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Tegoprazan-Based Triple Therapy for *Helicobacter pylori* Eradication: A Phase III Multicenter Randomized Clinical Trial

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ABSTRACT

Background: Tegoprazan, a potassium-competitive acid blocker, offers potent and sustained acid inhibition and potentially improves eradication efficacy.

Aim: This study aimed to evaluate the efficacy and safety of tegoprazan-based triple therapy with two dosing regimens compared with that of lansoprazole-based therapy for first-line *Helicobacter pylori* eradication.

Methods: This randomized, double-blind, active-controlled, multicenter trial was conducted at 19 referral hospitals in South Korea (February 2023–April 2024). Treatment-naïve adults with *H. pylori* infection were randomized 1:1:1 to receive 14-day triple therapy with tegoprazan, 50 mg (TAC1), tegoprazan, 100 mg (TAC2), or lansoprazole, 30 mg (LAC), each combined with amoxicillin 1000 mg and clarithromycin 500 mg, administered twice daily. The primary endpoint was *H. pylori* eradication rate in the modified intention-to-treat (mITT) population, with a non-inferiority margin of −10%. Secondary endpoints included subgroup analyses based on clarithromycin resistance and safety assessments.

Results: Of the 564 screened patients, 382 were randomized. In the mITT analysis (mean age, 54.9 years; 54.3% male), eradication rates were 86.0%, 85.5%, and 78.7% for TAC1, TAC2, and LAC, respectively. Both tegoprazan-based regimens met the non-inferiority criteria. Among clarithromycin-resistant infections, the eradication rates were higher for TAC1 (47.8%) and TAC2 (50.0%) than for LAC (35.5%), although the difference was not statistically significant. Safety profiles were comparable across the groups, with no serious drug-related adverse events.
Conclusion: Tegoprazan-based triple therapies, at 50- and 100-mg doses, were non-inferior to lansoprazole-based therapy and were well tolerated. Our findings indicated that tegoprazan-based triple therapy is a viable first-line option for *H. pylori* eradication.
Trial Registration: ClinicalTrials.gov identifier: NCT05933031

1 | Introduction

Tegoprazan is a novel potassium-competitive acid blocker (P-CAB) developed in South Korea, approved for the treatment of gastroesophageal reflux disease and other acid-related disorders [1, 2]. Unlike proton pump inhibitors (PPIs), which require activation by acid and act only on active proton pumps, P-CABs competitively inhibit the potassium-binding site of H^+/K^+-ATPase in gastric parietal cells without acid activation, leading to more rapid, potent, and sustained acid suppression.

Helicobacter pylori is a major etiological agent of chronic gastritis and peptic ulcers and plays a key role in gastric carcinogenesis [3]. Effective eradication requires a combination of antibiotics and potent acid suppression to stabilize acid-labile agents and enhance their bioavailability [4]. For instance, the bactericidal activity of β-lactam antibiotics is significantly reduced under highly acidic conditions due to impaired bacterial division, while clarithromycin shows optimal tissue penetration at near-neutral pH [5, 6]. Due to their pharmacologic advantages, P-CABs have emerged as promising alternatives to PPIs, particularly in *H. pylori* eradication therapy. In recent studies, P-CAB-based triple therapy achieved superior eradication rates to PPI-based regimens, likely owing to its effective acid suppression [7–9].

Standard triple therapy (STT) with PPI, amoxicillin, and clarithromycin has long been the recommended first-line treatment worldwide [10, 11]. However, the efficacy of 7-day STT has declined in recent years, with eradication rates dropping below 80% in many regions, mainly owing to increasing clarithromycin resistance [12]. To address this issue, extended treatment duration and use of higher dose acid suppressants have been proposed to overcome antibiotic resistance. In South Korea, the revised 2020 Clinical Practice Guidelines recommend 14-day STT as the standard first-line regimen [11]. Supporting this recommendation, real-world data have shown that the 14-day tegoprazan-based triple regimen achieves higher eradication rates (78.6%) than the 7-day regimen (63.9%) [13]. Additionally, an exploratory trial evaluating the effectiveness of a 10-day regimen showed a significantly higher eradication rate with 100 mg of tegoprazan (78.8%) than with 50 mg (60.6%) [14], suggesting a dose–response relationship, possibly attributable to stronger acid suppression at higher doses.

Despite the growing need for effective alternatives in the era of increasing antibiotic resistance, prospective clinical trials evaluating the optimal dose of tegoprazan for *H. pylori* eradication therapy remain scarce. Therefore, the present study aimed to evaluate the efficacy and safety of two dosing regimens of tegoprazan (50 and 100 mg) in STT compared with lansoprazole-based triple therapy for *H. pylori*-positive patients.

