Online Registry for Nationwide Database of Current Trend of *Helicobacter pylori* Eradication in Korea: Interim Analysis

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Eradication of *Helicobacter pylori* using first-line therapy is becoming less effective. Subjects who had been treated for *H. pylori* infection were prospectively enrolled through an on-line database registry from October 2010 to December 2012. Demographic data, detection methods, treatment indication, regimens, durations, compliance, adverse events, and eradication results for *H. pylori* infection were collected. Data of 3,700 patients from 34 hospitals were analyzed. The overall eradication rate of the first-line therapy was 73.0%. Eradication failure was significantly associated with old age, concomitant medication, and comorbidity. Regional differences in eradication rates were observed. The most common first-line therapy was proton pump inhibitor-based triple therapy (standard triple therapy, STT) for 7 days (86.8%). The eradication rates varied with regimens, being 73% in STT, 81.8% in bismuth-based quadruple therapy, 100% in sequential therapy, and 90.3% in concomitant therapy. The eradication rate in treatment-naïve patients was higher than that in patients previously treated for *H. pylori* infection (73.8% vs. 58.5%, *P* < 0.001). The overall eradication rate for second-line therapy was 84.3%. There was no statistical difference in eradication rates among various regimens. *H. pylori* eradication rate using STT is decreasing in Korea and has become sub-optimal, suggesting the need for alternative regimens to improve the efficacy of first-line therapy for *H. pylori* infection.

Keywords: *Helicobacter pylori*; Eradication Success; First-line Therapy; On-line Registry

INTRODUCTION

Helicobacter pylori infection affects 20%-50% of the population in the Western world and up to 80% of those in developing countries (1). *H. pylori* infection causes chronic gastritis and increases the risk of several upper gastrointestinal diseases including peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma (2,3).

In East Asian countries, such as Korea and Japan, where the incidence of gastric cancer is high, eradication of *H. pylori* has been a key strategy in controlling gastric cancer incidence. The incidence of *H. pylori* infection has declined in developed countries, but has remained persistently high in Korea.

The first-line therapy for *H. pylori* infection used world-wide as standard triple therapy (STT) comprising proton pump inhibitor (PPI) and the antibiotics amoxicillin and clarithromycin (4,5). The eradication rate with first-line therapy is disappointingly low (70%-85%). In recent decades, substantial decrease in the efficacy of STT to ≤ 80% has been observed in most countries (5-7). Thus, the continued use of STT as the first-line regimen has been questioned (8).

The optimal regimen reflects local preference and experience. Continuous evaluation of treatment outcomes in clinical practice should also be taken into account (9). There is no large-scale, systematic registry on *H. pylori* eradication in any nation.

The aims of the present study were to obtain a prospective systematic registry database on a nation-wide scale in Korea, and to sample representative Koreans in routine

clinical practice to gauge *H. pylori* eradication in Korea. This study focused on epidemiology, efficacy, and safety of the commonly-used treatment regimens to eradicate *H. pylori* in Korea.

MATERIALS AND METHODS

Study design

This multicenter, prospective, and observational study (cris.nih. go.kr/KCT0001390) was trial conducted from October 2010 to June 2015. The planned interim analysis was performed in the first half period, from October 2010 to December 2012.

Subjects

Patients who were confirmed to be infected by *H. pylori* and treated for the ensuing infection were enrolled. Patients were not eligible for the study if one of the following criteria was met: known or suspected allergy to PPIs or antibiotics, previous history of gastric surgery, pregnancy or lactation, or therapy with a PPI or antibiotics within 4 weeks of entry.

Evaluation of *H. pylori* infection

H. pylori infection was diagnosed in patients based on histologic evidence of *H. pylori* by Giemsa staining, positive rapid urease test, positive *H. pylori* culture test, and positive 13C-urea breath test. Patients were diagnosed as infected if any of these tests was positive.

Eradication therapy

Investigators prescribed the eradication regimen in accordance with the guidelines established by the Korean College of *Helicobacter* and Upper Gastrointestinal Research group. First-line STT therapy included standard-dose PPI (esomeprazole 40 mg, omeprazole 40 mg, lansoprazole 30 mg, pantoprazole 40 mg, or rabeprazole 20 mg) plus amoxicillin (1,000 mg) and clarithromycin (500 mg) twice a day for 7-14 days. Second-line therapy (PBMT) included the standard-dose twice daily PPI, 120 mg bismuth four times a day, 500 mg metronidazole three times a day, and 500 mg tetracycline four times a day for 7-14 days. Other eradication regimens including sequential therapy (SQ) or concomitant therapy (CT) were also prescribed as first-line or second-line therapy.

