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Original Article

Korean Registry on the Current Management of *Helicobacter pylori* (K-Hp-Reg): Interim Analysis of Adherence to the Revised Evidence-Based Guidelines for First-Line Treatment

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Background/Aims: The Korean guidelines for *Helicobacter pylori* treatment were revised in 2020, however, the extent of adherence to these guidelines in clinical practice remains unclear. Herein, we initiated a prospective, nationwide, multicenter registry study in 2021 to evaluate the current management of *H. pylori* infection in Korea.

Methods: This interim report describes the adherence to the revised guidelines and their impact on first-line eradication rates. Data on patient demographics, diagnoses, treatments, and eradication outcomes were collected using a web-based electronic case report form.

Results: A total of 7,261 patients from 66 hospitals who received first-line treatment were analyzed. The modified intention-to-treat eradication rate for first-line treatment was 81.0%, with 80.4% of the prescriptions adhering to the revised guidelines. The most commonly prescribed regimen was the 14-day clarithromycin-based triple therapy (CTT; 42.0%), followed by tailored therapy (TT; 21.2%), 7-day CTT (14.1%), and 10-day concomitant therapy (CT; 10.1%). Time-trend analysis demonstrated significant increases in guideline adherence and the use of 10-day CT and TT, along with a decrease in the use of 7-day CTT (all p<0.001). Multivariate logistic regression analysis revealed that guideline adherence was significantly associated with first-line eradication success (odds ratio, 2.03; 95% confidence interval, 1.61 to 2.56; p<0.001).

Conclusions: The revised guidelines for the treatment of *H. pylori* infection have been increasingly adopted in routine clinical practice in Korea, which may have contributed to improved first-line eradication rates. Notably, the 14-day CTT, 10-day CT, and TT regimens are emerging as the preferred first-line treatment options among Korean physicians. **(Gut Liver, 2025;19:364-375)**

Key Words: *Helicobacter pylori*; Anti-bacterial agents; Drug resistance, bacterial; Registries; Guideline adherence

INTRODUCTION

Although its prevalence is decreasing, *Helicobacter pylori* infection remains a common infectious disease, with a global prevalence of 43.9% reported in 2022.[1] In Korea, the prevalence was 51.0% between 2015 and 2016.[2] *H. pylori* eradication prevents the recurrence of peptic ulcer disease, induces remission of gastric mucosa-associated lymphoid tissue lymphoma, and reduces the risk of gastric cancer in high-risk patients.[3-6] However, the eradication rate of the most commonly used first-line treatment, clarithromycin-based triple therapy (CTT) with a proton pump inhibitor, amoxicillin, and clarithromycin, has been decreasing, and the therapy has become suboptimal over the past decades.[7,8] This decline is primarily due to increasing resistance to clarithromycin.[9-11]

The previous Korean guidelines, published in 2014, recommended 7- to 14-day CTT as the first-line treatment for *H. pylori* eradication.[12] However, a nationwide registry study involving 6,738 patients registered between 2010 and 2015 reported an overall first-line eradication rate of 71.8% in a modified intention-to-treat (mITT) analysis, despite 91.8% of cases adhering to the guidelines.[13]

In 2021, the Korean College of *Helicobacter* and Upper Gastrointestinal Research revised the guidelines for *H. pylori* treatment.[14] The revised evidence-based guidelines recommended against the previously endorsed 7-day CTT as a first-line treatment. Instead, they proposed five regimens: 14-day CTT, 10-day sequential therapy (ST), 10-day concomitant therapy (CT), 10- to-14-day bismuth quadruple therapy (BQT), and tailored therapy (TT).

Despite these revisions, several questions remained unanswered. It is unclear how widely these guidelines will be adopted in clinical practice, which of the five options for first-line treatment will be most commonly used, and whether adherence to the revised guidelines and the choice of regimen will contribute to an increased *H. pylori* eradication rate. Overall, there is an urgent need for comprehensive insights into the clinical practice of *H. pylori* eradication.

The Korean Registry on the Current Management of *Helicobacter pylori* (K-Hp-Reg) is the second prospective nationwide online registry, following a previous registry conducted between 2010 and 2015.[13] It aims to prospectively evaluate the current management of *H. pylori* infections in routine clinical practice in Korea. This study aimed to describe adherence to the revised guidelines, choice of individual regimens, and impact of guideline adherence on eradication rates following first-line treatments.

MATERIALS AND METHODS

1. Study design and population

We conducted this prospective, nationwide, multicenter, registry study at 66 primary, secondary, and tertiary hospitals in Korea. This study is registered at https://cris.nih.go.kr/KCT0005620. It was approved by the institutional review boards of the participating hospitals, including Chung-Ang University Hospital (approval number: 2062-002-427), or by a central review board where an individual board was not available. This study conforms to the Declaration of Helsinki. The study was initiated in March 2021, with a projected 5-year duration, and reached its midpoint in August 2023. At this point, a scheduled interim analysis was conducted.

Patients eligible for enrollment were men and women aged 19 years or older diagnosed with *H. pylori* infection and prescribed treatment accordingly. The exclusion criteria included individuals who were negative for *H. pylori* infection, cases with unresolved poor data quality, and individuals who dropped out before receiving first-line *H. pylori* treatment. Informed consent was obtained from all patients before registration.