2 | Methods

2.1 | Study Design

This was a randomized, double-blind, active-controlled, multicenter, therapeutic exploratory clinical trial designed to evaluate the safety and efficacy of tegoprazan-based triple therapy at two different doses for *H. pylori* eradication in treatment-naïve patients. The trial was conducted at 19 sites in South Korea between February 23, 2023, and April 23, 2024. The study protocol was registered at ClinicalTrials.gov prior to initiation. The study adhered to the approved protocol, Declaration of Helsinki, Good Clinical Practice guidelines, and regulations set forth by the Ministry of Food and Drug Safety. Institutional Review Board approval was obtained from each site, and all participants provided written informed consent. Data were recorded using electronic case report forms.

2.2 | Study Participants

The eligibility criteria included adults aged 19–75 years with confirmed *H. pylori* infection, as evidenced by a positive ^{13}C-urea breath test (UBT), and at least one of the following clinical indications at screening: active gastric or duodenal ulcer, peptic ulcer scars, low-grade gastric mucosa-associated lymphoid tissue lymphoma, history of endoscopic resection for early gastric cancer or gastric adenoma requiring eradication therapy, or chronic atrophic gastritis. All patients were treatment-naïve for *H. pylori* infection. The exclusion criteria included prior *H. pylori* eradication therapy, abnormal gastric acid secretion, and medical conditions or laboratory abnormalities deemed unsuitable for study participation. The full criteria are listed in Appendix S1.

2.3 | Randomization and Interventions

Eligible participants were randomized in a 1:1:1 ratio to receive one of three regimens: 50 mg tegoprazan, twice daily (TAC1 group), 100 mg tegoprazan, twice daily (TAC2 group), or 30 mg lansoprazole, twice daily (LAC group), each combined with 1000 mg of amoxicillin and 500 mg of clarithromycin. All medications were to be taken twice daily before meals for 14 days. Patients were randomized using a central password-protected web-based system with block randomization and predefined

seed codes to minimize allocation bias and ensure balanced distribution across groups. Double blinding was maintained using identical packaging and a double-dummy technique, concealing treatment allocation from all participants and study personnel. The rationale for selecting the dose and duration of the study drugs is detailed in Appendix S1.

2.4 | Procedures and Trial Assessments

Participants were screened during a 28-day screening period and randomly assigned to the study treatment group, followed by a 14-day medication period and an eradication assessment visit 28–38 days after the last dose (Figure 1).

At the screening visit (Visit 1), eligibility was assessed through medical history, review of prior medications, demographics, vital signs, physical examination, upper gastrointestinal endoscopy, clinical laboratory tests (hematology, blood chemistry, coagulation, and urinalysis), electrocardiography (ECG), and pregnancy testing, if applicable. *H. pylori* infection was confirmed by a positive result on the ^{13}C-UBT. Clarithromycin resistance was assessed in participants who consented to biospecimen use, by collecting gastric mucosal tissue during screening endoscopy, followed by 23S rRNA point mutation analysis (A2142G and A2143G) using a commercial PCR kit (Allplex *H. pylori* & ClariR Assay; Seegene Inc., Seoul, South Korea).

At the end of the treatment (Visit 3), clinical laboratory tests, vital signs, ECG, physical examination, adverse event (AE) assessment, and treatment compliance evaluation were conducted. Compliance was defined as the proportion of doses taken within the allowable window; intake of fewer than 23 of the 28 prescribed doses (i.e., $\geq$6 missed doses) by Day 15 + 3 was considered noncompliance (< 80%).

At Visit 4 (28–38 days after the last dose), *H. pylori* eradication was assessed using a centrally analyzed ^{13}C-UBT (in accordance with the FDA guidance for *H. pylori* studies). Eradication was defined as a negative ^{13}C-UBT result within the predefined window or, for the modified intention-to-treat (mITT) analysis, within 28–56 days after the last dose. Failure was defined as a positive UBT result, an indeterminable result, undergoing testing outside the predefined window, or the absence of Visit 4. The primary endpoint was the eradication rate comparing TAC1 with LAC under the non-inferiority hypothesis, while secondary endpoints included the eradication rate comparing TAC2 with LAC and subgroup analyses results stratified by clarithromycin resistance.

AEs and the use of concomitant medications were monitored throughout the study. All AEs, including severity, causality, and outcomes, such as serious AEs (SAEs), adverse drug reactions (ADRs), and treatment discontinuation, were summarized by treatment group. AEs were coded using the Medical Dictionary for Regulatory Activities, version 27.0, and summarized by System Organ Class (SOC) and Preferred Term (PT).

