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Original Article

Efficacy and Tolerability of 14-Day Tegoprazan- versus Rabeprazole-Based Triple Therapy for Eradication of *Helicobacter pylori*: A Real-World Evidence Study

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Background/Aims: Tegoprazan, a new, fast, and strong potassium-competitive acid blocker, has been approved for the treatment of gastric acid-related diseases in Korea. However, real-world clinical data regarding this drug are scarce. We aimed to compare the *Helicobacter pylori* eradication rates of tegoprazan- and rabeprazole-based triple therapy.

Methods: We retrospectively reviewed data from patients who received first-line treatment for *H. pylori* infection using tegoprazan- or rabeprazole-based triple therapy for 2 weeks (50 mg tegoprazan or 20 mg rabeprazole+1,000 mg amoxicillin+500 mg clarithromycin twice daily). The primary endpoint was the eradication rate as determined by intention-to-treat analysis.

Results: Of the 677 patients included in our study, 344 and 333 received tegoprazan-based and rabeprazole-based triple therapy, respectively. The eradication rate from intention-to-treat analysis was 76.7% (95% confidence interval [CI], 72.1% to 81.0%) for tegoprazan-based triple therapy and 75.4% (95% CI, 70.5% to 79.8%) for rabeprazole-based triple therapy. There was no significant difference in the eradication rates between the two groups (p>0.999). Per-protocol analysis also revealed no significant difference between the eradication rates of the two groups (tegoprazan 83.4% [95% CI, 79.0% to 87.2%] vs rabeprazole 83.5% [79.0% to 87.4%], p>0.999). Furthermore, there was no significant difference in adverse event rates between the two groups (tegoprazan, 27.6%; rabeprazole, 25.8%; p=0.604).

Conclusions: The eradication rate of tegoprazan-based triple therapy was similar to that of rabeprazole-based triple therapy. Further studies on the dose-escalation effect of tegoprazan for *H. pylori* eradication and the efficacy of tegoprazan in regimens other than conventional triple therapy are needed. **(Gut Liver, Published online December 13, 2022)**

Key Words: *Helicobacter pylori*; Eradication; Potassium-competitive acid blockers; Tegoprazan

INTRODUCTION

Approximately 50% of the global population is infected by *Helicobacter pylori*,[1] that causes various diseases including peptic ulcer disease and gastric cancer.[2-6] Recent studies have demonstrated that *H. pylori* eradication therapy has a beneficial effect on reducing the risk of gastric cancer development.[7-9] Active eradication of *H. pylori* infection has been attempted in East Asian countries,[10] where *H. pylori* and gastric cancer are prevalent. Almost all gastric cancers in East Asia are caused by *H. pylori*. In Japan, 99.3% of patients with gastric cancer had current or past *H. pylori* infection, whereas the prevalence of *H. pylori*-negative gastric cancer was only 0.7%.[11] In Japan and Korea, health insurance coverage has been expanded to include individuals with *H. pylori* infection.[12]

Approximately 30 years ago, as proton pump inhibitors (PPIs) became available, they began to be used for *H. pylori* eradication.[13] PPI-containing eradication regimens have superior efficacy compared to other regimens that do

not employ PPIs.[14] Since 1993, PPI-based triple therapy, consisting of PPIs, amoxicillin, and clarithromycin, has been widely used worldwide.[15-17] Recently, potassium-competitive acid blockers (P-CABs) have been used as alternative drugs for gastric acid inhibition. Because P-CABs have a faster onset and longer lasting acid-inhibitory effect compared with PPIs,[18] the P-CAB-based regimen is expected to be superior to PPI-based regimens in terms of efficacy. In a previous meta-analysis, a triple therapy regimen containing vonoprazan, a P-CAB approved in 2014 in Japan, demonstrated a 1.2 times better eradication rate than the PPI-based triple therapy regimen.[19] However, all individual studies in the meta-analysis were performed in Japan and did not evaluate the efficacy of P-CABs other than vonoprazan.[19]

In 2018, tegoprazan, a novel P-CAB with fast onset of action and strong acid-inhibitory potency, was approved for gastroesophageal reflux disease in Korea.[20] A multicenter, randomized controlled, noninferior study on erosive esophagitis showed that tegoprazan was noninferior to esomeprazole with regards to healing of esophageal erosion.[21] In addition, tegoprazan was shown to be superior to placebo in terms of symptom resolution in patients with non-erosive reflux disease.[22] In 2020, tegoprazan was approved for *H. pylori* eradication therapy and is now widely available in Korea. However, there is little evidence of the clinical efficacy of tegoprazan-based triple therapy for *H. pylori* eradication. Therefore, this study aimed to evaluate the efficacy and tolerability of tegoprazan-based triple therapy by comparing it with rabeprazole-based triple therapy, based on real-world data.

