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Original Article

Triple Therapy-Based on Tegoprazan, a New Potassium-Competitive Acid Blocker, for First-Line Treatment of *Helicobacter pylori* Infection: A Randomized, Double-Blind, Phase III, Clinical Trial

Yoon Jin Choi[1], Yong Chan Lee[1], Jung Mogg Kim[2], Jin Il Kim[3], Jeong Seop Moon[4], Yun Jeong Lim[5], Gwang Ho Baik[6], Byoung Kwan Son[7], Hang Lak Lee[8], Kyoung Oh Kim[9], Nayoung Kim[10], Kwang Hyun Ko[11], Hye-Kyung Jung[12], Ki-Nam Shim[12], Hoon Jai Chun[13], Byung-Wook Kim[14], Hyuk Lee[15], Jie-Hyun Kim[16], Hyunsoo Chung[17], Sang Gyun Kim[17], and Jae Young Jang[18]

[1]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, [2]Department of Microbiology and Institute of Biomedical Science, Hanyang University College of Medicine, [3]Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, [4]Department of Internal Medicine, Inje University Seoul Paik Hospital, Inje University College of Medicine, Seoul, [5]Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, Goyang, [6]Department of Internal Medicine, Hallym University Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, [7]Department of Internal Medicine, Uijeongbu Eulji Medical Center, Eulji University, Uijeongbu, [8]Department of Internal Medicine, Hanyang University Medical Center, Seoul, [9]Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, [10]Department of Internal Medicine, Seoul National University Bundang Hospital, [11]Department of Internal Medicine, Digestive Disease Center, CHA Bundang Medical Center, CHA University, Seongnam, [12]Department of Internal Medicine, Ewha Womans University Mokdong Hospital, [13]Department of Internal Medicine, Korea University College of Medicine, Seoul, [14]Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, [15]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, [16]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, [17]Department of Internal Medicine, Seoul National University Hospital, and [18]Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea

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Corresponding Author
Yong Chan Lee
ORCID https://orcid.org/0000-0001-8800-6906
E-mail leeyc@yuhs.ac

Jung Mogg Kim
ORCID https://orcid.org/0000-0002-6506-7519
E-mail jungmogg@hanyang.ac.kr

Background/Aims: We examined the efficacy and safety of tegoprazan as a part of first-line triple therapy for *Helicobacter pylori* eradication.

Methods: A randomized, double-blind, controlled, multicenter study was performed to evaluate whether tegoprazan (50 mg)-based triple therapy (TPZ) was noninferior to lansoprazole (30 mg)-based triple therapy (LPZ) (with amoxicillin 1 g and clarithromycin 500 mg; all administered twice daily for 7 days) for treating *H. pylori*. The primary endpoint was the *H. pylori* eradication rate. Subgroup analyses were performed according to the cytochrome P450 (CYP) 2C19 genotype, the minimum inhibitory concentration (MIC) of amoxicillin and clarithromycin, and underlying gastric diseases.

Results: In total, 350 *H. pylori*-positive patients were randomly allocated to the TPZ or LPZ group. The *H. pylori* eradication rates in the TPZ and LPZ groups were 62.86% (110/175) and 60.57% (106/175) in an intention-to-treat analysis and 69.33% (104/150) and 67.33% (101/150) in a per-protocol analysis (non-inferiority test, p=0.009 and p=0.013), respectively. Subgroup analyses according to MICs or CYP2C19 did not show remarkable differences in eradication rate. Both first-line triple therapies were well-tolerated with no notable differences.

Conclusions: TPZ is as effective as proton pump inhibitor-based triple therapy and is as safe as first-line *H. pylori* eradication therapy but does not overcome the clarithromycin resistance of *H. pylori* in Korea (ClinicalTrials.gov identifier NCT03317223). **(Gut Liver 2022;16:535-546)**

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

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INTRODUCTION

Helicobacter pylori has infected nearly 50% of the world's population;[1] many studies have reported this organism as a major pathological factor in chronic gastritis and stomach cancer since it was first identified in 1983.[2,3] In 1994, the International Agency for Research on Cancer of the World Health Organization classified *H. pylori* as a definitive carcinogen.[4] *H. pylori* eradication is indicated for the treatment of peptic ulcer and gastric mucosa-associated lymphoid-type lymphoma and prevention of metachronous gastric cancer recurrence after endoscopic resection.[5] Increasing evidence suggests that *H. pylori* eradication helps prevent gastric cancer, and the revised guidelines of the Kyoto global consensus report and Maastricht V/Florence consensus report led to the expansion of therapeutic targets for *H. pylori* eradication.[6,7] These new guidelines[6,7] recommended that all *H. pylori* infections should be eradicated, with a few exceptions.

Most of the anti-*H. pylori* treatment regimens include proton pump inhibitors (PPIs), to maximize the effectiveness of antibiotics through maintaining a gastric lumen pH ≥6.[8] The increased intragastric pH preserves the stable conformation of antibiotics, resulting in increased antibiotic levels in gastric juice and decreased minimum inhibitory concentrations (MICs).[9]

Despite the combined administration of PPIs and the combination of several antibiotics, treating *H. pylori* infection is becoming a challenge; mainly because of antibiotic resistance.[10] The rapid metabolism of PPI also contributes to the eradication failure to some extent. Therefore, a strategy focused on increasing the gastric pH using high-dose or potent PPIs can be one of the strategies to overcome the eradication failure.

Although the recommended first-line regimen was revised according to the increase in antibiotic resistance, a 7-day triple regimen comprising a PPI, amoxicillin, and clarithromycin is still widely prescribed first-line therapeutic option globally, including in Korea.[5]

Tegoprazan (trade name: K-CAB 50 mg tablet), a potassium-competitive acid blocker (P-CAB), was developed and launched by HK inno.N Corp. (Seoul, Korea) for the treatment of gastroesophageal reflux disease, gastric ulcer, and *H. pylori* eradication in 2018.[11] P-CABs, such as vonoprazan, exhibit competitive binding to the potassium-binding site of H^+/K^+-ATPase pumps on parietal cells without activation by gastric acid. P-CABs can inhibit both active and inactive H^+/K^+-ATPases. P-CABs are less dependent on cytochrome P450 (CYP) 2C19. These characteristics of P-CABs make them have faster, stronger and longer action compared to PPIs.[12,13] The combination of 100 mg of tegoprazan with amoxicillin and clarithromycin twice a day for 7 days maintained the intragastric pH at ≥6 for ≥20 hours from the first day,[14] which was equivalent to or better than when PPIs were combined. Considering the potent acid-inhibitory effect of tegoprazan, tegoprazan-based therapy can be expected as effective as PPI-based therapy for *H. pylori* eradication. However, the effectiveness of tegoprazan in regions with high clarithromycin resistance rates (>20%) remains unclear.