2.5 | Sample Size Calculation

Sample size calculations for this study were based on the non-inferiority hypothesis. Assuming an *H. pylori* eradication rate of 78.6% in the TAC1 group and 68.5% in the LAC group [9, 13], with a non-inferiority margin (δ) set at −0.1, a significance level (α) of 0.025, and a power of 90%, the required sample size per group was determined to be 101 participants [15]. Considering a 20% dropout rate, the final sample size per group was increased to 127 participants, resulting in a total of 381 participants in the TAC1, TAC2, and LAC groups.

2.6 | Statistical Analysis

The demographic and baseline characteristics were summarized using descriptive statistics. Primary and secondary efficacy outcomes were compared using two-sided 95% confidence intervals (CIs) for differences in proportions. Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference in eradication rates exceeded 10%. Missing values for the efficacy endpoints were imputed as treatment failure in the mITT analysis. Subgroup analyses stratified by clarithromycin resistance were conducted using the chi-square or Fisher's exact tests, as appropriate.

The mITT population, defined as all randomized participants who received at least one dose of the study medication and met the key eligibility criteria, was subjected to efficacy analyses.

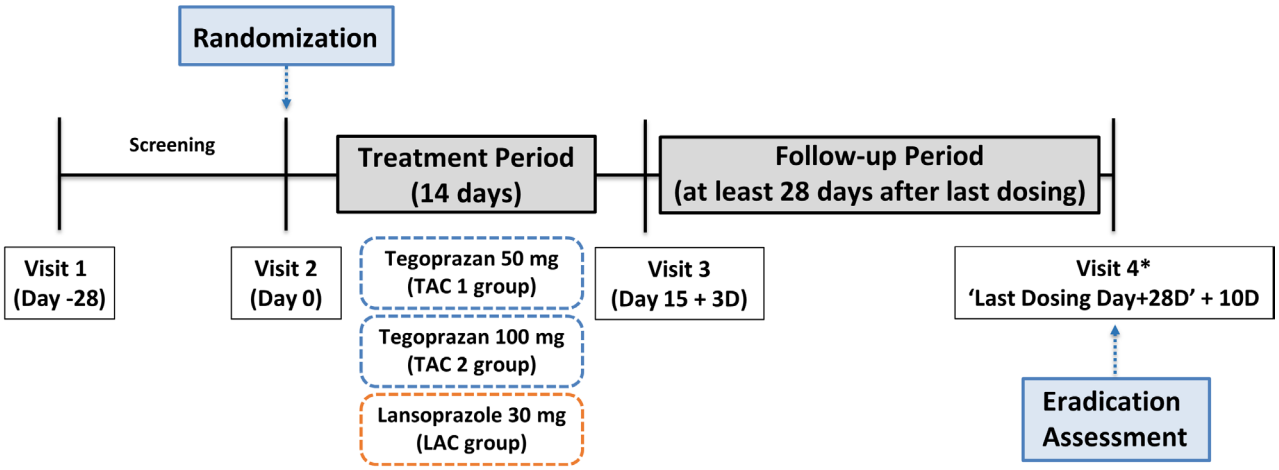

FIGURE 1 | Overview of study protocol.

The per-protocol set (PPS) excluded participants with major protocol deviations including noncompliance, early withdrawal, or intake of prohibited medications. Safety analyses were based on the safety analysis set (SAS), comprising all participants who received at least one dose and provided post-baseline safety data. Between-group comparisons of AE and ADR incidence were conducted using chi-square or Fisher's exact tests, as appropriate. All tests were two-sided with a significance level of 0.05, unless otherwise specified. All the statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

3 | Results

3.1 | Patient Disposition and Baseline Characteristics

A total of 564 participants were screened, of whom 382 were randomly assigned to the TAC1 ($n = 127$), TAC2 ($n = 127$), or LAC ($n = 128$) groups (Figure 2). A total of 364 participants completed the study, and safety was assessed using the SAS ($n = 375$). In the mITT population, three participants (two in TAC1, one in TAC2) from the SAS group were excluded because they violated the eligibility criteria. In the mITT population ($n = 372$), 17 were excluded from the PPS ($n = 355$) because of noncompliance ($n = 6$), consent withdrawal ($n = 5$), use of prohibited concomitant medications ($n = 3$), out-of-window efficacy visits ($n = 2$), or loss to follow-up ($n = 1$).

The baseline characteristics were comparable across the treatment groups in the mITT population (Table 1). The mean age was 54.9 years, and the proportion of male participants was 54.3%. The characteristics of the PPS are summarized in Table S1. Treatment compliance was high, with mean compliance rates of 97.7%, 98.0%, and 98.0% in the mITT population and 99.2%, 99.2%, and 99.2% in the PPS population for the LAC, TAC1, and TAC2 groups, respectively. Clarithromycin resistance-associated 23S rRNA mutations were identified in 19.0% (23/121), 25.8% (32/124), and 24.4% (31/127) of the participants in the TAC1, TAC2, and LAC groups, respectively.