MATERIALS AND METHODS

1. Study population

We retrospectively reviewed the data of consecutive adult patients (≥19 years of age) with *H. pylori* infection who received tegoprazan-based or rabeprazole-based triple therapy between March and July 2021 at Kangbuk Samsung Hospital and Hanyang University Guri Hospital in Korea. The exclusion criteria were as follows: (1) previous history of *H. pylori* eradication therapy and (2) previous history of subtotal gastrectomy. Patient demographics, symptoms, upper endoscopic findings, medications, *H. pylori* eradication therapy-related adverse events, and results of *H. pylori* eradication therapy were obtained. The institutional review boards of each institution approved this study (IRB numbers: Kangbuk Samsung Hospital [KBSMC 2021-08-021] and Hanyang University Guri Hospital [GURI 2021-09-004]). The informed consent was waived.

2. *H. pylori* eradication therapy

First-line treatment of *H. pylori* infection involved the administration of an acid suppressant (either 50 mg tegoprazan or 20 mg rabeprazole) in combination with 1,000 mg amoxicillin and 500 mg clarithromycin twice daily for 2 weeks according to the current Korean guidelines.[23] The Ministry of Food and Drug Safety of Korea approved both PPIs and tegoprazan for *H. pylori* eradication therapy. There were no clinical practice guidelines for the selection of acid suppressants. In our institutes, acid suppressant for *H. pylori* eradication therapy was selected at the clinicians' discretion. Because the antibiotics susceptibility test was unavailable in our clinical setting, either PPI or tegoprazan was selected regardless of antibiotics resistance status. Eradication status was usually evaluated at least 4 weeks after treatment. If eradication of *H. pylori* infection had failed, second-line *H. pylori* eradication therapy was initiated with an acid suppressant (one of 50 mg tegoprazan, 20 mg rabeprazole, or 40 mg esomeprazole) twice daily in combination with 120 mg bismuth four times a day, 500 mg metronidazole three times a day, and 500 mg tetracycline four times a day for 2 weeks. Eradication status following second-line therapy was also evaluated at least 4 weeks after treatment.

3. Study endpoint and measurements

The primary study endpoint was *H. pylori* eradication rate with first-line treatment in the intention-to-treat (ITT) analysis. The secondary study endpoints were *H. pylori* eradication rate with first-line therapy in the per-protocol (PP) analysis, *H. pylori* eradication rate with second-line treatment in the ITT and PP analyses, and adverse events of *H. pylori* eradication therapy.

The presence of *H. pylori* was detected using one or more of the following tests: rapid urease test, ^{13}C-urea breath test (Korea Otsuka Pharmaceutical Co., Ltd., Seoul, Korea), and/or histologic evaluation with modified Giemsa staining. *H. pylori* infection was defined as a positive result obtained using any of the above three tests.

Indications for *H. pylori* eradication were classified based on endoscopic findings according to the current guidelines for the management of *H. pylori* infections.[23] The severity of atrophic gastritis was determined visually based on the Kimura-Takemoto classification,[24] which classifies atrophic gastritis into three categories as follows: mild (C-1, C-2), moderate (C-3, O-1), and severe (O-2, O-3). Additionally, drug adherence was determined by the administration of ≥80% of prescribed medications.

4. Statistical analysis

Continuous and categorical variables were compared

using the t-test and Fisher exact test, respectively. *H. pylori* eradication rate was primarily evaluated in the ITT population. All enrolled patients were included in the ITT analysis, and those who received insufficient medications (<80% of the prescribed medications) or were lost to follow-up were regarded as failing to be cured. PP analysis was performed after excluding patients with insufficient medications and those lost to follow-up. Logistic regression analysis was used to identify factors associated with the failure of first-line *H. pylori* eradication therapy. Age, sex, and variables with p-values <0.1 in the univariable logistic regression model were considered as covariates for the multivariable analysis.

All reported p-values were two-sided and statistical significance was set at p<0.05. All statistical analyses were conducted using R statistical software version 4.0.4 (R