Although the recommended first-line regimen was revised according to the increase in antibiotic resistance, a 7-day triple regimen comprising a PPI, amoxicillin, and clarithromycin is still widely prescribed first-line therapeutic option globally, including in Korea.[5]

We aimed to assess the efficacy and safety of tegoprazan-based triple therapy versus PPI-based triple therapy in *H. pylori*-positive patients. Subgroup analyses were performed according to the CYP2C19 genotype, the MICs of amoxicillin and clarithromycin, and underlying gastric diseases (i.e., peptic ulcer disease or chronic atrophic gastritis).

MATERIALS AND METHODS

1. Study design

This study was a phase III, randomized, double-blind, multicenter, active-controlled, comparative study for assessing the non-inferiority of tegoprazan-based triple therapy to lansoprazole-based triple therapy in *H. pylori*-positive patients with chronic atrophic gastritis and/or peptic ulcer diseases (gastric ulcer or duodenal ulcer). The study involved 21 investigators at 18 centers in South Korea. The protocol for this study was approved by the institutional review boards of each institution including Severance Hospital (IRB number: 4-2017-0795). The study was conducted in accordance with the Declaration of Helsinki and the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice guidelines. The study was registered at ClinicalTrials.gov (NCT03317223; A Phase 3 Study to Evaluate the Efficacy and Safety of Triple Therapy with CJ-12420 in *H. Pylori* Positive Patients).

2. Study participants

Male or female patients who met all of the following inclusion criteria were eligible to participate in the study: age, 20 to 75 years; living in South Korea; outpatients with complaints of epigastric discomfort; *H. pylori* positivity; and had been diagnosed with peptic ulcer diseases (i.e., gastric ulcer or duodenal ulcer) and/or chronic atrophic gastritis using upper gastrointestinal endoscopy at screening.

Patients with any of the following conditions were excluded from the study: prior therapy for *H. pylori* eradication; acute epigastric hemorrhage; acute gastric mucosal lesion; acute duodenal mucosal lesion; had undergone or planned to undergo surgery which might affect gastric acid secretion; Zollinger-Ellison syndrome; gastric acid hypersecretion disorder; gastric outlet obstruction; endoscopic diagnosis of gastric cancer during screening; history of malignancy within the last 5 years; pregnancy; breast-feeding women; history of allergy to any of the study drugs or their related compounds; clinically significant hepatic or renal disease; use of a PPI or H_2-receptor antagonist 14 days before screening; or use of bismuth or antibiotics with known efficacy in *H. pylori* eradication within 28 days before screening. All the participants provided written informed consent before participating in the study.

3. Study protocol

During screening, the baseline characteristics and medical history (including history of *H. pylori* eradication therapy) of the participants were recorded. Physical examinations, vital sign assessments, clinical laboratory tests, pregnancy tests, and electrocardiography were performed. For diagnosis of *H. pylori* infection status, ^{13}C-urea breath test (UBT) was mandatory. In addition, at least one among the three tests—stool antigen test, rapid urease test, or biopsy-based culture—was performed before treatment. It was determined as *H. pylori*-positive when the participant was positive for UBT and at least one of the other tests was positive. Upper gastrointestinal endoscopy was performed to determine the status of underlying diseases, such as gastric or duodenal ulcer or chronic atrophic gastritis. Antimicrobial susceptibility tests were performed on the biopsied gastric mucosal tissues (collected after obtaining consent), which were cultured and analyzed at a designated single center (Department of Microbiology, Hanyang University College of Medicine, Seoul, Korea).

The participants were allocated to the therapy group in a 1:1 ratio using stratified block randomization. If eligible based on assessments for the inclusion/exclusion criteria, the participant was assigned a participant number in the chronological order of enrolment. All randomization information was securely stored and accessible only to authorized personnel.

The participants were instructed to take the following drugs: one tegoprazan 50 mg or lansoprazole 30 mg tablet and one matched placebo capsule; two amoxicillin 500 mg capsules; and one clarithromycin 500 mg tablet. All the drugs including tegoprazan or lansoprazole and antibiotics were administered orally twice a day for 7 days after meals at the same time.

At the end of the treatment period, physical examination, vital sign assessments, and clinical laboratory tests were performed. CYP2C19 genotyping were performed using the blood samples by Green Cross LabCell Corp. Adverse events (AEs), concomitant medications, and treatment compliance were assessed by a well-trained investigator. The participants were followed up and evaluated for *H. pylori* status after an additional 28 to 56 days, after the end of the treatment (Fig. 1). Because some drugs could affect the accuracy of the UBT, the study participants were not allowed to take any antibiotics, PPIs, or bismuth products within 4 weeks prior to the test.

H. pylori eradication was determined using ^{13}C-UBTs performed by a central laboratory (Green Cross LabCell Corp., Yongin, Korea). The cutoff value was 2.0%; if the UBT result was ≤2%, it was considered "negative." The CYP2C19 genotyping and antimicrobial susceptibility tests were performed only for the participants who consented to the tests. The final result of this study will be disseminated to the participants by mail.

1) *H. pylori* culture and isolation

Two biopsy specimens were obtained from the antrum of the stomach of each patient, stored in a deep freezer below –80℃. The samples were maintained at a temperature of –80℃ to –20℃ during transport to a designated laboratory center, at the Department of Microbiology, Hanyang University College of Medicine. The transportation time of most specimens did not exceed 2 hours. Bacteria were isolated from frozen specimens under microaerophilic conditions (5% O_2, 10% CO_2, and 85% N_2). The specimens were