2. Evaluation of *H. pylori* infection

H. pylori infection was diagnosed based on positivity in at least one of the following tests: histological evaluation using Giemsa staining, rapid urease test, serum anti-*H. pylori* immunoglobulin G test, ^{13}C-urea breath test, polymerase chain reaction (PCR), and *H. pylori* culture. In cases where results were inconsistent across multiple tests, the infection status was determined as positive if at least one test was positive. When PCR or culture was performed, data regarding the resistance of *H. pylori* to antibiotics were obtained.

3. Treatment regimens

The investigators were advised to prescribe treatment regimens in accordance with the revised evidence-based guidelines published in 2020 by the Korean College of *Helicobacter* and Upper Gastrointestinal Research.[14] These guidelines provide five options for first-line treatment: a 14-day CTT, a 10-day ST, a 10-day CT, a 10- to 14-day BQT, and a TT, while excluding the previously endorsed 7-day CTT. BQT and levofloxacin-based triple therapy were recommended for salvage treatment. CTT included amoxicillin and clarithromycin. ST involved amoxicillin for 5 days, followed by clarithromycin and metronidazole for another 5 days. CT included amoxicillin, clarithromycin, and metronidazole. BQT comprised bismuth, metronidazole, and tetracycline. In all regimens, antibiotics were

combined with a standard-dose proton pump inhibitor or potassium-competitive acid blocker. TT was defined as treatment prescribed based on antibiotic susceptibility testing using either PCR or culture, in contrast to empirical therapy, which is prescribed without susceptibility test results. The definition of TT did not rely on specific treatment regimens.

The success of the eradication therapy was confirmed by the negativity of either a single ^{13}C-urea breath test or at least two of the following methods: histological evaluation, rapid urease test, PCR, or culture, performed at least 4 weeks after the completion of the treatment. Additionally, information on drug compliance and adverse events was collected.

4. Registry data collection, entry, and management

The study data were collected and managed using a web-based electronic case report form hosted by PANTHEON (https://cdms.inno-n.com/), a clinical data management system developed by HK inno.N. This system complies with the regulatory requirements set forth in the Food and Drug Administration Title 21 Code of Federal Regulations Part 11, governing electronic records and signatures.

Upon enrollment, demographic data, including age, sex, and area of residence, were collected, along with information on comorbidities and history of *H. pylori* eradication. Data on *H. pylori* infection, including diagnostic methods and antibiotic resistance, were also collected. During each visit for treatment, information on the treatment regimen was recorded. At the follow-up visits, data regarding eradication success, drug compliance, and adverse events were collected. The database was managed by addressing missing data and resolving logical queries.

5. Study oversight

Investigators were provided with monthly newsletters detailing patient accrual. Moreover, annual investigators' meetings were held, with 61 attendees at the first meeting and 34 at the second, to discuss registry outcomes, including adherence to the revised guidelines and the rates of eradication success, both overall and according to individual regimens. HK inno.N contributed to database management and data analysis. However, the company was not involved in the study design, data interpretation, or manuscript preparation.

6. Statistical analysis

The primary outcome of this registry study was the success of the eradication therapy. The eradication rates were evaluated as percentages with 95% confidence intervals in the intention-to-treat (ITT), mITT, and per-protocol (PP) populations. The ITT population included all patients registered until August 31, 2023, who were prescribed *H. pylori* eradication treatment. For the current interim analysis, the follow-up period was allowed until February 29, 2024. Patients who did not have a follow-up visit by this date were considered to have treatment failure in the ITT analysis. The mITT population included ITT patients who completed a follow-up visit with an *H. pylori* test for successful eradication within 6 months. The PP population comprised mITT patients who had ≥80% treatment compliance.

The primary outcome of the interim analysis was adherence to the guidelines for prescribing first-line treatments. Guideline adherence was defined as the prescription of one of the five recommended regimens: a 14-day CTT, 10-day ST, 10-day CT, 10- to 14-day BQT, or TT. Non-adherence was defined as the prescription of any other regimen, including a 7-day CTT.

We conducted a time-trend analysis to assess adherence to the revised guidelines in the first-line treatment. The entire 2.5-year study period was divided into five intervals, each lasting 6 months, designated as periods 1 through 5. Using the Cochrane-Armitage test, we analyzed whether adherence to the revised guidelines increased during these periods. Additionally, we examined the time trends in the prescription of individual regimens.

Multivariate logistic regression analysis was performed to evaluate the factors associated with first-line eradication success. Due to the presence of multicollinearity between guideline adherence and treatment regimens, two separate models were developed. Model 1 included guideline adherence and treatment duration, while model 2 focused on treatment regimens. Both models accounted for age, sex, body mass index, levels of care centers, area of residence, previous eradication, smoking, alcohol consumption, medication, drug compliance, and adverse events. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a two-sided $p<0.05$ was considered significant.