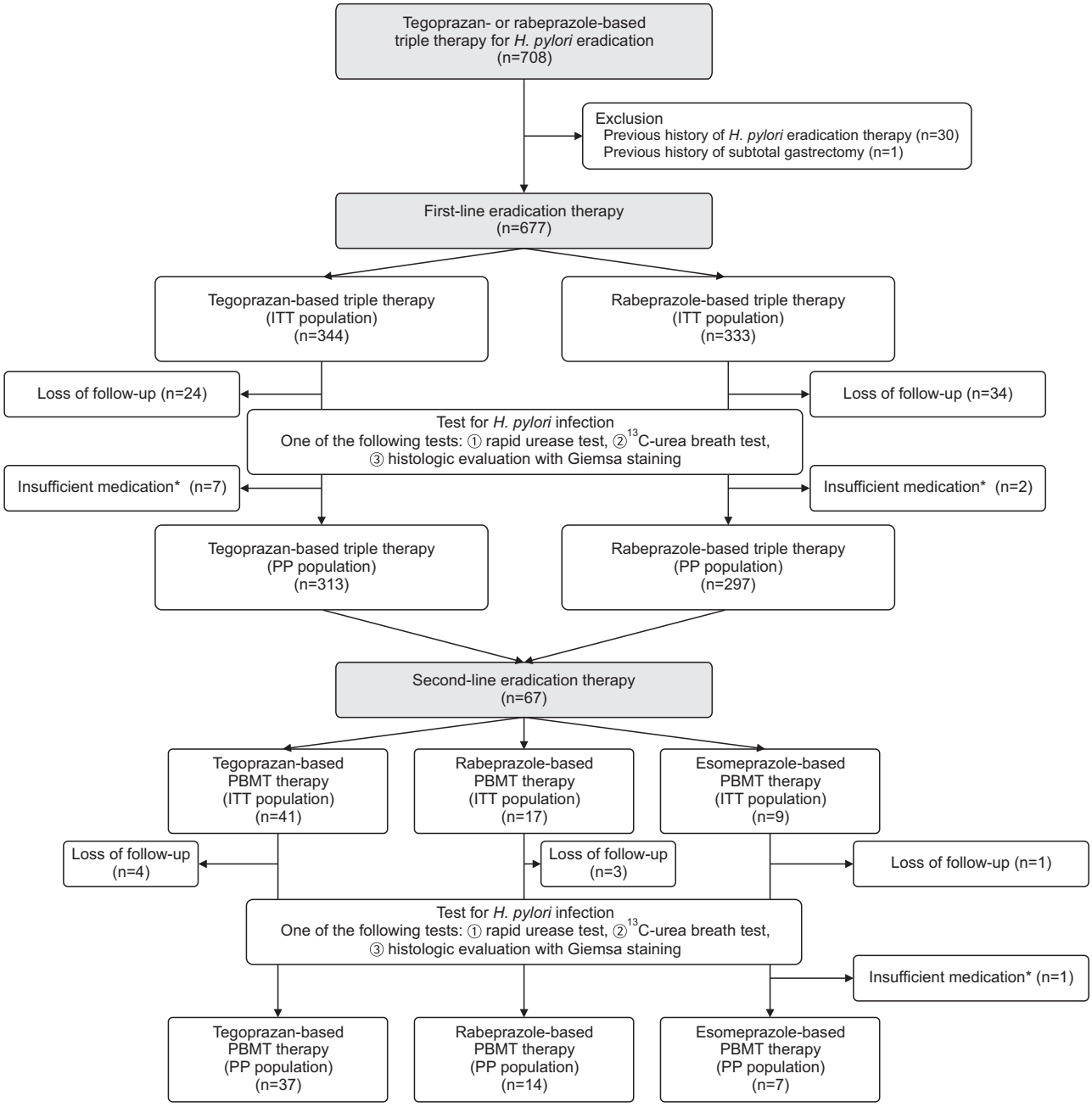

Fig. 1. Study flow diagram. PBMT indicates *Helicobacter pylori* eradication regimens consisting of proton pump inhibitor (or P-CAB), bismuth, metronidazole, and tetracycline.
ITT, intention-to-treat; PP, per protocol; P-CAB, potassium-competitive acid blocker. *Insufficient medication is determined as administration of <80% of prescribed medications.

Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Study population and baseline characteristics

During the study period, 1,264 patients received *H. pylori* eradication therapy. Of them, 708 patients who underwent 14-day tegoprazan- or rabeprazole-based triple therapy for *H. pylori* infection were eligible for inclusion in this study (Fig. 1). Of these, 30 patients were excluded due to a history of *H. pylori* eradication therapy. One patient with a history of subtotal gastrectomy was excluded from this study. Consequently, a total of 677 patients were included in the analyses. For ITT analysis, 344 patients in the tegoprazan-based triple therapy group and 333 in the rabeprazole-based triple therapy group were included. After excluding 65 patients due to insufficient medication or loss to follow-up, 313 patients in the tegoprazan-based triple therapy group and 297 patients in the rabeprazole-based triple therapy group were included in the PP analysis. Second-line *H. pylori* eradication therapy was administered to 67 patients for whom first-line eradication therapy failed.

Baseline patient characteristics are shown in Table 1. The mean age was 56.2±11.4 years in the tegoprazan-based triple therapy group and 57.4±11.6 years in the rabeprazole-based triple therapy group (p=0.147). The proportion of male sex was 54.9% in the tegoprazan-based triple therapy group and 54.4% in the rabeprazole-based triple therapy group (p=0.938). Body mass index, smoking habits, alcohol use, comorbidity, and the use of antithrombotic agents did not differ between the tegoprazan- and rabeprazole-based triple therapy groups.

Baseline patient symptoms and endoscopic findings are shown in Table 2. Although abdominal discomfort was more common in the tegoprazan-based triple therapy group (13.4%) than in the rabeprazole-based triple therapy group (8.1%), other symptoms, including reflux, nausea or vomiting, gastric soreness, and abdominal pain did not differ between the groups. The most common indication for *H. pylori* eradication was *H. pylori*-associated gastritis, followed by gastric or duodenal ulcers, in both the tegoprazan- and rabeprazole-based triple therapy groups. Atrophic gastritis was present in 79.6% and 84.4% of the tegoprazan-based and rabeprazole-based triple therapy groups, respectively (p=0.410).