To evaluate the success of the eradication therapy, follow-up endoscopy with a rapid urease test and histologic examination, or a 13C-urea breath test was performed at least 4 weeks after the completion of the therapy. The eradication success for *H. pylori* was defined as a negative rapid urease test and histology or a negative 13C-urea breath test, which was confirmed within 6 months after *H. pylori* eradication therapy. Eradication failure was defined as a positive result in any of these tests. Compliance was considered to be satisfactory when drug intake exceeded 80%. Adverse events associated with treatment were also investigated.

Data collection

The electronic data management system for this study was developed by the Seoul National University Medical Research Collaborating Center using the Pharmacoepidemiology and Clinical Trial Application X (Phacta X) system. Data entry was completed by selecting appropriate icons. Data from clinical information and laboratory test results were entered into a web-based electronic case-reporting form (CRF) following the standard protocol for data-entry (www.phactax.org). The electronic CRF included variables including demographic data (e.g., age, sex, residence, smoking status, alcohol consumption, and comorbidity including hypertension, diabetes, ischemic heart disease, liver cirrhosis, chronic renal failure, and malignancy), diagnostic methods for *H. pylori* infection, treatment indication, regimens, durations, compliance, and treatment-related adverse events. All patients provided written informed consent to participate prior to enrollment. The study was approved by the representative Institutional Review Boards of participating hospitals in Korea.

Statistical analyses

Patient characteristics and eradication rate of *H. pylori* were summarized using mean and standard deviation for continuous variables and frequency or percentage for categorical variables. Comparison of continuous variable was performed using Student *t*-test. Fisher's exact test was performed to compare categorical variables. Age was categorized as < 30, 30-40, 40-50, 50-60, 60-70, or ≥ 70 years. Eradication success rate for the first-line therapy was evaluated by geographic regions. The standardized rates were calculated using patients receiving STT regimens as standard population within the Korean national health insurance database that covered all patients in 2010. Logistic regression analysis was used to examine the associations between *H. pylori* eradication therapy and each of the following factors: age, sex, residence, current smoking, alcohol consumption, medication, previous gastrointestinal disorder, comorbidity, previous *H. pylori* eradication, PPI, duration of treatment, treatment compliance, and treatment-related complications. A multivariate model was constructed using variables with $P < 0.2$ in univariate logistic regression analysis. SAS version 9.2 (SAS institute Inc., Cary, NC, USA) was used for statistical analysis. Statistical significance was considered for $P < 0.05$. All P values were two-sided.

Ethics statement

The protocol was approved by the institutional review board at each center (Chung-Ang University Yongsan Hospital, IRB No. 10-031-04-08). All of the patients provided written informed consent for participation in the study.