RESULTS

1. Patients

From March 2021 to August 2023, 7,451 patients were prospectively registered in this study, which involved 66 hospitals representing all geographic regions of Korea (Fig. 1). Of these patients, 7,261 (97.5%) were prescribed first-line treatment for *H. pylori*, comprising the ITT population. Among them, 6,319 (87.0%) completed follow-up

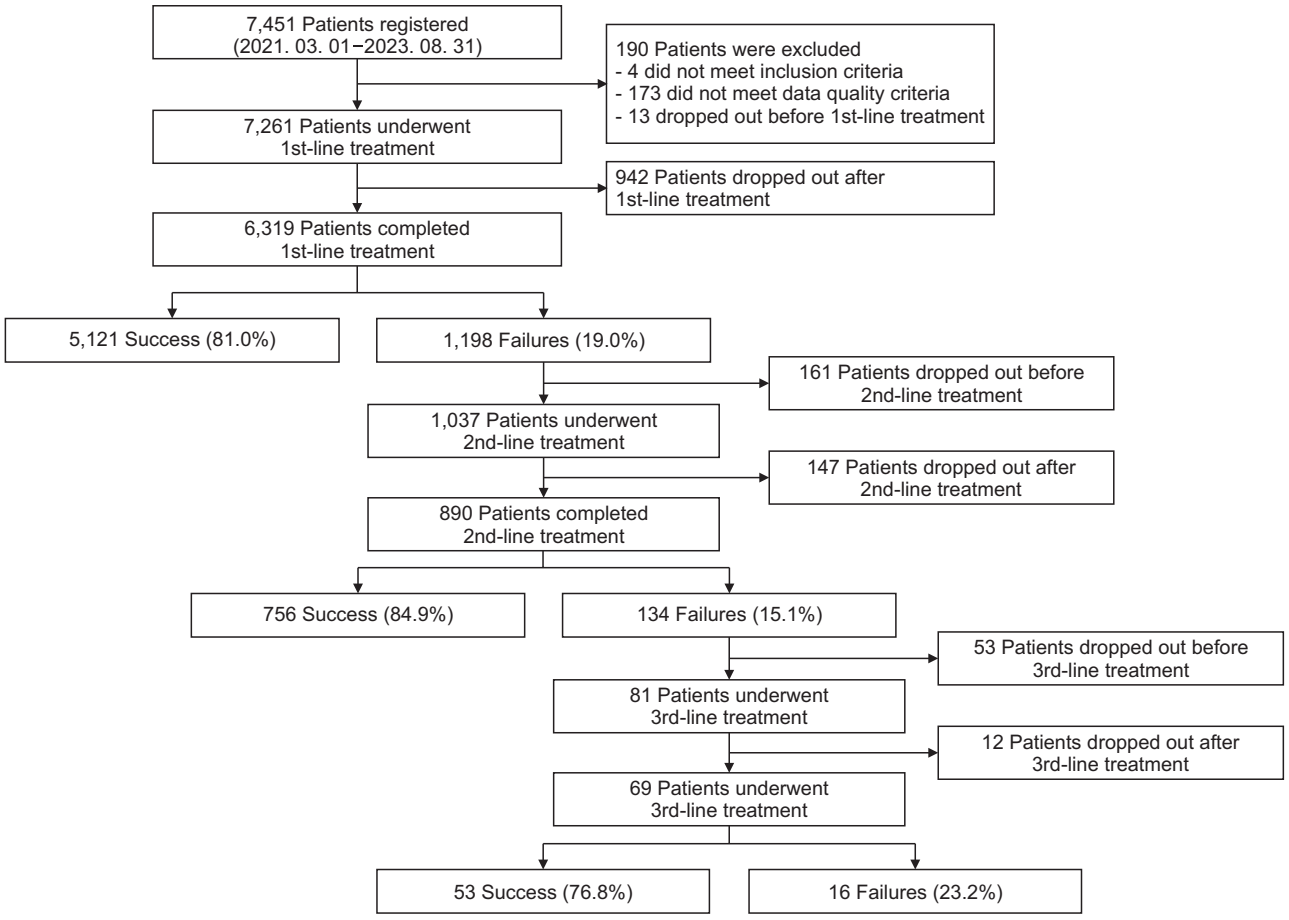

Fig. 1. Study flow of patient registration, treatment, and follow-up. A total of 7,451 patients were registered for the study. After four patients who did not meet inclusion criteria, 173 patients who did not meet the data quality criteria, and 13 patients who dropped out before receiving first-line treatment were excluded, 7,261 patients who received first-line treatment were included in the analysis. Among the patients who completed follow-up, the eradication rates were 81.0% for first-line, 84.9% for second-line, and 76.8% for third-line treatments.

tests, and 6,230 (98.6%) had ≥80% treatment compliance, comprising the mITT and PP populations, respectively. The baseline characteristics of the ITT population are summarized in Table 1. The mean (standard deviation) age was 58.8 (11.7) years, and 56.2% of the patients were men. Among those who underwent *H. pylori* culture with antibiotic susceptibility testing, the resistance rates for clarithromycin, metronidazole, and dual resistance were 33.3%, 31.8%, and 15.1%, respectively. The clarithromycin resistance rate, as evaluated by PCR, was 31.3%.

2. First-line eradication rates

The mITT eradication rates for the first-, second-, and third-line treatments were 81.0%, 84.9%, and 76.8%, respectively (Fig. 1). The first-line ITT, mITT, and PP eradication rates were 70.5%, 81.0%, and 81.5%, respectively.

The first-line eradication outcomes are summarized in Table 2. The most common indications for treatment were chronic atrophic gastritis and/or intestinal metaplasia (42.8%), other gastritis or patient preferences (34.5%), endoscopic treatment for early gastric cancer or adenoma (25.8%), duodenal ulcers (13.7%), and gastric ulcers (12.0%). The first-line mITT eradication rate was the highest in patients with gastric mucosa-associated lymphoid tissue lymphoma (91.8%) and the lowest in patients with duodenal ulcers (73.6%). Most patients (88.2%) were treatment-naïve, and the eradication rate was lowest among those who had undergone eradication therapy within the past year (mITT rate, 69.1%).