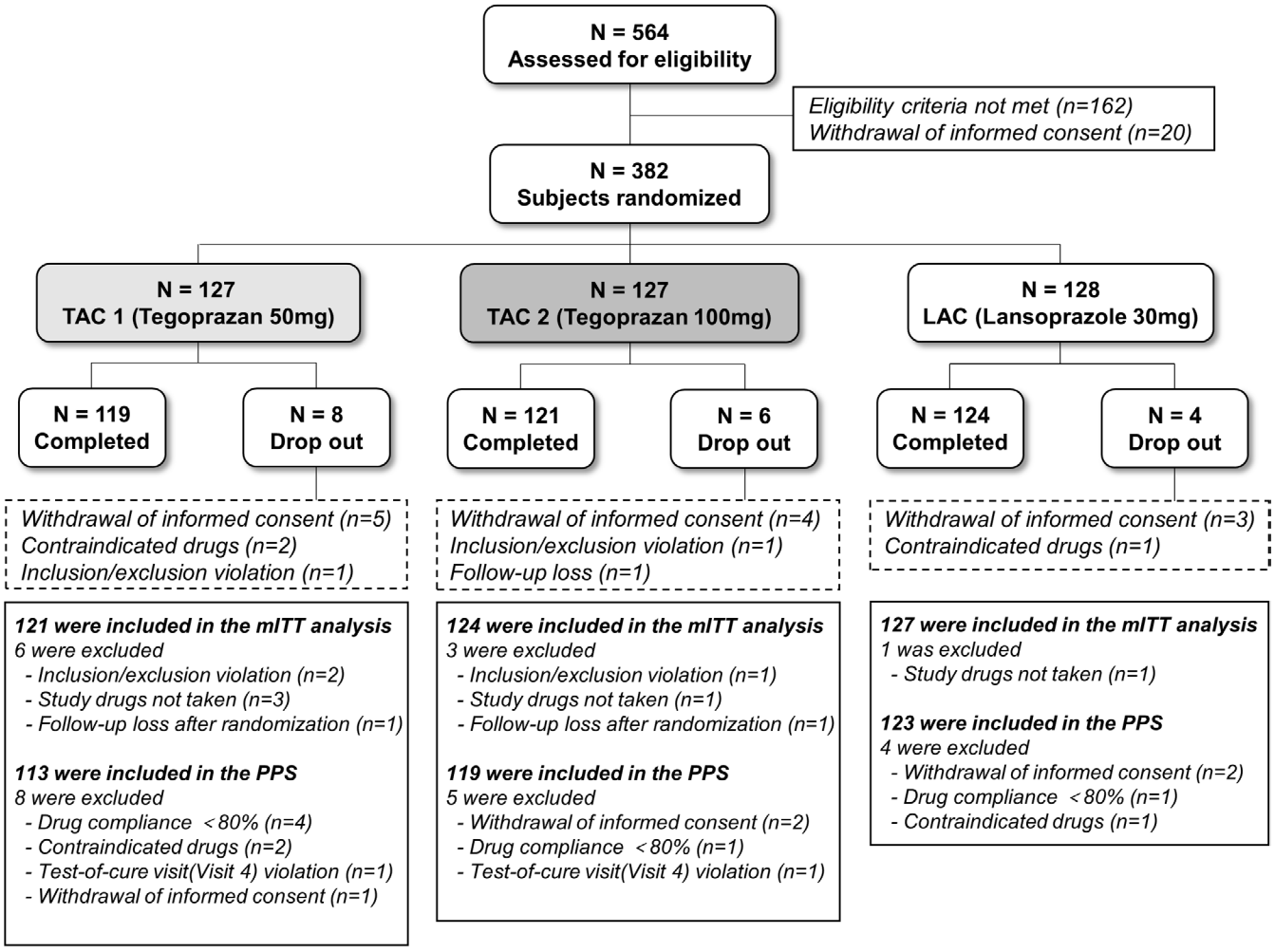

FIGURE 2 | Study enrolment, randomization, and treatment allocation. LAC: lansoprazole 30 mg-based triple therapy; TAC1: tegoprazan 50 mg-based triple therapy; TAC2: tegoprazan 100 mg-based triple therapy. All regimens included amoxicillin 1000 mg and clarithromycin 500 mg, administered orally twice daily before meals for 14 days. The modified intention-to-treat (mITT) population comprised all randomized participants who met the eligibility criteria and received at least one dose of the study drug. Participants with < 80% treatment compliance (assessed at Visit 3 within Day 15 + 3) were excluded from the per-protocol set (PPS), along with those with major protocol deviations (e.g., early withdrawal, prohibited medication use). Missing data for *Helicobacter pylori* eradication were handled as treatment failure in the mITT analyses.