2. Efficacy of the first-line eradication therapy

The success rate of first-line *H. pylori* eradication therapy is shown in Fig. 2. In the ITT analysis, there was

Table 1. Baseline Patient Characteristics

Variable	Tegoprazan-based triple therapy (n=344)	Rabeprazole-based triple therapy (n=333)	p-value
Age, yr	56.2±11.4	57.4±11.6	0.147
Male sex	189 (54.9)	181 (54.4)	0.938
Body mass index, kg/m^2*	24.2±3.1	23.9±3.3	0.380
Smoking habit			0.623
Never smoker	196 (57.0)	199 (59.8)	
Former smoker	94 (27.3)	80 (24.0)	
Current smoker	54 (15.7)	54 (16.2)	
Alcohol use			0.818
Absent	177 (51.5)	168 (50.5)	
Present	167 (48.5)	165 (49.5)	
<2/wk	102 (29.7)	82 (24.6)	
≥2/wk	65 (18.9)	83 (24.9)	
Comorbidity			
Hypertension	81 (23.5)	88 (26.4)	0.424
Cardiovascular disease	11 (3.2)	6 (1.8)	0.327
Diabetes	35 (10.2)	28 (8.4)	0.509
Cerebrovascular accident	11 (3.2)	10 (3.0)	>0.999
Antithrombotic agent			
Any antithrombotic agent	26 (7.6)	28 (8.4)	0.777
Aspirin	15 (4.4)	15 (4.5)	>0.999
Clopidogrel	8 (2.3)	10 (3.0)	0.639
Other antiplatelet agent	5 (1.5)	1 (0.3)	0.217
Warfarin	0	2 (0.6)	0.242
Non-vitamin K-dependent oral anticoagulant	2 (0.6)	0	0.499
Others (types unknown)	0	2 (0.6)	0.242

Data are presented as mean±SD or number (%).
*Body mass index is missing in one patient from the tegoprazan-based triple therapy group.

Table 2. Baseline Symptoms and Endoscopic Findings

Variable	Tegoprazan-based triple therapy (n=344)	Rabeprazole-based triple therapy (n=333)	p-value
Symptom			
Reflux symptom*	9 (2.6)	10 (3.0)	0.819
Nausea or vomiting	5 (1.5)	4 (1.2)	>0.999
Gastric soreness	30 (8.7)	32 (9.6)	0.692
Abdominal discomfort	46 (13.4)	27 (8.1)	0.035
Abdominal pain	10 (2.9)	7 (2.1)	0.625
Others†	7 (2.0)	6 (1.8)	>0.999
Indication for *H. pylori* eradication			0.182
Gastric and duodenal ulcers	0	1 (0.3)	
Gastric ulcer	27 (7.8)	17 (5.1)	
Duodenal ulcer	27 (7.8)	33 (9.9)	
EGC treated with ESD	5 (1.5)	1 (0.3)	
Gastric adenoma treated with ESD	3 (0.9)	1 (0.3)	
H. pylori-associated gastritis	282 (82.0)	280 (84.1)	
Nodular gastritis	18 (5.2)	11 (3.3)	0.256
Atrophic gastritis‡,§			0.410
Absent (C-0)	70 (20.4)	52 (15.6)	
Present			
C-1	79 (23.0)	90 (27.0)	
C-2	48 (14.0)	44 (13.2)	
C-3	56 (16.3)	70 (21.0)	
O-1	30 (8.7)	25 (7.5)	
O-2	39 (11.4)	32 (9.6)	
O-3	21 (6.1)	20 (6.0)	

Data are presented as number (%).
H. pylori, Helicobacter pylori; EGC, early gastric cancer; ESD, endoscopic submucosal dissection.
*Reflux symptoms include heartburn and acid regurgitation; †Other symptoms include anorexia, globus sensation, belching, and diarrhea; ‡Severity of atrophic gastritis is determined by Kimura-Takemoto classification;[24] §There is one missing value for atrophic gastritis in the tegoprazan-based triple therapy group.

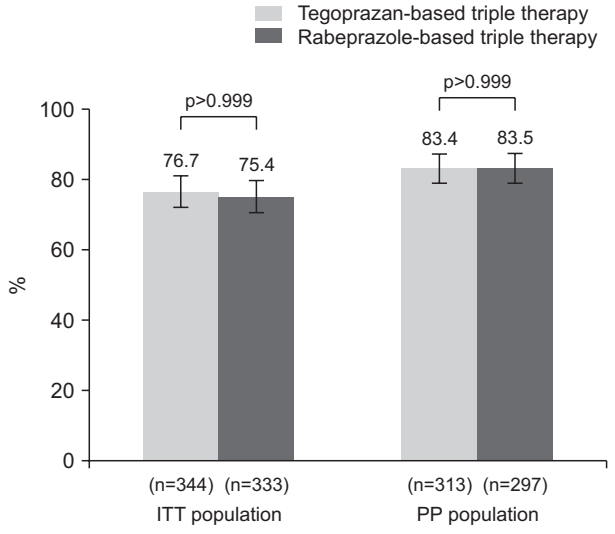

Fig. 2. Success rate of first-line *Helicobacter pylori* eradication therapy. ITT, intention-to-treat; PP, per-protocol.