The most commonly prescribed regimen was the 14-day CTT (42.0%), followed by TT (21.2%), 7-day CTT (14.1%), and 10-day CT (10.1%). The highest mITT eradication rate was achieved with the 10- to 14-day BQT (92.1%), followed by TT (88.4%), 10-day ST (86.0%), 10-day CT (83.9%), and 14-day CTT (77.9%). The 7-day CTT was associated with the lowest mITT eradication rate (71.1%). Accordingly, approximately 80.4% of the prescriptions adhered to the treatment guidelines. The mITT eradication rate was 82.5% in guideline-adherent patients and 75.2% in non-adherent patients. Regimens non-adherent to guide-

Table 1. Baseline Characteristics of the Patients Who Underwent First-Line *Helicobacter pylori* Eradication Treatment

Characteristics	Patients (n=7,261)
Age, yr	58.8±11.7
Male sex	4,084 (56.2)
Body mass index, kg/m^2	24.2±4.9
Area of residence	
Seoul	1,235 (17.0)
Gyeonggi	1,467 (20.2)
Gangwon	535 (7.4)
Chungcheong	413 (5.7)
Gyeongsang	2,904 (40.0)
Jeolla	391 (5.4)
Jeju	316 (4.3)
Levels of care centers	
Primary	191 (2.6)
Secondary	2,268 (31.3)
Tertiary	4,802 (66.1)
Symptom	
No symptom	4,822 (66.4)
Dyspepsia	968 (13.3)
Epigastric pain/soreness	1,161 (16.0)
Heartburn/reflux	423 (5.8)
Nausea/vomiting	178 (2.5)
Previous GI disorder	
Endoscopic resection for EGC	500 (6.9)
Gastric ulcer	379 (5.2)
Duodenal ulcer	233 (3.2)
Comorbidity	
Hypertension	2,235 (30.8)
Diabetes	1,173 (16.2)
Liver cirrhosis	328 (4.5)
Current smoking	1,188 (16.4)
Alcohol consumption	2,623 (36.1)
Medication	
Aspirin	277 (3.8)
NSAIDs	70 (1.0)
Antiplatelet agents/anticoagulants	370 (5.1)
Penicillin allergy	15 (0.2)
H. pylori antibiotics resistance	
PCR	
Cla-r	358/1,143 (31.3)
Culture	
Cla-r	167/501 (33.3)
Met-r	154/484 (31.8)
Cla-r + Met-r	73/484 (15.1)

Data are presented as mean±SD or number (%).
GI, gastrointestinal; EGC, early gastric cancer; NSAIDs, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; Cla-r, clarithromycin resistance; Met-r, metronidazole resistance.

lines are summarized in Supplementary Table 1.

Treatment compliance was ≥80% in 98.6% of the mITT population. However, the mITT eradication rate dropped to <60% when compliance was <80%. Adverse events occurred in approximately 26.8% of the patients in the mITT population. The most common events were diarrhea (8.0%), nausea or vomiting (7.1%), metallic taste (6.4%), and abdominal pain or dyspepsia (6.2%).

3. Time-trend analysis

Fig. 2A illustrates the trends in guideline adherence during the study period. Adherence to the guidelines for prescribing first-line treatment was 63.9% in period 1 and increased to 88.6% in period 5, representing a significant increasing trend in guideline adherence (p<0.001).

Fig. 2B depicts the prescription trends for the individual first-line regimens. A significant shift in prescription patterns was observed during the study period. The proportions of TT and 10-day CT prescriptions significantly increased from 10.7% and 4.0% in period 1 to 28.8% and 20.1% in period 5, respectively (both p<0.001). Conversely, the prescription rate of the 7-day CTT regimen decreased from 29.0% in period 1 to 5.2% in period 5 (p<0.001). The 14-day CTT was the most commonly prescribed regimen throughout the study period, with its proportion increasing from 41.2% in period 1 to 46.7% in period 3, and then decreasing to 34.5% in period 5 (p<0.001). The use of the 10- to 14-day BQT, 10-day ST, and other regimens constituted a minor portion of prescriptions throughout the study period.

4. Factors associated with first-line eradication success

In the univariate logistic regression analysis, factors negatively associated with first-line eradication success included being female, residing in the Jeju region, having undergone *H. pylori* eradication within the past year, drug compliance <80%, occurrence of adverse events, and the use of the 7-day CTT (Table 3). Conversely, a treatment duration of 10 days, adherence to treatment guidelines, and the prescription of 10-day ST, 10-day CT, 10- to 14-day BQT, TT, or other regimens were positively associated with eradication success.