3.2 | Efficacy Analysis

The *H. pylori* eradication rates in the mITT population were 86.0% (104/121), 85.5% (106/124), and 78.7% (100/127) in the TAC1, TAC2, and LAC groups, respectively (Table 2). Compared with LAC, the differences in eradication rate were 7.2% (95% CI: −2.2 to 16.6) for TAC1 and 6.7% (95% CI: −2.7 to 16.2) for TAC2. Both TAC regimens met the non-inferiority criterion compared with LAC, with lower bounds of the confidence intervals exceeding the −10% margin ($p = 0.0002$ for TAC1; $p = 0.0003$ for TAC2).

Similar findings were observed in the PPS population, with eradication rates of 88.5% (100/113), 87.4% (104/119), and 81.3% (100/123) for TAC1, TAC2, and LAC groups, respectively. The

TABLE 1 | Demographic and baseline characteristics (mITT population).

	Tegoprazan 50 mg ($n = 121$)	Tegoprazan 100 mg ($n = 124$)	Lansoprazole 30 mg ($n = 127$)	Total ($n = 372$)
Age, years, mean ± SD	55.32 ± 11.62	55.03 ± 12.82	54.46 ± 12.26	54.93 ± 12.22
Sex, *n* (%)				
Male	58 (47.93)	68 (54.84)	76 (59.84)	202 (54.30)
Female	63 (52.07)	56 (45.16)	51 (40.16)	170 (45.70)
Height, cm, mean ± SD	164.10 ± 8.78	164.73 ± 8.98	165.83 ± 8.86	164.90 ± 8.88
Weight, kg, mean ± SD	66.20 ± 12.93	66.04 ± 12.84	67.23 ± 11.85	66.50 ± 12.52
Smoking, *n* (%)	19 (15.70)	16 (12.90)	33 (25.98)	68 (18.28)
Drinking, *n* (%)	48 (39.67)	41 (33.06)	53 (41.73)	142 (38.17)
Upper gastrointestinal disease[a], *n* (%)				
Peptic ulcer (including ulcer scars)	14 (11.57)	19 (15.32)	24 (18.90)	57 (15.32)
Low-grade gastric MALT lymphoma	1 (0.83)	0 (0.00)	0 (0.00)	1 (0.27)
Endoscopic resection of EGC	12 (9.92)	22 (17.74)	9 (7.09)	43 (11.56)
Endoscopic resection of gastric adenoma	10 (8.26)	20 (16.13)	16 (12.60)	46 (12.37)
Chronic atrophic gastritis	112 (92.56)	113 (91.13)	111 (87.40)	336 (90.32)
23S rRNA genotype, *n* (%)				
No mutation (%)	98 (80.99)	92 (74.19)	96 (75.59)	286 (76.88)
A2142G or A2143G (%)	23 (19.01)	32 (25.81)	31 (24.41)	86 (23.12)

Note: Data are presented as mean ± standard deviation or number (%).
Abbreviations: EGC, early gastric cancer; MALT, mucosa-associated lymphoid tissue; mITT, modified intention-to-treat; SD, standard deviation.
[a]Duplicate counting.

TABLE 2 | *Helicobacter pylori* eradication rates and comparison with LAC group (mITT and PPS populations).

Population	Treatment group	Eradication rate, % (n/N)	Difference vs. LAC, % (95% CI)[a]	*p*
mITT	TAC1	85.95% (104/121)	7.21% (−2.22 to 16.64)	0.0002
	TAC2	85.48% (106/124)	6.74% (−2.69 to 16.18)	0.0003
	LAC	78.74% (100/127)	Reference	—
PPS	TAC1	88.50% (100/113)	7.19% (−1.87 to 16.26)	< 0.0001
	TAC2	87.39% (104/119)	6.09% (−3.02 to 15.21)	0.0003
	LAC	81.30% (100/123)	Reference	—

Note: LAC: lansoprazole 30 mg, amoxicillin 1000 mg, clarithromycin 500 mg. TAC1: tegoprazan 50 mg, amoxicillin 1000 mg, clarithromycin 500 mg. TAC2: tegoprazan 100 mg, amoxicillin 1000 mg, clarithromycin 500 mg.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; PPS, per-protocol set.
[a]Non-inferiority was concluded if the lower limit of the 95% CI exceeded 10%.

differences from LAC were 7.2% (95% CI: −1.9 to 16.3) for TAC1 and 6.1% (95% CI: −3.0 to 15.2) for TAC2, again supporting non-inferiority ($p < 0.0001$ and $p = 0.0003$, respectively).