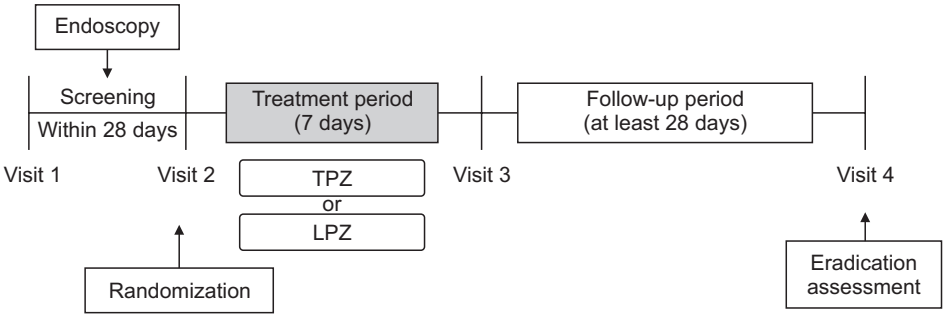

Fig. 1. Schematic diagram showing the study design.
TPZ, tegoprazan-based triple therapy; LPZ, lansoprazole-based triple therapy.

inoculated onto Brucella agar base supplemented with 7% sheep blood, vancomycin (10 mg/mL), trimethoprim (5 mg/mL), amphotericin B (5 mg/mL), and polymyxin B (1.25 U/mL). The plates were incubated at 37℃ under microaerophilic conditions for 5 to 7 days. The isolated bacteria were placed in a Brucella liquid medium containing 15% glycerol and stored in a deep freezer below –80℃.

Suspected *H. pylori* colonies were subcultured and evaluated based on the colony morphological features; Gram staining; and positive reaction with urease, oxidase, and catalase. Subsequently, *H. pylori* was identified using polymerase chain reaction for the *UreC* gene. The primers for *H. pylori UreC* (GenBank Accession No. M60398.1) were as follows: sense primer, 5′-AAG CTT TTA GGG GTG TTA GGG GTT T-3′ (positions 1293–1317); and antisense primer, 5′-AAG CTT ACT TTC TAA CAC TAA CGC-3′ (positions 1586–1563). The polymerase chain reactions were performed in an automated thermal cycler (2720 Thermal Cycler; Applied Biosystems, Foster City, CA, USA) under the following conditions: 35 cycles each of 1 minute at 94℃, 1 minute at 55℃, and 1 minute at 72℃. The polymerase chain reaction products were assessed using gel electrophoresis (expected amplicon size, 294 bp), for verifying the presence of the *UreC* gene in the cultured bacteria.

2) MIC analysis

The MICs of amoxicillin (Sigma Chemical Co., St. Louis, MO, USA) and clarithromycin (Sigma Chemical Co.) in the isolates were measured using the serial 2-fold agar dilution method. The reference used for susceptibility testing was chosen based on the recommendations of the Clinical and Laboratory Standards Institute. *H. pylori* ATCC 43504 was used as the reference strain. The resistance breakpoint for amoxicillin was defined as >0.125 μg/mL, as recommended by the European Committee on Antimicrobial Susceptibility Testing guidelines. The breakpoint for clarithromycin was defined as >0.5 μg/mL, according to Clinical and Laboratory Standards Institute guidelines.

3) Outcome parameters used to assess efficacy

The primary efficacy endpoint was the *H. pylori* eradication rate determined based on the UBT performed at the central laboratory. The secondary efficacy endpoints were as follows: (1) *H. pylori* eradication rate according to the MICs of clarithromycin and amoxicillin; (2) *H. pylori* eradication rate according to the endoscopic underlying disease; and (3) *H. pylori* eradication rate according to the CYP2C19 genotype.

4) Safety assessment

Safety was evaluated via physical examination, electrocardiography, vital signs, laboratory tests (complete blood count with differential, blood chemistry, blood coagulation tests and urinalysis), and incidence of treatment-emergent adverse events (TEAEs). A TEAE was defined as an AE occurring after the participant received the study drug. TEAEs were categorized based on severity and relativity and compared between the treatment groups. All TEAEs, including AEs, adverse drug reactions, and serious AEs, were coded based on the System Organ Classes and Preferred Terms by using MedDRA and compared between treatment groups.

4. Statistical analyses

The *H. pylori* eradication rate was assumed as 79.8% for lansoprazole-based triple therapy based on earlier reports[15] and 86.0% for tegoprazan-based triple therapy, using the upper limit of the confidence interval (CI). The sample size was determined as 140 participants per treatment group to achieve 95% power to detect the non-inferiority of tegoprazan to lansoprazole with a non-inferiority margin of 10%. The non-inferiority margin was determined according to previous studies.[15,16] The sample size was 350 participants with 175 participants per group, considering a 20% dropout rate. Efficacy were primarily assessed in the per-protocol set (PPS) according to Food and Drug Administration;[17] Primary endpoint was assessed in an intention-to-treat (ITT), full analysis set (FAS) and PPS, but subgroups were analyzed primarily in the PPS. The PPS was defined as all participants in the FAS after excluding any of the following criteria: (1) withdrawal from the study without participation for the entire duration; (2) incomplete procedures for the primary endpoint; (3) never administered study drug; (4) administered with any contraindicated medication; (5) less than 80% of compliance; (6) performing UBT within 14 days from the last dose of rescue drug (H2-receptor antagonist); and (7) other significant protocol violations. The safety analysis set (SAS) was defined as all participants enrolled in the study who received at least one dose of study treatment and had at least one safety assessment.

Non-inferiority tests were used to compare the primary endpoints. The chi-square test or the Fisher exact test was used to assess the differences between the treatment groups which included age, sex, underlying endoscopic disease, clarithromycin resistance, amoxicillin resistance, and CYP2C19 genotype. The risk factors for *H. pylori* eradication failure were used for the multivariable logistic regression analysis. Statistical analyses were performed using the SAS software (version 9.3; Windows, SAS Institute, NC, USA). The non-inferiority test was used if the lower

limit of the two-sided 95% CI for the difference between the two arms was greater than the non-inferiority margin, –10%. Two-sided p-values <0.05 were considered statistically significant. Subgroup analyses were conducted using the chi-square test or the Fisher exact test.

RESULTS

1. Baseline characteristics

Among the 528 participants who provided written informed consent, 350 eligible participants were randomly allocated to receive triple therapy with tegoprazan (n=175, TPZ) or lansoprazole (n=175, LPZ) (Fig. 2). Three and two patients who either withdrew consent or did not meet the inclusion criteria were excluded from the TPZ and LPZ groups, respectively. All participants who received at least one dose of the study drug were assigned to the set for safety analysis. Therefore, 172 and 173 participants were assigned to the TPZ and LPZ groups, respectively (SAS). The FAS included all the eligible patients based on inclusion and exclusion criteria from the SAS. A total of 321 participants (161 TPZ group and 160 LPZ group) completed the eradication therapy (Fig. 2).