Due to the multicollinearity between guideline adherence and first-line treatment regimens, two multiple logistic regression models were constructed. In both models, sex, area of residence, previous eradication, and drug compliance were identified as independent factors associated with first-line eradication success. After adjusting for these covariates, model 1 revealed that adherence to the treatment guidelines in the prescription of first-line treatment was associated with higher eradication success (odds ratio, 2.03; 95% confidence interval, 1.61 to 2.56; p<0.001). In model 2, the prescription of 7-day CTT was associated with eradication failure, compared with 14-day CTT (odds ratio, 0.75; 95% confidence interval, 0.62 to 0.90; p=0.002). Conversely, the 10-day ST (p=0.001), 10-day CT (p<0.001), 10- to 14-day BQT (p<0.001), and TT (p<0.001) showed

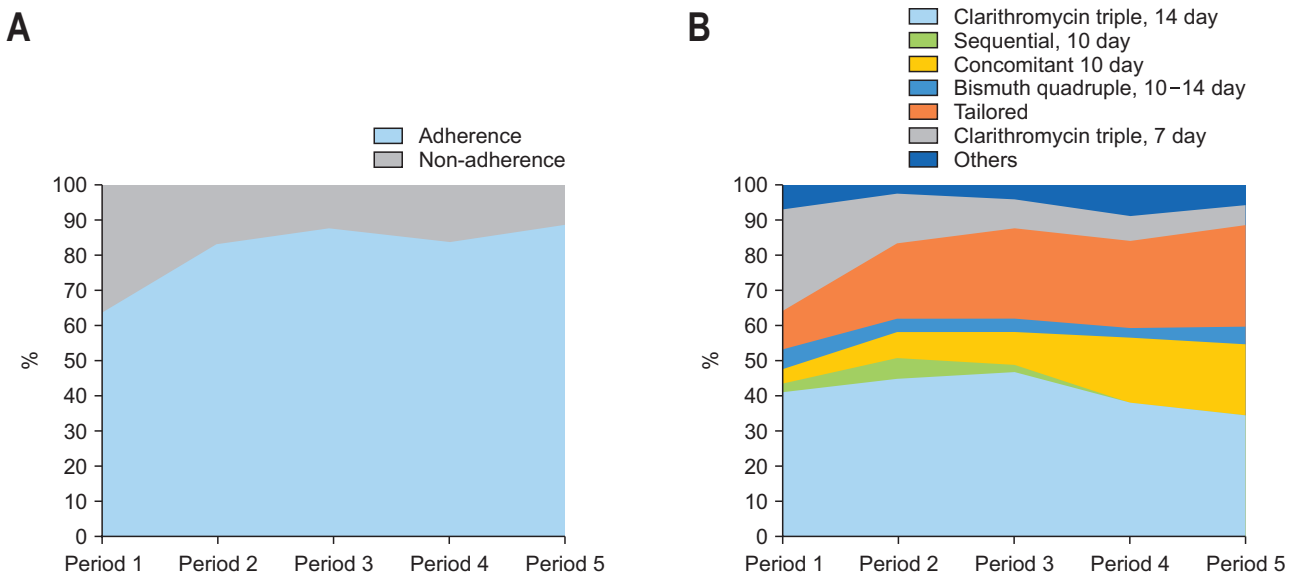

Fig. 2. Time trends in first-line treatment prescription. The study period (March 2021 to August 2023) was divided into five 6-month intervals, labeled as periods 1 through 5. (A) Trends in the guideline adherence when prescribing first-line treatments. (B) Trends in prescription of individual first-line regimens. Guideline adherence was defined as the prescription of one of the five recommended regimens: 14-day clarithromycin-based triple therapy, 10-day sequential therapy, 10-day concomitant therapy, 10- to-14-day bismuth quadruple therapy, or tailored therapy. Non-adherence was defined as the prescription of any other regimens, including 7-day clarithromycin-based triple therapy.

significantly higher odds of eradication success than the 14-day CTT did.

DISCUSSION

In this interim analysis of a prospective nationwide registry, approximately 80.4% of the patients received first-line treatments adhering to the revised evidence-based guidelines for *H. pylori* infection in Korea, resulting in an interim eradication rate of 81.0% in the mITT analysis. The most commonly used regimen was the 14-day CTT, followed by TT, 7-day CTT, and 10-day CT. Notably, the time-trend analysis demonstrated that guideline adherence and use of the 10-day CT and TT increased, whereas the use of 7-day CTT decreased throughout the study period. Moreover, adherence to the guidelines was associated with first-line treatment success, whereas the use of a 7-day CTT was associated with treatment failure. Among the guideline-recommended first-line regimens, the use of the 10-day ST, 10-day CT, 10- to 14-day BQT, and TT was associated with successful eradication.

The increasing antimicrobial resistance of *H. pylori* has been a significant issue, necessitating revisions of clinical practice guidelines over the last two decades.[9-11,15] The appropriate utilization of practice guidelines is key to the successful eradication of *H. pylori* in real-world practice.[16-18] When the revised evidence-based guidelines were introduced in Korea in 2020, the long-standing preference for 7-day CTT and the complexity of the new first-line treatment were considered potential obstacles to their widespread adoption.[19,20] Previous Korean registry data showed that the 7-day CTT was used in 79.9% of first-line treatments between 2010 and 2015, despite a 71.7% mITT eradication rate.[13] The revised guidelines, offering five parallel choices for first-line treatment instead of a single choice of 7- to 14-day CTT, seemed too complex for daily practice.[14] However, our results revealed that the revised guidelines have been well integrated into clinical practice despite these concerns. Moreover, guideline adherence was independently associated with successful first-line eradication. Previous studies on adherence to *H. pylori* treatment guidelines have mainly been survey-based and focused on primary care physicians.[16-18] Our study's strength lies in evaluating guideline adherence using nationwide registry data comprising primary to tertiary care physicians and demonstrating that adherence to the revised guidelines can improve treatment outcomes.