3.3 | Subgroup Analysis by Clarithromycin Resistance Status

Subgroup analysis based on clarithromycin susceptibility was performed. In the mITT population subgroup without clarithromycin resistance ($n = 286$), the eradication rates were 94.9% (93/98), 97.8% (90/92), and 92.7% (89/96) for TAC1, TAC2, and LAC, respectively (Table 3). The differences between treatment groups were not statistically significant ($p = 0.5267$ for TAC1 vs. LAC; $p = 0.1700$ for TAC2 vs. LAC).

In the subgroup with clarithromycin-resistant *H. pylori* strains ($n = 86$), the eradication rates were 47.8% (11/23), 50.0% (16/32), and 35.5% (11/31) for TAC1, TAC2, and LAC, respectively, with higher rates for TAC1 and TAC2, although the differences were not statistically significant (TAC1 vs. LAC, $p = 0.3614$; TAC2 vs. LAC, $p = 0.2444$). Similarly, no significant differences were observed between the treatment groups in the PPS analysis (Table 3).

3.4 | Safety Analysis

Safety was evaluated for the 375 participants who received at least one dose of the study drug and had available safety data (SAS). The overall incidence of AEs was 45.5% (56/123 participants, 97 events) in the TAC1 group, 46.4% (58/125 participants, 115 events) in the TAC2 group, and 39.4% (50/127 participants, 83 events) in the LAC group (Table 4). The most frequently reported AE was diarrhea, which occurred in 12.2% (15/123), 22.4% (28/125), and 16.5% (21/127) of the patients in the TAC1, TAC2, and LAC groups, respectively. Most laboratory test results showed similar patterns before and after treatment or remained within normal ranges. Abnormal values were generally transient, mild in severity, nonspecific across all treatment arms, and not considered clinically significant. The incidences of AEs, ADRs, and AEs leading to treatment discontinuation were comparable across the groups. No AEs were classified as "severe" in any treatment group, and no SAEs occurred during the study period.

4 | Discussion

In this randomized, double-blind, multicenter trial, we evaluated the efficacy and safety of two tegoprazan-based triple regimens (50 and 100 mg) compared with a standard lansoprazole-based triple regimen for *H. pylori* eradication. Both tegoprazan-based regimens achieved non-inferior eradication rates to lansoprazole in the mITT population, exceeding the clinically relevant threshold of 80% recommended by Korean guidelines [11].

The declining efficacy of STT has been a growing concern due to increasing resistance to clarithromycin, especially in regions with widespread use of macrolides. In South Korea, resistance rates have risen to approximately 18%–31%,

TABLE 3 | *Helicobacter pylori* eradication rates by clarithromycin resistance status (mITT and PPS populations).

CLR resistance status	Treatment group	Eradication rate, % (*n*/*N*)	Difference vs. LAC, % (95% CI)[a]	*p*
mITT analysis				
No resistance	TAC1	94.90% (93/98)	2.19% (−4.59 to 8.97)	0.5267[a]
	TAC2	97.83% (90/92)	5.12% (−0.88 to 11.11)	0.1700[b]
	LAC	92.71% (89/96)	Reference	—
Resistance	TAC1	47.83% (11/23)	12.34% (−14.12 to 38.81)	0.3614[a]
	TAC2	50.00% (16/32)	14.52% (−9.65 to 38.68)	0.2444[a]
	LAC	35.48% (11/31)	Reference	—
PPS analysis				
No resistance	TAC1	96.74% (89/92)	2.06% (−3.75 to 7.87)	0.7206[a]
	TAC2	98.88% (88/89)	4.20% (−0.84 to 9.23)	0.2120[b]
	LAC	94.68% (89/94)	Reference	—
Resistance	TAC1	52.38% (11/21)	14.45% (−13.27 to 42.17)	0.3097[a]
	TAC2	53.33% (16/30)	15.40% (−9.71 to 40.51)	0.2352[a]
	LAC	37.93% (11/29)	Reference	—

Note: LAC: lansoprazole 30 mg, amoxicillin 1000 mg, clarithromycin 500 mg. TAC1: tegoprazan 50 mg, amoxicillin 1000 mg, clarithromycin 500 mg. TAC2: tegoprazan 100 mg, amoxicillin 1000 mg, clarithromycin 500 mg.
Abbreviations: CI, confidence interval; CLR, clarithromycin; mITT, modified intention-to-treat; PPS, per-protocol set.
[a]Chi-square test.
[b]Fisher's exact test.