The primary endpoint was evaluated for the participants in an ITT set, FAS and PPS. Finally, 150 patients each from the TPZ and LPZ groups were included in the efficacy evaluation (PPS) (Fig. 2). The demographic and other baseline characteristics of the TPZ and LPZ groups in the ITT and PPS are summarized (Table 1, Supplementary Table 1). The baseline characteristics were not remarkably different between the treatment groups in both ITT and PPS.

2. Efficacy analyses

The *H. pylori* eradication rate of each TPZ and LPZ group was 62.86% (110/175) and 60.57% (106/175) in an

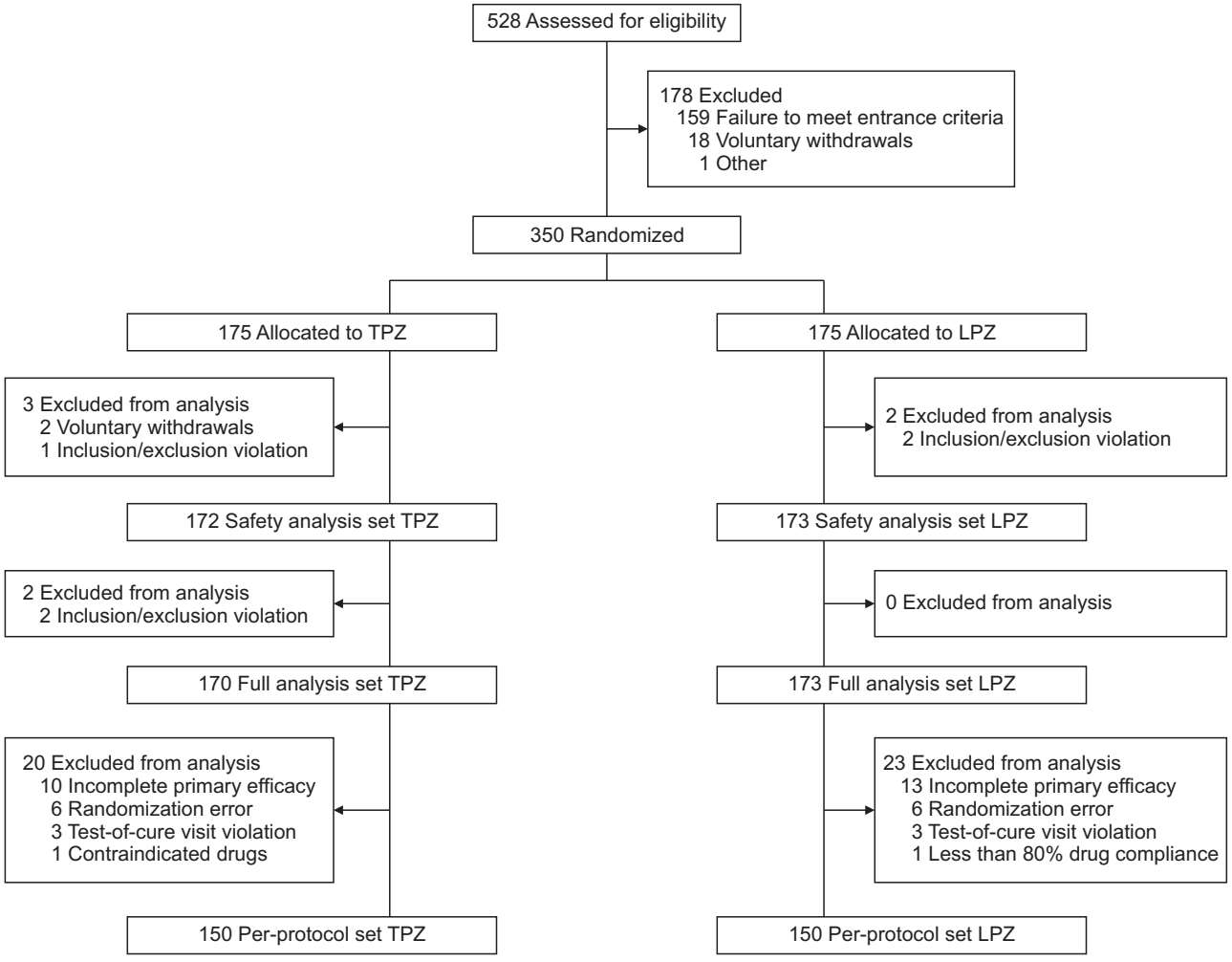

Fig. 2. CONSORT flow diagram. From the tegoprazan-based triple therapy (TPZ) and lansoprazole-based triple therapy (LPZ) groups, 161 and 160 participants, respectively, completed the eradication therapy.

Table 1. Demographic and Baseline Characteristics (Intention-to-Treat)

Characteristics	TPZ (n=175)	LPZ (n=175)
Age, yr	54.71±11.24	53.19±10.88
Sex		
Male	85 (48.57)	83 (47.43)
Female	90 (51.43)	92 (52.57)
Height, cm	164.03±9.32	163.31±8.56
Weight, kg	65.64±11.26	64.17±11.95
Smoking		
Yes	26 (14.86)	24 (13.71)
No	149 (85.14)	151 (86.29)
Alcohol drinking		
Yes	57 (32.57)	76 (43.43)
No	118 (67.43)	99 (56.57)
Underlying gastric diseases		
Peptic ulcer disease	50 (28.57)	50 (28.57)
Chronic atrophic gastritis	125 (71.43)	125 (71.43)
CYP2C19 genotype test*		
Extensive/Intermediate metabolizer	127 (88.81)	129 (85.43)
Poor metabolizer	16 (11.19)	22 (14.57)
Clarithromycin susceptibility†		
Susceptible or intermediate (MIC ≤0.5 μg/mL)	27 (72.97)	26 (66.67)
Resistant (MIC >0.5 μg/mL)	10 (27.03)	13 (33.33)
AMX susceptibility†		
Susceptible or intermediate (MIC ≤0.125 μg/mL)	29 (78.38)	28 (71.79)
Resistant (MIC >0.125 μg/mL)	8 (21.62)	11 (28.21)

Data are presented as mean±SD or number (%).
TPZ, tegoprazan-based triple therapy; LPZ, lansoprazole-based triple therapy; CYP, cytochrome P450; MIC, minimum inhibitory concentration; AMX, amoxicillin.
*Only the participants who consented to the genetic test were tested; †Gastric mucosa specimens were obtained from only 88 patients; among them, the MIC test was performed for the 76 patients in whose samples *Helicobacter pylori* culture was successful.