The 14-day CTT was selected in approximately two-thirds of the cases, whereas the use of the TT and 10-day CT increased, making these the three most preferred regimens in the last 6 months of the study period. The 14-day CTT was the only first-line regimen brought forward from the previous guidelines and seemed familiar to practitioners.[12,14] This may have been considerably influenced by the widespread perception that 7- to 14-day CTT was practically the only first-line regimen approved by Health Insurance Review and Assessment Service of the Korean

Table 2. First-Line *Helicobacter pylori* Eradication Treatment Outcomes

Variables	mITT set, No. (%)	Success, No.	Failure, No.	Eradication rate, %		
				ITT	mITT	PP
Overall	6,319 (100.0)	5,121	1,198	70.5	81.0	81.5
Indication						
Gastric ulcer	759 (12.0)	616	143	67.4	81.2	81.4
Duodenal ulcer	866 (13.7)	638	228	62.9	73.7	74.2
Endoscopic treatment for EGC/adenoma	1,632 (25.8)	1,380	252	78.5	84.6	85.3
Gastric MALT lymphoma	98 (1.6)	90	8	86.5	91.8	91.8
Family history of gastric cancer	209 (3.3)	177	32	77.3	84.7	85.9
CAG IM	2,704 (42.8)	2,168	536	71.6	80.2	80.8
Other gastritis/patient preference	2,183 (34.5)	1,775	408	68.1	81.3	81.5
Others	702 (11.1)	580	122	74.2	82.6	83.0
Previous *H. pylori* eradication						
No	5,571 (88.2)	4,536	1,035	70.8	81.4	81.9
≤1 yr	139 (2.2)	96	43	64.0	69.1	69.9
>1 yr	366 (5.8)	289	77	67.4	79.0	79.2
Unclear	243 (3.8)	200	43	72.2	82.3	82.2
First-line treatment regimens						
CTT, 14 day	2,655 (42.0)	2,068	587	66.9	77.9	78.4
ST, 10 day	164 (2.6)	141	23	77.5	86.0	85.9
CT, 10 day	640 (10.1)	537	103	69.9	83.9	84.7
BQT, 10–14 day	280 (4.4)	258	22	84.6	92.1	92.0
TT	1,342 (21.2)	1,186	156	76.8	88.4	88.9
CTT, 7 day	888 (14.1)	631	257	64.3	71.1	71.3
Others	350 (5.6)	300	50	77.3	85.7	86.4
Guideline adherence						
Adherent	5,081 (80.4)	4,190	891	71.1	82.5	83.0
Non-adherent	1,238 (19.6)	931	307	68.0	75.2	75.5
Durations						
7 day	1,797 (28.4)	1,434	363	71.8	79.8	80.1
10 day	1,054 (16.7)	910	144	74.4	86.3	86.9
14 day	3,465 (54.8)	2,776	689	68.8	80.1	80.6
Others	3 (0.1)	1	2	25.0	33.3	33.3
Compliance						
100%	5,933 (93.9)	4,844	1,089	NA	81.6	NA
80%–99%	297 (4.7)	234	63	NA	78.8	NA
50%–79%	39 (0.6)	21	18	NA	53.9	NA
<50%	50 (0.8)	22	28	NA	44.0	NA
Adverse events (n=6,144)						
No	4,496 (73.2)	3,666	830	81.3	81.5	81.9
Yes	1,648 (26.8)	1,307	341	78.3	79.3	80.1
Abdominal pain/dyspepsia	382 (6.2)	298	84	77.4	78.0	79.1
Nausea/vomiting	434 (7.1)	359	75	81.8	82.7	83.5
Metallic taste	395 (6.4)	312	83	79.0	79.0	79.5
Diarrhea	490 (8.0)	386	104	77.8	78.8	79.7
Others	447 (7.3)	363	84	78.7	81.2	82.2

The intention-to-treat (ITT) set included all patients who were registered and received first-line *H. pylori* treatment. The modified ITT (mITT) set included all patients who completed follow-up after first-line treatment. The per-protocol (PP) set included all patients who completed follow-up with ≥80% drug compliance for first-line treatment.

EGC, early gastric cancer; MALT, mucosa-associated lymphoid tissue; CAG, chronic atrophic gastritis; IM, intestinal metaplasia; CTT, clarithromycin-based triple therapy; ST, sequential therapy; CT, concomitant therapy; BQT, bismuth quadruple therapy; TT, tailored therapy; NA, not available.

government until recently, despite the criteria being somewhat vague.[21,22] However, the 14-day CTT is not recommended as a first-line option in the Maastricht VI,[23] American College of Gastroenterology,[24] or Toronto guidelines[25] owing to the clarithromycin resistance rate exceeding 15% in Korea.[11] In our study, the clarithromycin resistance rates were 31.3% based on PCR and 33.3% based on culture. Indeed, 14-day CTT showed significantly lower success compared to the other first-line regimens in the adjusted logistic regression analysis, which primarily contributed to

Table 3. Logistic Regression Analysis for the Success of First-Line *Helicobacter pylori* Eradication Treatment