RESULTS

Baseline demographics

Thirty four tertiary and academic hospitals, which were representative of Korean hospitals, prospectively enrolled 5,331 patients. Of them, 3,700 were identified using their eradication results within 6 months after *H. pylori* eradication therapy (Fig. 1). The baseline characteristics of these patients who received first-line eradication therapy are summarized in Table 1. Eradication success in first-line therapy was achieved in 2,701 (73.0%) patients. Eradication success declined with age ($P < 0.001$). However, there was no significant difference ($P = 0.328$) in eradication success between sexes. Concerning regional differences, the eradication rate in Jeju province was the highest (76.1%) and the rate in Chugcheong province was the lowest (60.3%). The difference was significant ($P < 0.001$) (Fig. 2). There was no significant difference between patients with a current smoking status or currently consuming alcohol and those not currently smoking or drinking ($P = 0.799$ and $P = 0.261$, respectively). The eradication rate in patients who had taken other medications, especially non-steroidal anti-inflammatory drugs, was lower than that in those who had not ($P < 0.019$). Patients with previous gastrointestinal disorders or comorbidities had significantly lower eradication rates ($P = 0.018$ and $P = 0.031$, respectively). The eradication rate in patients with liver cirrhosis or chronic renal failure was significantly lower than in patients who were free of these diseases (47.0% and 52.9%, respectively). Common adverse events were diarrhea, abdominal pain, nausea, and vomiting (Table 2). Diarrhea and abdominal pain were especially common in STT (144 and 35 cases, respectively).
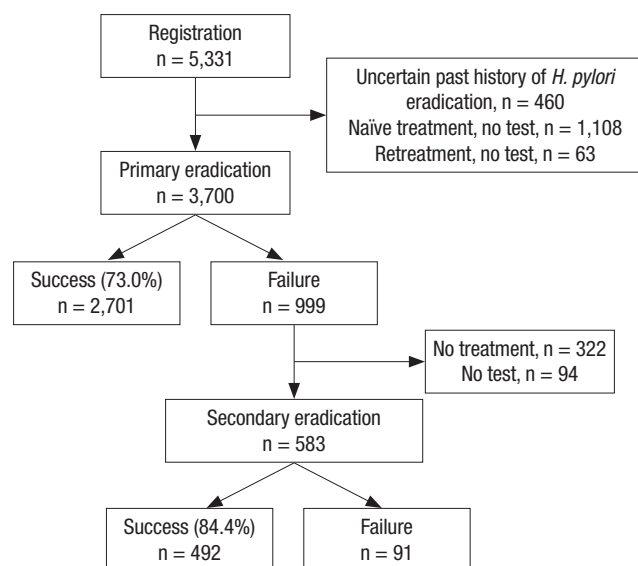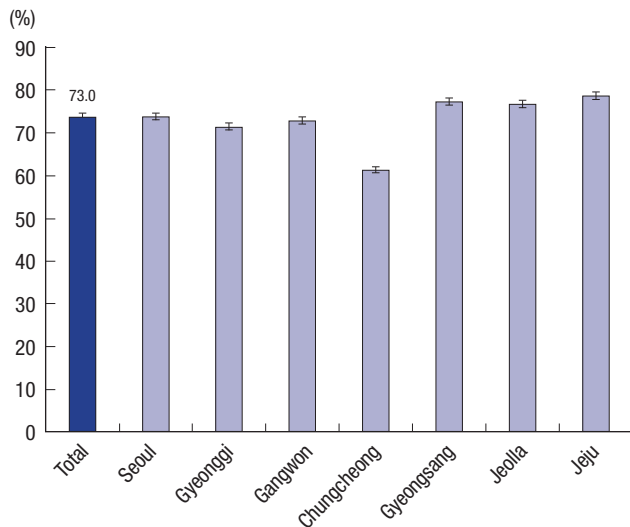

Fig. 1. *Helicobacter pylori* eradication in first-line and second-line therapy. A total of 3,700 patients participated in the study. First-line and second-line therapy overall eradication rate was 73.0% and 84.3%, respectively.

First-line *H. pylori* eradication

The results of *H. pylori* eradication after the first-line therapy are summarized in Table 2. The most common indication for *H. pylori* eradication was benign gastric and duodenal ulcers (53.5%). The eradication rates were significantly different among various gastroduodenal diseases. The eradication rate in patients with gastric MALT lymphoma and benign gastric ulcer was 89.7% and 67.9%, respectively ($P < 0.001$). The eradication success in naïve patients was higher than that in patients with past history

Table 1. Baseline characteristics of 3,700 Korean patients who underwent first-line *H. pylori* eradication therapy

Parameters	Total participants with first-line therapy (n = 3,700) No. (%)	Eradication success (n = 2,701) No. (%)	P value
Age in years			0.001
< 30	144 (3.89)	105 (72.92)	
30-39	322 (8.70)	251 (77.95)	
40-49	666 (18.0)	511 (76.73)	
50-59	1,247 (33.7)	917 (73.54)	
60-69	884 (23.89)	625 (70.7)	
≥ 70	437 (11.81)	292 (66.82)	
Sex			0.328
Male	2,233 (60.35)	1,643 (73.58)	
Female	1,467 (39.65)	1,058 (72.12)	
Residence			< 0.001
Seoul	809 (21.86)	592 (73.18)	
Gyeonggi	692 (18.7)	496 (71.68)	
Gangwon	93 (2.51)	68 (73.12)	
Chungcheong	310 (8.38)	187 (60.32)	
Gyeongsang	1,162 (31.41)	884 (76.08)	
Jeolla	276 (7.46)	201 (72.83)	
Jeju	358 (9.68)	273 (76.26)	
Current smoking			0.799
No	2,045 (67.6)	1,486 (72.67)	
Yes	795 (26.28)	568 (71.45)	
Alcohol consumption			0.261
No	1,637 (54.12)	1,165 (71.17)	
Yes	1,209 (39.97)	894 (73.95)	
Medication			0.019
No	1,759 (59.09)	1,285 (73.05)	
Yes	1,114 (37.42)	781 (70.11)	
Aspirin	215 (19.30)	155 (72.09)	
Non-steroidal anti-inflammatory drugs	82 (7.36)	46 (59.76)	
Antiplatelet/anticoagulation agents, or steroids	41 (3.68)	28 (68.29)	
Previous GI disorder			0.018
No	2,315 (77.27)	1,697 (73.3)	
Yes	567 (18.93)	382 (67.37)	
Peptic ulcer	417 (73.54)	276 (66.19)	
Others	242 (42.68)	158 (65.29)	
Comorbidity			0.031
No	1,743 (58.39)	1,289 (73.95)	
Yes	1,162 (38.93)	808 (69.54)	
Hypertension	721 (62.05)	517 (71.71)	
Diabetes	315 (27.11)	227 (72.06)	
Ischemic heart disease	62 (5.34)	41 (66.13)	
Liver cirrhosis	17 (1.46)	8 (47.06)	
Chronic renal failure	17 (1.46)	9 (52.94)	
Malignancy	43 (3.70)	28 (65.12)	
Others	422 (36.32)	277 (65.64)	