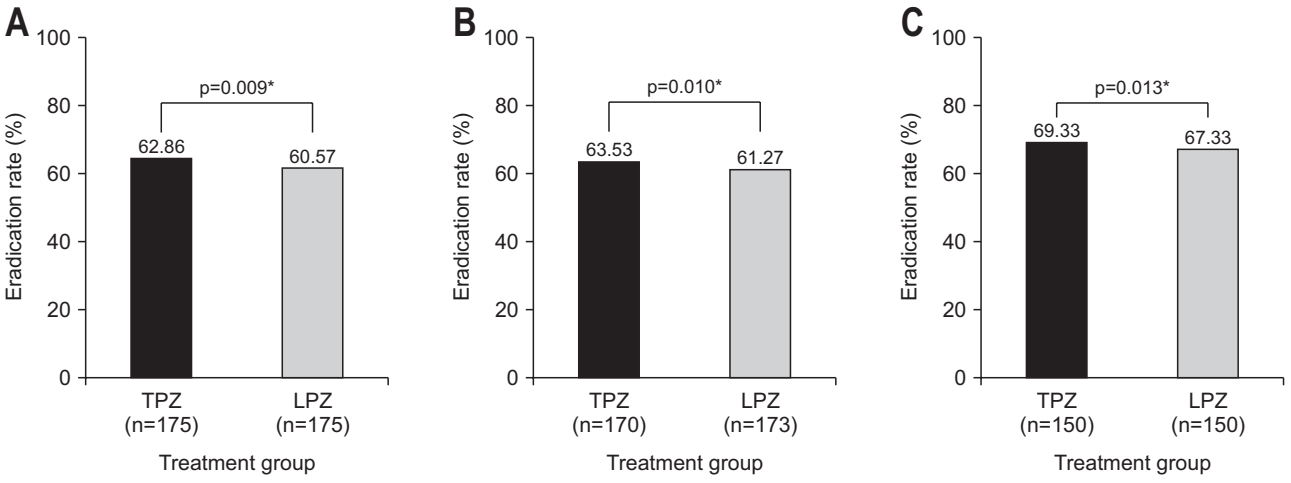

Fig. 3. *Helicobacter pylori* eradication rates with first-line triple therapy in an intention-to treat (A), full analysis (B), and per-protocol set (C). The p-values for non-inferiority tests are provided.
TPZ, tegoprazan-based triple therapy; LPZ, lansoprazole-based triple therapy. *Statistically significant.

ITT analysis, 63.53% (108/170) and 61.27% (106/173) in the FAS (non-inferiority test, p=0.009 and p=0.010) (Fig. 3A and B). In the PPS, the eradication rate was 69.33% (104/150) in the TPZ group and 67.33% (101/150) in the LPZ group (Fig. 3C).

The two-sided 95% CI for the difference in the *H. pylori* eradication rate between the TPZ and LPZ groups was –8.53 and 12.50, respectively. Therefore, tegoprazan-based triple

therapy was noninferior to lansoprazole-based triple therapy as the lower limit of the CI was above the non-inferiority margin of –10% (p=0.013).

Further analyses of *H. pylori* eradication rates were performed for the following subgroups in the PPS: underlying gastric diseases based on endoscopic findings, age, sex, resistance to clarithromycin or amoxicillin, and CYP2C19 genotype. The eradication rates of participants with peptic ulcers in the TPZ and LPZ groups were 76.19% and 66.67%, respectively. There was no statistically significant difference (p=0.327) (Fig. 4A).

The *H. pylori* eradication rate was lower in patients infected with clarithromycin-resistant strains (MIC >0.5 μg/mL) than in those with clarithromycin-susceptible or clarithromycin-intermediate sensitivity strains (MIC ≤0.5 μg/mL), in both regimen groups (Fig. 4B). However, subtype analysis according to the MIC differences of clarithromycin and amoxicillin or according to CYP2C19 polymorphisms showed no significant difference between the two regimens (Fig. 4B and C, Supplementary Tables 2 and 3). The eradication rates did not significantly differ between the two groups when analyzed by age and sex (Fig. 4D and