no significant difference between the tegoprazan- and rabeprazole-based triple therapy groups (tegoprazan 76.7% [95% confidence interval (CI), 72.1% to 81.0%] vs rabeprazole 75.4% [95% CI, 70.5% to 79.8%], p>0.999). Likewise, there was no significant difference between the two groups in the PP analysis (tegoprazan 83.4% [95% CI, 79.0% to 87.2%] vs rabeprazole 83.5% [95% CI, 79.0% to 87.4%], p>0.999). As shown in Table 3, the most common confirmation test after *H. pylori* eradication was the urea breath test (96.2% in the tegoprazan group and 99.7% in the rabeprazole group). Although the type of confirmation test and lag period for confirmation test after *H. pylori* eradication therapy slightly differed between the groups, the eradication rate did not differ according to the type of confirmation test (p=0.139) and lag period (p=0.664).

Here, we further performed the eradication rate according to the clinicians because acid suppressant for *H. pylori* eradication therapy was selected at the clinicians' discretion in this study. As shown in Supplementary Table 1, the eradication rate did not differ among the participated clinicians (p=0.160).

In total, there were 67 patients who received second-line *H. pylori* eradication therapy due to failure of first-line eradication therapy. Of the 41 patients with failed eradication in the tegoprazan-based triple therapy group,

Table 3. Adherence and Adverse Events of First-Line *Helicobacter pylori* Eradication Therapy

Variable	Tegoprazan-based triple therapy (n=344)	Rabeprazole-based triple therapy (n=333)	p-value
Adherence*	313 (91.0)	297 (89.2)	0.443
Loss of follow-up	24 (7.0)	34 (10.2)	
Insufficient medication	7 (2.0)	2 (0.6)	
Adverse event†			
Any adverse event	95 (27.6)	86 (25.8)	0.604
General weakness	1 (0.3)	0	>0.999
Dizziness	0	0	NA
Headache	3 (0.9)	2 (0.6)	>0.999
Myalgia	0	0	NA
Acid regurgitation	0	0 (0.1)	0.492
Nausea or vomiting	16 (4.7)	14 (4.2)	0.853
Dysgeusia	43 (12.5)	33 (9.9)	0.330
Abdominal discomfort	8 (2.3)	10 (3.0)	0.639
Abdominal pain	2 (0.6)	1 (0.3)	>0.999
Diarrhea	27 (7.8)	40 (12.0)	0.073
Constipation	3 (0.9)	0	0.249
Skin rash	5 (1.5)	2 (0.6)	0.451
Others‡	4 (1.2)	1 (0.3)	0.373
Confirmation test for *H. pylori* eradication			0.003
Urea breath test	307 (96.2)	302 (99.7)	
Histologic evaluation with modified Giemsa staining	12 (3.8)	1 (0.3)	
Lag period for confirmation test after eradication therapy			0.016
<2 wk	1 (0.3)	0	
2–4 wk	10 (3.1)	10 (3.3)	
4–12 wk	307 (96.2)	283 (93.4)	
12–24 wk	1 (0.3)	10 (3.3)	

Data are presented as number (%).

NA, not applicable.

*Adherence is determined as administration of ≥80% of prescribed medications; †Percentage is calculated based on the intention-to-treat population; ‡Other adverse events include sores on the tongue, dry mouth, palpitation, anal bleeding, and insomnia.

40 received tegoprazan-based second-line therapy and one received rabeprazole-based second-line therapy. Of the 26 patients with failed eradication in the rabeprazole-based triple therapy group, 16 received rabeprazole-based second-line therapy, nine received esomeprazole-based second-line therapy, and one received tegoprazan-based second-line therapy. Following second-line *H. pylori* eradication therapy, the eradication rate of tegoprazan-based therapy did not differ from that of rabeprazole- or esomeprazole-based therapy in both the ITT and PP analyses (ITT analysis: tegoprazan 85.4% [95% CI, 72.3% to 93.7%] vs rabeprazole 82.4% [95% CI, 60.0% to 94.8%], p>0.999 and vs esomeprazole 88.9% [95% CI, 58.6% to 98.8%], p>0.999; PP analysis: tegoprazan 94.6% [95% CI, 83.8% to 98.9%] vs rabeprazole 100.0% [95% CI, 83.8% to 100.0%], p>0.999 and vs esomeprazole 100.0% [95% CI, 70.8% to 100.0%], p>0.999) (Supplementary Fig. 1).

3. Adherence and adverse events

The adherence rate to first-line eradication therapy was 91.0% in the tegoprazan-based triple therapy group and 89.2% in the rabeprazole-based triple therapy group (p=0.443) (Table 3). The most common adverse events were dysgeusia (12.5%) and diarrhea (12.0%) in the tegoprazan-based and rabeprazole-based triple therapy groups, respectively. The proportion of patients who experienced adverse events was 27.6% in the tegoprazan-based triple therapy group and 25.8% in the rabeprazole-based triple therapy group (p=0.604). Furthermore, no adverse event was significantly different between the patients in the two groups.