Covariates	Categories	Univariate analysis		Multivariate analysis model 1		Multivariate analysis model 2	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age		1.00 (1.00–1.01)	0.710	1.00 (0.99–1.01)	0.894	1.00 (0.99–1.00)	0.592
Sex	Male	Reference		Reference		Reference	
	Female	0.83 (0.73–0.94)	0.004	0.81 (0.71–0.94)	0.005	0.81 (0.70–0.93)	0.003
Body mass index		1.00 (0.99–1.01)	0.847	1.00 (0.99–1.01)	0.860	1.00 (0.98–1.01)	0.653
Levels of care centers	Primary	Reference		Reference		Reference	
	Secondary	0.75 (0.46–1.22)	0.245	1.15 (0.64–2.05)	0.644	1.18 (0.65–2.12)	0.585
	Tertiary	0.73 (0.45–1.17)	0.190	1.04 (0.59–1.82)	0.906	1.02 (0.58–1.80)	0.936
Area of residence	Seoul	Reference		Reference		Reference	
	Gyeonggi	0.99 (0.81–1.21)	0.924	1.14 (0.93–1.40)	0.218	1.26 (1.02–1.55)	0.033
	Gangwon	1.68 (1.24–2.26)	0.001	1.81 (1.29–2.52)	0.001	1.96 (1.40–2.76)	<0.001
	Chungcheong	1.36 (1.13–1.62)	0.001	1.59 (1.32–1.92)	<0.001	1.56 (1.29–1.88)	<0.001
	Gyeongsang	1.24 (0.92–1.68)	0.155	1.25 (0.91–1.71)	0.176	1.30 (0.94–1.80)	0.112
	Jeolla	1.17 (0.86–1.59)	0.324	1.18 (0.82–1.71)	0.377	1.16 (0.78–1.73)	0.461
	Jeju	0.68 (0.50–0.92)	0.012	0.87 (0.62–1.23)	0.430	1.08 (0.76–1.52)	0.681
Previous *H. pylori* eradication	No	Reference		Reference		Reference	
	Yes (≤1 yr)	0.51 (0.35–0.73)	<0.001	0.60 (0.41–0.88)	0.010	0.30 (0.20–0.46)	<0.001
	Yes (>1 yr or unclear)	0.93 (0.75–1.15)	0.499	0.93 (0.74–1.16)	0.507	0.76 (0.60–0.96)	0.022
Smoking	No/past	Reference		Reference		Reference	
	Current	1.01 (0.84–1.20)	0.947	0.99 (0.82–1.21)	0.948	1.00 (0.82–1.21)	0.963
	Unknown	1.11 (0.83–1.49)	0.475	0.82 (0.39–1.72)	0.598	0.86 (0.41–1.80)	0.685
Alcohol consumption	No/past	Reference		Reference		Reference	
	Current	0.94 (0.82–1.07)	0.362	0.89 (0.77–1.04)	0.153	0.91 (0.78–1.06)	0.222
	Unknown	1.14 (0.84–1.55)	0.387	1.36 (0.63–2.93)	0.432	1.29 (0.60–2.78)	0.518
Medication	No	Reference		Reference		Reference	
	Yes	0.94 (0.82–1.06)	0.308	0.95 (0.83–1.09)	0.479	0.96 (0.83–1.10)	0.548
	Unknown	1.01 (0.64–1.60)	0.969	0.90 (0.55–1.47)	0.683	0.88 (0.53–1.44)	0.599
Duration	7 day	Reference		Reference		NA	
	10 day	1.61 (1.30–1.98)	<0.001	1.15 (0.88–1.50)	0.319	NA	
	14 day	1.03 (0.89–1.18)	0.735	0.63 (0.51–0.78)	<0.001	NA	
Compliance	100%	Reference		Reference		Reference	
	80%–99%	0.84 (0.63–1.11)	0.216	0.81 (0.57–1.16)	0.250	0.81 (0.54–1.19)	0.278
	<80%	0.21 (0.14–0.32)	<0.001	0.21 (0.14–0.33)	<0.001	0.21 (0.13–0.32)	<0.001
Adverse events	No	Reference		Reference		Reference	
	Yes	0.87 (0.75–1.00)	0.049	0.92 (0.79–1.06)	0.241	0.87 (0.75–1.02)	0.077
	Unknown	1.24 (0.82–1.88)	0.310	0.96 (0.58–1.57)	0.862	1.00 (0.61–1.63)	0.991
Guideline adherence	Non-adherence	Reference		Reference		NA	
	Adherence	1.55 (1.34–1.80)	<0.001	2.03 (1.61–2.56)	<0.001	NA	
First-line treatment regimens	CTT, 14 day	Reference		NA		Reference	
	ST, 10 day	1.74 (1.11–2.73)	0.016	NA		2.62 (1.51–4.56)	0.001
	CT, 10 day	1.48 (1.18–1.86)	0.001	NA		1.80 (1.40–2.31)	<0.001
	BQT, 10–14 day	3.33 (2.13–5.19)	<0.001	NA		5.46 (3.35–8.87)	<0.001
	TT	2.16 (1.78–2.61)	<0.001	NA		2.41 (1.97–2.95)	<0.001
	CTT, 7 day	0.70 (0.59–0.83)	<0.001	NA		0.75 (0.62–0.90)	0.002
	Others	1.70 (1.25–2.33)	0.001	NA		2.02 (1.44–2.82)	<0.001

OR, odds ratio; CI, confidence interval; CTT, clarithromycin-based triple therapy; ST, sequential therapy; CT, concomitant therapy; BQT, bismuth quadruple therapy; TT, tailored therapy; NA, not available.

the reduced eradication rates in guideline-adherent cases. This may explain the observed trend of increased prescription of 14-day CTT during the first 18 months of the study, followed by a subsequent decline. Given the clarithromycin resistance rates in our data, it is possible that 14-day CTT may be excluded from first-line eradication regimens in future guidelines. However, the prescription patterns of these regimens were evolving even during this interim analysis, indicating the need for further evaluation. Therefore, a final analysis of the prescription and eradication rates of these regimens is critical for future guideline revisions.