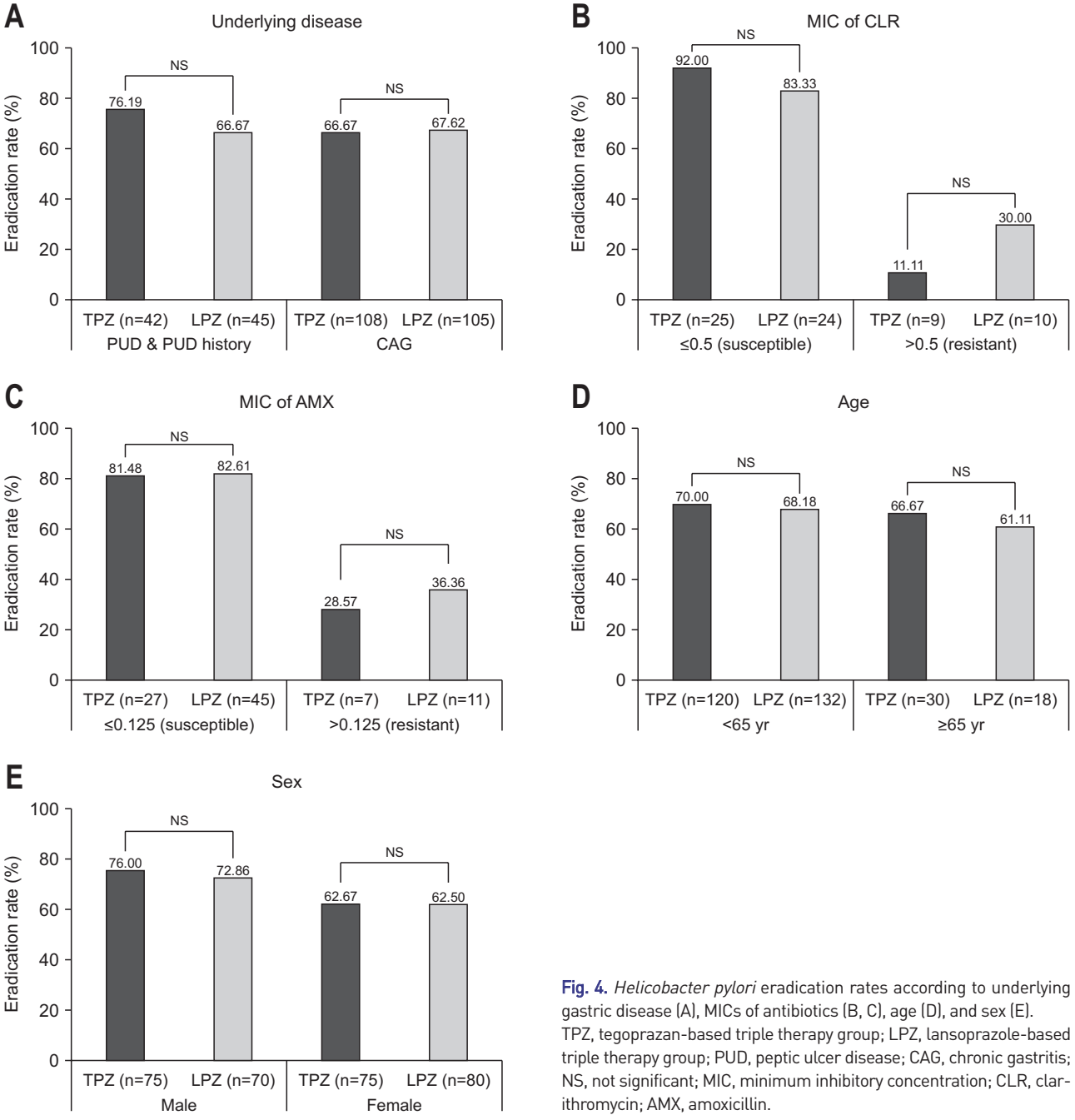

Fig. 4. *Helicobacter pylori* eradication rates according to underlying gastric disease (A), MICs of antibiotics (B, C), age (D), and sex (E).
TPZ, tegoprazan-based triple therapy group; LPZ, lansoprazole-based triple therapy group; PUD, peptic ulcer disease; CAG, chronic gastritis; NS, not significant; MIC, minimum inhibitory concentration; CLR, clarithromycin; AMX, amoxicillin.

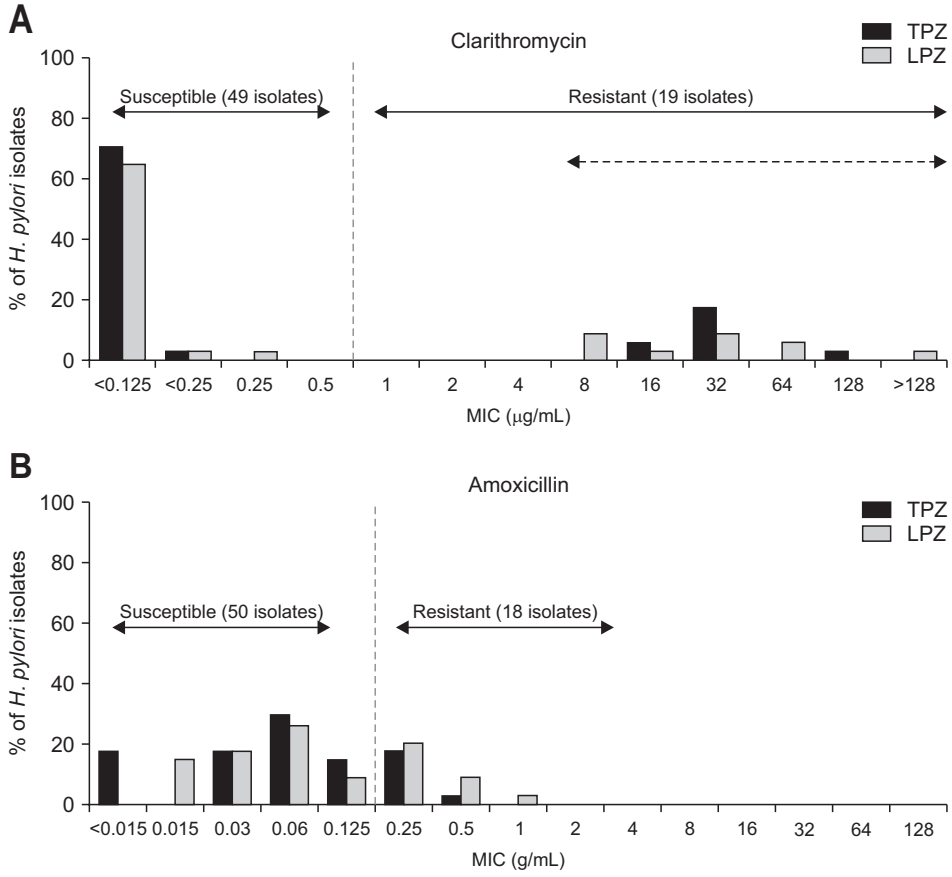

Fig. 5. Distribution of the minimum inhibitory concentration (MIC) of clarithromycin (A) and amoxicillin (B), determined using the *Helicobacter pylori* isolates obtained from study participants. The dotted line indicates the break point for each antibiotic. The breakpoints for clarithromycin and amoxicillin were 0.5 μg/mL and 0.125 μg/mL, respectively; however, they are placed a little to the right of the breakpoint, for readability. The majority of isolates (dotted arrow) resistant to clarithromycin had MIC values ranging from 8 to 128 μg/mL.
LPZ, lansoprazole-based triple therapy; TPZ, tegoprazan-based triple therapy.

E). Results from subgroup analyses for FAS were not different from those for PPS (Supplementary Fig. 1).

In addition, multivariate logistic regression analysis showed that sex, age, smoking, CYP2C19 genotype, and type of acid blocker did not significantly affect the eradication rate; however, clarithromycin resistance had a significant negative impact (odds ratio, 0.04; 95% CI, 0.01 to 0.19; p<0.001) (Supplementary Table 4).

3. Antimicrobial susceptibility results

Gastric tissue collection for antimicrobial susceptibility testing was performed only for participants who consented to the tissue collection procedure. Gastric mucosal specimens were collected from 88 of 350 participants. Antimicrobial susceptibility test results were obtained for 76 participants; for 12 participants, *H. pylori* could not be isolated from the specimens (*H. pylori* culture success rate, 86.3%). The resistance rates to clarithromycin and amoxicillin in this study were 30.3% (23/76) and 25.0% (19/76), respectively.