The adherence rates to second-line eradication therapy were 90.2%, 82.4%, and 77.8% in the tegoprazan-, rabeprazole-, and esomeprazole-based second-line therapy groups, respectively, and there was no significant difference in adherence between groups (p=0.390) (Supplementary Table 2). The most common adverse event was nausea or vomiting in the tegoprazan-based (24.4%) and esomeprazole-based (22.2%) second-line therapy groups. In the rabeprazole-based second-line therapy group, abdominal discomfort (11.8%) and diarrhea (11.8%) were the most common adverse events. There were no significant differences in adverse events between the groups.

4. Risk factor for *H. pylori* eradication failure

Table 4 shows the factors associated with the failure of first-line *H. pylori* eradication therapy. In the univariable analysis, non-adherence, female sex, former or current smoker, alcohol use ≥2/week, and diabetes were associated with failed eradication. In the multivariable analysis, diabetes (odds ratio, 2.03; 95% CI, 1.05 to 3.95) was significantly associated with eradication failure. The choice of acid suppressant did not affect eradication failure (tegoprazan vs rabeprazole: odds ratio, 1.02; 95% CI, 0.66 to 1.57).

Table 4. Factors Associated with Failure of First-Line *Helicobacter pylori* Eradication*

Variable	No.	Failure, No. (%)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	p-value	OR (95% CI)	p-value
Regimen						
Tegoprazan-based triple therapy	316	54 (17.1)	1.03 (0.67–1.57)	0.904	1.03 (0.67–1.59)	0.888
Rabeprazole-based triple therapy	299	50 (16.7)	1		1	
Adherence						
Adherent	611	101 (16.5)	1		1	
Non-adherent	4	3 (75.0)	5.03 (1.01–25.28)	0.050	4.05 (0.78–21.04)	0.097
Age						
<60 yr	339	55 (16.2)	1		1	
≥60 yr	276	49 (17.8)	1.12 (0.73–1.70)	0.615	0.98 (0.62–1.55)	0.928
Sex						
Male	338	42 (12.4)	1		1	
Female	277	62 (22.4)	2.03 (1.32–3.12)	0.001	1.49 (0.84–2.64)	0.169
Body mass index						
<25 kg/m^2	378	65 (17.2)	1			
≥25 kg/m^2	237	39 (16.5)	0.95 (0.61–1.47)	0.948		
Smoking habit						
Never smoker	358	75 (20.9)	1		1	
Former smoker	165	20 (12.1)	0.52 (0.31–0.89)	0.016	0.65 (0.33–1.27)	0.206
Current smoker	92	9 (9.8)	0.41 (0.20–0.85)	0.017	0.54 (0.23–1.25)	0.147
Alcohol use						
Absent	309	61 (19.7)	1		1	
<2/wk	173	28 (16.2)	0.79 (0.48–1.28)	0.335	1.08 (0.63–1.85)	0.778
≥2/wk	133	15 (11.3)	0.52 (0.28–0.95)	0.033	0.92 (0.45–1.86)	0.816
Comorbidity						
Hypertension	155	32 (20.6)	1.40 (0.88–2.23)	0.153		
Cardiovascular disease	17	5 (29.4)	2.10 (0.72–6.09)	0.172		
Diabetes	57	15 (26.3)	1.88 (1.00–3.54)	0.050	2.03 (1.05–3.95)	0.036
Cerebrovascular accident	20	1 (5.0)	0.25 (0.03–1.90)	0.181		
Antithrombotic agent	48	12 (25.0)	1.72 (0.86–3.43)	0.123		
Symptom						
Reflux symptom†	18	0	NA	0.998		
Nausea or vomiting	9	1 (11.1)	0.61 (0.08–4.93)	0.643		
Gastric soreness	53	8 (15.1)	0.86 (0.39–1.90)	0.712		
Abdominal discomfort	68	15 (22.1)	1.46 (0.79–2.70)	0.232		
Abdominal pain	16	2 (12.5)	0.70 (0.16–3.11)	0.635		
Others‡	11	2 (18.2)	1.09 (0.23–5.14)	0.910		
Indication for *H. pylori* eradication						
Peptic ulcer	92	16 (17.4)	1.08 (0.60–1.94)	0.809		
EGC treated with ESD	6	3 (50.0)	5.11 (1.01–25.74)	0.048		
Gastric adenoma treated with ESD	4	1 (25.0)	1.70 (0.18–16.56)	0.647		
H. pylori-associated gastritis	513	84 (16.4)	1			
Nodular gastritis	28	4 (14.3)	0.81 (0.28–2.39)	0.705		
Atrophic gastritis§						
Normal (C-0)	110	17 (15.5)	1			
Mild (C-1, C-2)	236	36 (15.3)	0.99 (0.53–1.84)	0.962		
Moderate (C-3, O-1)	168	32 (19.0)	1.29 (0.68–2.45)	0.443		
Severe (O-2, O-3)	101	19 (18.8)	1.27 (0.62–2.60)	0.518		

