazan treatment.⁷⁷ Vonoprazan treatment reduced the value of urea breath test in patients infected with *H. pylori*.⁷⁸ The long-term (5 years) effect of vonoprazan is currently

under examination in patients receiving maintenance treatment for healed erosive esophagitis, and complications of long-term vonoprazan use need to be re-evaluated in the future.

Conclusions

Vonoprazan, an effective P-CAB, improves the treatment of gastric acid-related conditions including GERD, *H. pylori* infection and LDA/NSAID-induced peptic ulcers. It is highly likely that global standard therapy for gastric acid-related conditions will change in the future. The long-term safety of vonoprazan is still being investigated. Because studies on other P-CABs are limited, further research is required to show the superiority of other P-CABs to conventional PPIs.

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Author contributions: Hideki Mori and Hidekazu Suzuki wrote the manuscript; Hideki Mori made the Figures; and Hidekazu Suzuki supervised the all preparation of this article.

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