TABLE 4 | Overall summary of adverse events.

	TAC1 ($n=123$)		TAC2 ($n=125$)		LAC ($n=127$)	
	Events	**Participants**	**Events**	**Participants**	**Events**	**Participants**
SAEs	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)
AEs leading to treatment discontinuation	7	3 (2.44)	4	1 (0.80)	0	0 (0.00)
ADRs	78	49 (39.84)[a]	98	53 (42.40)[a]	72	45 (35.43)[a]
AEs	97	56 (45.53)[a]	115	58 (46.40)[a]	83	50 (39.37)[a]
Most common (occurring in ≥ 2% patient)[b]						
Diarrhea		15 (12.20)		28 (22.40)		21 (16.54)
Taste disorder/dysgeusia		17 (13.82)		23 (18.40)		10 (7.87)
Nausea		6 (4.88)		6 (4.80)		6 (4.72)
Dyspepsia		5 (4.07)		3 (2.40)		3 (2.36)
Headache		2 (1.63)		4 (3.20)		5 (3.94)
Dizziness		6 (4.88)		1 (0.80)		1 (0.79)
Abdominal pain upper		3 (2.44)		2 (1.60)		3 (2.36)
Abdominal pain		0 (0.00)		4 (3.20)		2 (1.57)
Myalgia		3 (2.44)		3 (2.40)		0 (0.00)
Dry mouth		1 (0.81)		3 (2.40)		1 (0.79)
Constipation		1 (0.81)		3 (2.40)		0 (0.00)
Fatigue		1 (0.81)		0 (0.00)		3 (2.36)
Laboratory abnormalities (Grade ≥ 3)[c]						
Blood creatine phosphokinase increased		1 (0.81)		2 (1.60)		2 (1.57)
Gamma-glutamyl transferase increased		2 (1.63)		0 (0.00)		1 (0.79)
Alanine aminotransferase increased		1 (0.81)		0 (0.00)		0 (0.00)
White blood cell count decreased		0 (0.00)		1 (0.80)		0 (0.00)
Severe		0 (0.00)		0 (0.00)		0 (0.00)

Note: Data are presented as number (%). LAC: lansoprazole 30 mg, amoxicillin 1000 mg, clarithromycin 500 mg. TAC1: tegoprazan 50 mg, amoxicillin 1000 mg, clarithromycin 500 mg. TAC2: tegoprazan 100 mg, amoxicillin 1000 mg, clarithromycin 500 mg.

Abbreviations: ADR, adverse drug reaction; AE, adverse event; SAE, serious adverse event.

[a]No significant difference in ADR incidence between TAC1 and LAC ($p=0.4723$), and TAC2 and LAC ($p=0.2567$); AE incidence between TAC1 and LAC ($p=0.3246$), and TAC2 and LAC ($p=0.2595$).

[b]Only AEs occurring in ≥ 2% of patients in any group in the SAS are shown, using MedDRA (v.27.0) preferred terms.

[c]Grade ≥ 3 laboratory abnormalities are reported; Grade 2 abnormalities are additionally included for liver function tests. AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

compromising the performance of clarithromycin-containing regimens [12, 16]. In our study, the prevalence of clarithromycin resistance, determined by a 23S rRNA point mutation test, was consistent with that in previous reports and balanced across the treatment arms. Subgroup analysis in the PPS population revealed eradication rates above 96% in clarithromycin-sensitive patients in both tegoprazan groups but a marked reduction in eradication rates among clarithromycin-resistant patients. Although the eradication rates in clarithromycin-resistant strains were numerically higher in both tegoprazan arms (52.4%–53.3%) than in the lansoprazole arm (37.9%), the differences were not statistically significant. Therefore, definitive conclusions regarding their relative efficacy in resistant infections cannot be drawn from the present data. Notably, Korea harbors a substantially higher proportion of high-level clarithromycin resistance (e.g., MIC > 16 and > 32 μg/mL)

compared with other regions, indicating a particularly challenging resistance landscape [17, 18]. Further studies specifically designed to evaluate treatment response in resistant strains are warranted.

More potent acid suppression with P-CABs, including tegoprazan and vonoprazan, compared with traditional PPIs has been well documented. Vonoprazan-based triple therapy has demonstrated superior eradication efficacy to PPI-based STT, particularly in clarithromycin-resistant strains [7, 19]. In this context, our findings contribute to the growing body of evidence that P-CABs, including tegoprazan, offer a viable alternative to PPIs in the empiric treatment of *H. pylori*. The observed eradication rate of 86.0% with 50-mg tegoprazan was comparable to that reported with 20-mg vonoprazan in previous studies, despite potential differences in antibiotic resistance patterns, resistance mechanisms, and susceptibility thresholds according to regional differences [8, 9]. Further pharmacodynamic and microbiologic analyses are needed to determine whether these differences influence treatment efficacy across diverse regions and ethnic groups.