OR, odds ratio; CI, confidence interval; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; NA, not applicable.
*This analysis is performed on participants who received a follow-up test for *H. pylori* eradication; †Reflux symptoms include heartburn and acid regurgitation; ‡Other symptoms include anorexia, globus sensation, belching, and diarrhea; §Severity of atrophic gastritis is determined by Kimura-Takemoto classification.[24]

DISCUSSION

In this study, the *H. pylori* eradication rate of tegoprazan-based triple therapy was 76.7% in the ITT analysis and 83.4% in the PP analysis. Similarly, the eradication rate of rabeprazole-based triple therapy was 75.4% in the ITT analysis and 83.5% in the PP analysis. Our findings demonstrate that the choice of acid suppressant between tegoprazan and rabeprazole did not affect the eradication rate of first-line triple therapy lasting 2 weeks. Although tegoprazan showed a fast and strong acid inhibitory effect,[20] it did not increase the eradication rate of conventional triple therapy in our real-world data. Tegoprazan-based triple therapy demonstrated a good adherence rate (91.3%) and acceptable adverse events. However, given that acceptable regimens typically require a >85% eradication rate in ITT analysis and >90% eradication rate in PP analysis,[25] tegoprazan-based triple therapy did not achieve an acceptable eradication rate in either the ITT (76.7%) or PP (83.4%) analyses.

Owing to the strong acid-inhibitory potency of vonoprazan, vonoprazan-based triple therapy has been reported to increase the eradication rate.[26] Even in patients with clarithromycin-resistant *H. pylori* infection, the eradication rate of vonoprazan-based triple therapy is over 80%.[26] Effective acid suppression improves antibiotic potency by minimizing antibiotic degradation, maximizing the concentration of antibiotics in gastric juice, and increasing the susceptibility of *H. pylori* to antibiotics.[27] In a previous study, patients with *H. pylori* infection with strong acid inhibition (intragastric pH >6.5) were successfully treated with triple therapy despite clarithromycin resistance, whereas patients with modest acid inhibition (intragastric pH=6) who were infected with clarithromycin-resistant strains failed to respond to triple therapy.[28] These studies suggest that strong acid inhibition is helpful in increasing the eradication rate of *H. pylori* eradication therapy.

In contrast to the superior efficacy of vonoprazan in the treatment of *H. pylori* infection,[19] our study did not demonstrate superior efficacy of tegoprazan compared to PPIs; this may be due to an insufficient dosage of tegoprazan (50 mg, twice daily). For vonoprazan-based eradication therapy, the dosage of vonoprazan (20 mg, twice a day) is four-times higher than the maintenance dosage for reflux esophagitis (10 mg, once a day).[29] In Korea, 50 mg tegoprazan taken once daily has been approved for gastroesophageal reflux disease, including both erosive esophagitis and non-erosive reflux disease; however, only a 2-fold higher dosage (50 mg, twice daily) has been approved for *H. pylori* eradication therapy. A previous study demonstrated that tegoprazan inhibits proton pumps in a dose-dependent manner.[20] When the dosage of tegoprazan was increased from 100 mg once daily to 200 mg once daily, the median intragastric pH increased from 5.2 to 6.4.[20] In treating *H. pylori* infection, 100 mg tegoprazan taken twice daily may be more effective.

To date, two studies have compared the effects of tegoprazan and PPIs in *H. pylori* eradication.[30,31] One retrospective study by Kim *et al.*,[30] published in 2021, assessed the comparative efficacy of bismuth-containing quadruple regimens consisting of 50 mg tegoprazan, 30 mg lansoprazole, 1,000 mg amoxicillin, 500 mg clarithromycin, and 300 mg bismuth potassium citrate administered twice daily for 7 days. Consistent with our findings, this study did not demonstrate superior efficacy of tegoprazan-based therapy compared with PPI-based therapy. In the ITT analysis, the eradication rates in the tegoprazan and lansoprazole groups were 78.8% (152/193) and 74.5% (140/188), respectively (p=0.323). In the PP analysis, the eradication rates of the two groups were 88.3% (151/171) and 82.8% (140/169), respectively (p=0.151). Although the eradication regimens and treatment durations differed between the study by Kim *et al.*[30] and our study, the eradication rates were similar between tegoprazan-based and rabeprazole-based therapies in both studies. Additionally, in the study by Kim *et al.*,[30] clarithromycin resistance gene mutation analysis showed that the eradication rate of tegoprazan-based therapy was lower than 20%. However, a limitation of this study is that *H. pylori* eradication therapy was administered for only 1 week. Currently, Korean guidelines recommend several empirical eradication regimens, including conventional triple therapy for 2 weeks if an antibiotic susceptibility test is not performed.[23] In our study, we administered *H. pylori* eradication therapy for 2 weeks in accordance with these guidelines.[23] One recently published randomized controlled trial also evaluated the efficacy of 7-day tegoprazan-based triple therapy in the treatment of *H. pylori* infection.[31] In this study, the efficacy of 7-day tegoprazan-based triple therapy was similar to that of 7-day lansoprazole-based triple therapy. The *H. pylori* eradication rate in the ITT analysis was 62.9% in the tegoprazan group and 60.6% in the lansoprazole group. Comparing the results from the randomized controlled trial with our study findings, 50 mg of tegoprazan may have similar efficacy in terms of *H. pylori* eradication compared to the standard dose of PPI.