After excluding eight cases who were not included in the PPS, the antimicrobial susceptibility result was analyzed (Fig. 5). In 19 of the 68 participants (27%), *H. pylori* showed resistance to clarithromycin. The MIC distributions were as follows: 8 μg/mL (n=3), 16 μg/mL (n=3), 32 μg/mL (n=9), 64 μg/mL (n=2), 128 μg/mL (n=1), and 128 μg/mL or higher (n=1) (Fig. 5A). In the case of amoxicillin, 18 of the 68 participants (26.5%) showed resistance. The MIC profile was as follows: 0.25 μg/mL (n=13), 0.5 μg/mL (n=4), and 1 μg/mL (n=1) (Fig. 5B).

4. Safety analyses

The overall incidence of TEAEs was 41.86% in the TPZ group compared with 39.31% in the LPZ group (37.79% vs 33.53% for drug-related TEAEs). The incidence of TEAEs, drug-related TEAEs, TEAEs leading to study drug discontinuation, and serious TEAEs were comparable between the treatment groups (Table 2). One participant each in the TPZ and the LPZ groups, who experienced urticaria and diarrhea, respectively, quit the treatment; these participants voluntarily withdrew from the study (Table 2). TEAEs such as diarrhea, dysgeusia, upper abdominal pain, and headache were noted in >2% of the participants (Table 3). The TEAEs did not significantly differ between the tegoprazan-based and lansoprazole-based triple therapies. Two serious TEAEs were reported in patients receiving lansoprazole-based triple therapy. No significant changes were observed between the two groups with respect to the vital signs, or

Table 2. Summary of TEAEs for TPZ and LPZ (Safety Analysis Set)

Variable	TPZ (n=172)		LPZ (n=173)		p-value*
	Events	No. of subject (%)	Events	No. of subject (%)	
TEAEs	118	72 (41.9)	108	68 (39.3)	0.629
Related	105	65 (37.8)	91	58 (33.5)	
Not related	13	10 (5.8)	17	13 (7.5)	
Mild	109	69 (40.1)	88	57 (33.0)	
Moderate	9	5 (2.9)	18	13 (7.5)	
Severe†	0	0	2	2 (1.2)	
Leading to study drug discontinuation‡	1	1 (0.6)	1	1 (0.6)	
Serious TEAEs	0	0	2	2 (1.2)	0.499
Related	0	0	0	0	
Not related	0	0	2	2 (1.2)	

TEAEs, treatment-emergent adverse events; TPZ, tegoprazan-based triple therapy; LPZ, lansoprazole-based triple therapy.
*Chi-square test or Fisher exact test; †Both cases were not drug related; ‡The symptoms were not severe, but the subjects wanted to withdraw from the study.

Table 3. TEAEs Occurring in >2% of Subjects in the Treatment Groups

MedDRA (system organ class)*,†	TPZ (n=172)	LPZ (n=173)
Gastrointestinal disorders	46 (26.74)	44 (25.43)
Diarrhea	31 (18.02)	25 (14.45)
Upper abdominal pain	11 (6.40)	2 (1.16)
Abdominal distension	6 (3.49)	2 (1.16)
Dyspepsia	4 (2.33)	6 (3.47)
Nausea	4 (2.33)	3 (1.73)
Abdominal discomfort	0	4 (2.31)
Constipation	0	4 (2.31)
Dry mouth	0	4 (2.31)
Gastroesophageal reflux disease	0	4 (2.31)
Nervous system disorders	28 (16.28)	28 (16.18)
Dysgeusia	20 (11.63)	18 (10.40)
Headache	9 (5.23)	6 (3.47)
Dizziness	2 (1.16)	4 (2.31)
Skin and subcutaneous tissue disorders	4 (2.33)	1 (0.58)
Urticaria	4 (2.33)	1 (0.58)

Data are presented as number (%).
TEAEs, treatment-emergent adverse events; TPZ, tegoprazan-based triple therapy; LPZ, lansoprazole-based triple therapy.
*MedDRA (version 21.1); †Chi-square test or Fisher exact test.

electrocardiogram findings mean laboratory test values including aspartate aminotransferase and alanine aminotransferase. In particular, no TEAE suggesting hepatotoxicity occurred in either group.

DISCUSSION

To the best of our knowledge, this is the first randomized, double-blind, controlled phase III study for evaluating the efficacy of *H. pylori* eradication using a triple therapy regimen containing tegoprazan, a novel P-CAB, in *H. pylori*-infected South Korean participants. The results indicated the non-inferiority of tegoprazan-based first-line triple therapy to lansoprazole-based triple therapy, in terms of *H. pylori* eradication rate, with a non-inferiority margin of 10%. Subgroup analyses according to MICs or CYP2C19 did not show remarkable differences in the eradication rate. Both first-line triple therapies were well tolerated with no notable differences.

A recent, randomized, active comparator-controlled phase III study conducted by Murakami *et al.*[16] in Japan showed that the triple therapy including vonoprazan had a markedly higher *H. pylori* eradication rate than the PPI-based triple therapy (82% vs 40%) in patients infected with clarithromycin-resistant *H. pylori* strains. The increased eradication rates were partly attributable to the potential synergy between vonoprazan and the antimicrobials used because *H. pylori* is more susceptible to antimicrobials when its replicative capability is restored at a pH higher than 6. Our previous study on healthy participants showed that treatment with tegoprazan (50 or 100 mg)-based triple therapy enabled significantly higher gastric acid suppression than PPI-based triple therapy.[14] However, in this study, triple therapy containing tegoprazan, a new P-CAB, failed to provide a better outcome, unlike that in the vonoprazan-based triple therapy in Japan.[16] The tegoprazan-based triple therapy showed non-inferiority, and not superiority, to lansoprazole-based triple therapy in terms of *H. pylori* eradication. This result was not significantly different from that of the analysis based on susceptibility to clarithromycin or amoxicillin or CYP2C19 gene polymorphism.