The safety profiles of all the treatment arms were favorable and comparable. No SAEs or severe AEs occurred, and the rates of ADRs and treatment discontinuation were low across groups. Diarrhea was the most common AE and was generally mild and self-limiting. These findings support the tolerability of tegoprazan-based regimens, which is a critical factor for treatment adherence and long-term effectiveness in clinical practice.

One of the strengths of this study was the prospective genotypic evaluation of clarithromycin resistance in all randomized participants, allowing for a robust subgroup analysis based on resistance status. Such data are rarely available in large-scale phase III trials and offer clinically meaningful insights into the performance of specific regimens for real-world antimicrobial resistance. Additionally, to our knowledge, this is the first randomized clinical trial (RCT) to evaluate both 50- and 100-mg tegoprazan doses in a 14-day triple regimen for *H. pylori* eradication. A prior exploratory trial using a 10-day duration suggested a dose-dependent benefit of tegoprazan. However, our current data indicate that a 14-day regimen mitigates this difference, with similar eradication rates between the two doses [14]. This finding may inform cost-effectiveness considerations, since a lower dose may provide equivalent efficacy to a reduced medication burden.

Nevertheless, this study has some limitations. First, while the mITT eradication rates of tegoprazan-based regimens exceeded 80%, the PPS eradication rates did not reach the ideal 90% standard proposed by international guidelines [11, 20]. However, achieving an eradication rate of over 90% with non-bismuth triple therapy remains challenging, particularly in regions with high clarithromycin resistance. Alternative regimens such as bismuth-containing quadruple therapy are often associated with higher rates of adverse events and lower patient compliance [11]. In this context, our findings suggest that tegoprazan-based triple therapy can serve as a clinically effective and better-tolerated first-line treatment option by providing enhanced acid suppression, especially in populations with a moderate-to-high prevalence of clarithromycin resistance. Second, the study did not include vonoprazan as a direct comparator, which is increasingly regarded as the standard of care in Japan and has been endorsed in recent US guidelines [21]. Nevertheless, a previous pilot study demonstrated that the efficacy of a 10-day triple therapy regimen using tegoprazan at 100 mg was comparable to that using vonoprazan (20 mg), supporting the clinical relevance of our treatment regimen [14]. Future comparative studies directly evaluating tegoprazan and other P-CABs, including pharmacodynamic and mechanistic assessments in resistant *H. pylori* strains, would provide important additional evidence. Multinational studies across regions with different antibiotic resistance patterns and ethnic backgrounds are also needed to clarify the relative roles of P-CAB–based regimens in global practice, particularly considering geographic differences in antibiotic resistance patterns. Lastly, although clarithromycin resistance was evaluated using a validated PCR-based method targeting 23S rRNA mutations (A2142G and A2143G), this approach does not account for other potential resistance mechanisms, nor does it assess resistance to amoxicillin. Comprehensive phenotypic susceptibility testing may provide additional insights into tailored therapies, although it is less feasible in large-scale trials.

In conclusion, this phase III RCT demonstrated that 14-day tegoprazan-based triple therapy (50 or 100 mg) was non-inferior to lansoprazole-based therapy for *H. pylori* eradication and met the efficacy threshold for first-line treatment in South Korea. Tegoprazan-based regimens were well tolerated and effective in clarithromycin-sensitive patients, while offering potential advantages in resistant strains through potent acid suppression, although eradication rates in this subgroup were relatively modest. Tegoprazan-based triple therapy may represent a viable first-line option for *H. pylori* eradication; however, its effectiveness in clarithromycin-resistant infections remains to be fully clarified, and additional research is needed in regions with a high burden of resistance.

Author Contributions

All authors contributed to patient enrolment and data collection. J.Y.P. contributed to data interpretation and drafting of the original manuscript. J.G.K., as the corresponding author, supervised the study, contributed to its conceptualization and methodology, and oversaw manuscript revisions. All authors have reviewed and approved the final manuscript.

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Ethics Statement

The study adhered to the approved protocol, Declaration of Helsinki, Good Clinical Practice guidelines, and regulations set forth by the

Ministry of Food and Drug Safety. Institutional Review Board approval was obtained from each site.

Consent

All participants provided written informed consent. Data were recorded using electronic case report forms.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data used in this study are available from the corresponding author upon reasonable request and are subject to approval for legitimate research purposes.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Exclusion criteria and rationale for the selection of dose and duration of study drugs. **Table S1:** Demographic and baseline characteristics (PPS population).