In our study, nonadherence to medication was associated with eradication failure. Although both tegoprazan- and rabeprazole-based triple therapies showed acceptable adherence rates, insufficient medication (<80% of prescribed medications) may increase the risk of eradication failure; thus, it is essential to educate patients about the risks of nonadherence. Diabetes is a significant risk factor

for eradication failure; patients with diabetes had a 2-fold higher risk of eradication failure than those without. This finding is consistent with previous studies. In a meta-analysis of eight studies comparing eradication rates between patients with and without diabetes, the pooled risk ratio of *H. pylori* eradication failure was 2.19.[32] Several potential mechanisms may contribute to the poor eradication rate in patients with diabetes.[32] First, glycosylation reduces drug binding in the blood.[33] Second, the impaired microvasculature of the gastric mucosa in patients with diabetes may reduce antibiotic absorption.[34] Third, diabetic gastroparesis may result in reduced antibiotic absorption.[35,36] And fourth, antibiotic resistance may be common in patients with diabetes because of the frequent use of antibiotics.[37]

Although our study is the first comparative study of tegoprazan- versus PPI-based triple therapy for *H. pylori* eradication, it has several limitations. First, as a retrospective study, there may have been selection bias as the treatment groups were not allocated randomly, but rather were selected according to the clinicians' preference. However, the potential bias arising from clinicians may be minimal as the treatment process for *H. pylori* infection, including diagnosis, prescription tools, medication preparation, and follow-up tests, is similar across clinicians in our institutes. Second, we did not perform antibiotic susceptibility tests. Also, the frequency of previous antibiotic use was not identified. Therefore, the efficacy of tegoprazan-based therapy in patients with clarithromycin-resistant *H. pylori* infections could not be assessed. However, bias due to a lack of antibiotics susceptibility tests may be minimal because *H. pylori* eradication regimens were chosen according to the clinicians' preference without knowing the antibiotics susceptibility status. According to current guidelines, conventional triple therapy is not recommended if clarithromycin-resistant *H. pylori* infection is confirmed.[23] In other words, most real-world patients confirmed to be infected with clarithromycin-resistant *H. pylori* are treated with eradication regimens other than conventional triple therapy. Therefore, our real-world study on tegoprazan-based triple therapy could only be conducted in an empirical treatment setting. Third, cytochrome P450 2C19 (CYP2C19) status was unavailable in this study. The eradication rate of PPI-based triple therapy may differ depending on CYP2C19 status since most PPIs are metabolized by CYP2C19.[38] However, rabeprazole is mainly metabolized via nonenzymatic pathway, rather than CYP2C19.[38] Additionally, tegoprazan is metabolized by cytochrome P450 3A4, and not CYP2C19. The eradication efficacy of rabeprazole- or tegoprazan-based triple therapy likely does not differ between patients with different CYP2C19 genetic polymorphisms.[39] Fourth, we investigated atrophic gastritis status based on gross endoscopic findings. Therefore, atrophic gastritis may not be fully evaluated in some patients with endoscopic findings associated with current *H. pylori* infection, including hemorrhagic spots, diffuse redness, mucosal edema, and thick and sticky mucus. If atrophic gastritis was assessed by histologic examination, the proportion of atrophic gastritis may have increased. Lastly, our study included only patients who received triple therapy consisting of an acid suppressant, amoxicillin, and clarithromycin. Accordingly, the effect of tegoprazan in combination with other antibiotic regimens, including concomitant therapy, could not be evaluated. As both the 2-week tegoprazan- and 2-week rabeprazole-based triple therapies did not achieve acceptable eradication rates, the clinical efficacy of tegoprazan should be investigated in more effective *H. pylori* eradication regimens.

Our study enhances the understanding of the clinical efficacy of tegoprazan-based triple therapy for the treatment of *H. pylori* infection. Although tegoprazan-based triple therapy demonstrated good adherence and acceptable adverse events, its eradication rate was similar to that of rabeprazole-based triple therapy. Future studies are warranted to evaluate the dose-escalation effect of tegoprazan in the treatment of *H. pylori* infection and the efficacy of tegoprazan in regimens other than conventional triple therapy.

CONFLICTS OF INTEREST

Y.S.J. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: C.H.P. Data acquisition: Y.S.J., C.H.P. Data analysis and interpretation: Y.S.J., C.H.P. Drafting of the manuscript; critical revision of the manuscript for important intellectual content: Y.S.J., S.K., H.Y.K., S.J.N., J.H.P., C.I.S., C.H.P. Statistical analysis: Y.S.J., C.H.P.

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SUPPLEMENTARY MATERIALS

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