The reason why tegoprazan failed to show superiority over a PPI in *H. pylori* eradication is not clear; however, there are several hypotheses. First, it is possible that the tegoprazan dose used in this study was not sufficient to enhance the effects of clarithromycin and its metabolites. The administration of 100 mg of tegoprazan increases the levels of clarithromycin and its metabolite (14-hydroxy-

clarithromycin) by only 1.1 and 1.3 times, respectively.[14] The minimal concentration of tegoprazan (as a component of triple therapy) that can elicit an anti-*H. pylori* effect is 128 μg/mL. This cannot be reached easily in humans, considering that the highest concentration observed in human plasma is 1.4 μg/mL.[18] Second, although both vonoprazan and tegoprazan are P-CABs, they differ in their binding sites, half-life, efficacy, and serum gastrin levels. These differences could contribute to the differences in the anti-*H. pylori* properties of vonoprazan- and tegoprazan-based triple therapy regimens. Third, the potential inhibitory effect on P-glycoprotein and CYP3A4/5 and acid inhibition could increase the concentrations of clarithromycin and its metabolite at the systemic level.[19] Another possible cause for the differences between the effects reported for vonoprazan and tegoprazan could be the differences in the characteristics of the study participants rather than that of the drugs. The MIC distribution of clarithromycin- or amoxicillin-resistant *H. pylori* strains varies across countries. Such regional differences in antimicrobial resistance rates could be a plausible explanation for eradication rates lower than that in the Japanese study.[20-22] There is a possibility that in this study, the MIC distributions for clarithromycin- or amoxicillin-resistant *H. pylori* strains are skewed to the right compared with those reported in the Japanese study on *H. pylori* eradication with vonoprazan-based triple therapy.[16]

In another Japanese study,[22] MICs ≥16 μg/mL were not obtained. However, the majority of the clarithromycin-resistant *H. pylori* in this study had MICs >8 μg/mL and some even had an MIC >128 μg/mL (Fig. 5A). There was almost no resistance to amoxicillin in the earlier study;[22] however, in this study, many of the isolated *H. pylori* colonies showed an MIC ≥0.03 mg/mL for amoxicillin; this was used as a breakpoint in the previous Japanese study with vonoprazan.[16] The resistance rate to clarithromycin is similar to that previously reported in Korea,[21] but the resistance rate to amoxicillin was high, which could be attributed to the low cutoff value of >0.125 μg/mL. Low *H. pylori* eradication rates (68.4%) with 14-day vonoprazan-based triple therapy was reported in a study in Thailand, where the rate of clarithromycin-resistant strains is high (16%).[23] If the clarithromycin resistance increases with the vonoprazan-based triple therapy regimen as second-line therapy, the effectiveness of vonoprazan is reduced.[24] Therefore, considering the results from the various studies, the differences are possibly related to the strength of resistance. Future studies on alternative P-CAB-based triple therapies targeting a population with varying antimicrobial MIC profiles are necessary.

Additionally, the subgroups analysis with ulcer-patients revealed that the eradication rate tended to be higher in the tegoprazan group than in the lansoprazole group (76.19% vs 66.67%), although there was no significant difference (p=0.327). TPZ is superior to LPZ in a strong acidic environment; however, further studies are needed to determine whether TPZ is more effective in the ulcer group. In the present study, clarithromycin resistance was the only significant risk factor for eradication failure (Supplementary Table 4).

The current study reported the safety of tegoprazan-based triple therapy. The SAS analysis showed that the TEAE incidence did not significantly differ between the tegoprazan- and lansoprazole-based triple therapy regimens (41.9% [72/172] vs 39.3% [68/173]). The incidence of upper abdominal pain was significantly higher in the tegoprazan group (11 patients) than that in the lansoprazole group (two patients). However, the patients had only mild symptoms and showed spontaneous improvement. In addition, no significant drug-related TEAEs or newly identified safety profiles were observed in the study.

This study has several limitations. The MIC tests were performed only in a part of the study population because many participants refused consent for the mucosa biopsy, which is essential for MIC testing. Therefore, the sub-analysis on antibiotic resistance based on the MIC should be interpreted carefully. However, the MIC distributions and eradication rates were similar to those observed in a Korean nationwide study on 590 adults.[25] The strict randomization process enabled a considerably low possibility of an uneven distribution of antibiotic-resistant strains between the two groups.

This randomized, double-blind study provided evidence that tegoprazan-based 7-day triple therapy can be used for first-line *H. pylori* therapy, similar to the standard PPIs-based 7-day triple therapy. However, simply replacing PPIs with tegoprazan in triple therapies may not be sufficient to manage clarithromycin-resistant *H. pylori* strains. Analyses according to the MIC values, studies on other tegoprazan-based therapeutic regimens including 14-day triple therapy, high-dose amoxicillin dual therapy or quadruple therapy are warranted to ascertain whether tegoprazan-based therapy is more effective than PPIs-based therapy for *H. pylori* eradication.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Study concept and design: Y.C.L., J.M.K. Data acquisition: all authors. Data analysis and interpretation: all authors. Drafting of the manuscript: Y.J.C. Critical revision of the manuscript for important intellectual content: Y.C.L., J.M.K. Approval of final manuscript: all authors.

ORCID

Yoon Jin Choi https://orcid.org/0000-0002-1922-9388
Yong Chan Lee https://orcid.org/0000-0001-8800-6906
Jung Mogg Kim https://orcid.org/0000-0002-6506-7519
Jin Il Kim https://orcid.org/0000-0001-6801-6891
Jeong Seop Moon https://orcid.org/0000-0002-5909-8159
Yun Jeong Lim https://orcid.org/0000-0002-3279-332X
Gwang Ho Baik https://orcid.org/0000-0003-1419-7484
Byoung Kwan Son https://orcid.org/0000-0002-9299-5476
Hang Lak Lee https://orcid.org/0000-0002-2825-3216
Kyoung Oh Kim https://orcid.org/0000-0002-5365-2550
Nayoung Kim https://orcid.org/0000-0002-9397-0406
Kwang Hyun Ko https://orcid.org/0000-0001-5168-1377
Hye-Kyung Jung https://orcid.org/0000-0002-6653-5214
Ki-Nam Shim https://orcid.org/0000-0003-4004-6292
Hoon Jai Chun https://orcid.org/0000-0002-5539-361X
Byung-Wook Kim https://orcid.org/0000-0002-2290-4954
Hyuk Lee https://orcid.org/0000-0003-4271-7205
Jie-Hyun Kim https://orcid.org/0000-0002-9198-3326
Hyunsoo Chung https://orcid.org/0000-0001-5159-357X
Sang Gyun Kim https://orcid.org/0000-0003-1799-9028
Jae Young Jang https://orcid.org/0000-0002-7930-1468

SUPPLEMENTARY MATERIALS

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