The TT and 10-day CT appeared to be preferred in our study because of their favorable eradication outcomes reported in randomized controlled trials (RCTs) conducted

in Korea.[21,26] However, it is noteworthy that the mITT and PP eradication rate of TT in our study was below 90%. In contrast, recent RCTs have reported eradication rates exceeding 90% with TT.[26,27] In our study, mITT eradication rate of CTT in cases without clarithromycin resistance and those of BQT in cases with clarithromycin resistance were both below 90% (data were not shown). Similar discrepancy was also observed for CT.[21] Thus, the low eradication rates observed in our study appear to be related to all regimens collectively rather than any specific regimen. Several factors may explain the discrepancies in eradication rates between our study and those reported in RCTs. First, our inclusion and exclusion criteria were more inclusive compared to RCTs. Notably, we included patients with a previous history of *H. pylori* eradication treatment. Second, treatment regimens were not randomly assigned but rather selected at the discretion of investigators, potentially introducing selection bias. Third, our study was performed in real-world settings with more variable follow-up and heterogeneous evaluation methods compared to RCTs. In summary, out data suggest that *H. pylori* eradication rates, including TT and CT, in real-world setting may be lower than those reported in RCTs.

Non-adherence to the guidelines was mainly due to the empirical prescription of a 7-day CTT, which significantly increased the risk of treatment failure. These results are consistent with those of a previous RCT in Korea.[21] The use of this regimen has decreased, although the reduction has been gradual. In a previous registry, the prescription rate for this regimen was 79.9%; however, it is now 14.1%.[13] Even during the study period, the prescription rate decreased significantly from 29.0% in the first 6 months to 5.2% in the last 6 months. The revision of treatment guidelines and updates on prescription rates and outcomes during annual investigator meetings may have contributed to this significant reduction.

The overall first-line eradication rate of 81.0% in our study seemed lower than that reported in a European registry, which increased from 83.9% in 2013 to 87.8% in 2018.[28] Several differences between our registry and the European registry may account for this discrepancy. First, the proportion of cases with clarithromycin resistance was over 30% in our data, compared with 23% in the European registry, leading to a difference in the CTT eradication rates (76.2% in our data vs 84.1% in the European registry).[28-30] Second, most non-bismuth quadruple therapies used in our study lasted 10 days. In the European registry, 14-day treatments had similar or slightly higher eradication rates than did 10-day treatments, reflecting a trend towards longer treatment durations.[28] The Maastricht guidelines recommend 14-day treatments for non-BQT,[23] whereas the American College of Gastroenterology guidelines recommend 10- to 14-day treatments.[24] Third, BQT was used in only 4.4% of prescriptions in our registry but was increasingly used in the European registry, reaching 20% in 2018.[28] The low use of BQT as a first-line treatment in Korea may be due to its high adverse event rate or perceived complexity.[14] However, BQT was used in 92% of second-line treatments in our study, suggesting a belief that BQT should be reserved for salvage treatment. Notably, 10- to 14-day BQT was the only regimen to achieve an eradication rate of over 90%, a suggested cutoff for treatment success,[31,32] underscoring the need to investigate why BQT is not widely used as a first-line treatment in Korea and explore new effective salvage treatment options.

Our study has some limitations. First, these findings are interim results; therefore, a final analysis is required to confirm the eradication rates of the overall first-line treatment and individual regimens. Second, most patients are included from secondary or tertiary care centers, resulting in limited reflection of the outcomes in primary care centers. In reality, a substantial portion of *H. pylori* therapy is performed in primary care centers in Korea. Third, the results of the time-trend analysis should be interpreted cautiously, as changes in guideline adherence rates or prescription patterns could be influenced by the varying inclusion rates of participating hospitals or investigators rather than actual changes in prescription practices. Furthermore, discussions of registry outcomes during the annual investigators' meetings may have influenced subsequent treatment choices, potentially limiting the generalizability of the time-trend analysis results. Fourth, because this study was not an RCT, comparisons of the eradication rates between individual regimens should be performed with caution. Although our analysis was adjusted for important covariates such as age, sex, residential area, and compliance, the efficacy of individual regimens should be interpreted using data from RCTs, particularly those conducted in Korea during a similar period.[26,27,33] These comparisons are reserved for the final analysis.

In conclusion, this interim analysis of nationwide registry data indicates that the revised evidence-based treatment guidelines for *H. pylori* infection have been increasingly adopted in routine clinical practice in Korea, which may have contributed to improved first-line eradication rates. Notably, the 14-day CTT, 10-day CT, and TT are emerging as the preferred first-line treatment options. The present outcomes support the subsequent final analysis. The overall eradication rates, including both first-line and salvage treatments, will be assessed at the end of the study period.

CONFLICTS OF INTEREST

J.Y.A. and G.H.K. are editorial board members of the journal but were 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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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl240489.

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