Fig. 2. Standardized *Helicobacter pylori* eradication rates in first-line therapy according to residence in Korea. The overall eradication rate in seven regions in Korea was 73.0%. Jeju province showed the highest eradication rate in the first-line therapy, whereas Chungcheong province had the lowest (76.1 vs. 60.3, *P* < 0.001).

of *H. pylori* eradication treatment (73.8% vs. 58.5%, *P* < 0.001). The most common first-line therapy was the 7-day PPI-based STT (86.8%). The eradication rates varied among different treatment regimens including STT, CT, PBMT, ST, and others (*P* < 0.001). The eradication rate with STT therapy was 73.0% compared to 90.3% with CT. The eradication rate of the 7-day treatment was 73.5%. Patients with good compliance to therapy had higher eradication rates than those with poor compliance (73.5% vs. 52.3%, *P* < 0.001). There was no significant difference in the eradication rate of patients who experienced complications (*P* = 0.626).

H. pylori eradication rates according to treatment regimens

The frequency of prescribing regimens in the final analysis (n = 3,700) did not differ significantly from those in the total population (n = 5,331). For the first-line therapy, the frequencies of STT were 3,550/3,700 (95.9%) in the final analysis and 5,099/5,331 (95.6%) in the total analysis. For the second-line therapy, the frequency of PBMT in the final analysis and the total analysis was 456/583 (78.2%) and 531/677 (78.4%), respectively. The *H. pylori* eradication rates in the first-line and second-line therapy according to treatment regimens are summarized in Table 2. For patients who had first-line therapy, most commonly STT (95.9%), the overall eradication rate was 73.0%. There was significant difference in the eradication rates according to treatment regimen: 73.0% in STT, 81.8% in PBMT, 100% in SQ, and 90.3% in CT. Table 3 shows the results of first-line *H. pylori* eradication rate according to the regimen and treatment duration. The most common regimen and treatment duration was STT for 7 days (3,214/3,700, 86.8%), which achieved a 74% eradica-

Table 2. Eradication success rates and related characteristics of 3,700 Korean patients who underwent the first-line *H. pylori* eradication therapy

Related parameters	Total participants with first-line therapy (n = 3,700) No. (%)	Eradication success (n = 2,701) No. (%)	*P* value
Indication for eradication			
BGU	1,083 (29.27)	736 (67.96)	< 0.001
DU	1,057 (28.57)	811 (76.73)	0.001
BGU+DU	1,982 (53.57)	1,426 (71.95)	0.121
Bleeding peptic ulcer	14 (0.38)	12 (85.71)	0.377
After endoscopic resection for early gastric cancer	444 (12)	337 (75.9)	0.142
Gastric MALT lymphoma	39 (1.05)	35 (89.74)	0.018
Others	870 (23.51)	632 (72.64)	0.787
Previous *H. pylori* eradication			< 0.001
No	3,495 (94.46)	2,581 (73.85)	
Yes (within 1 yr)	60 (1.62)	33 (5.5)	
Yes (before 1 yr)	145 (3.92)	87 (6.0)	
STT	157 (76.59)	85 (54.14)	
PBMT	32 (15.61)	26 (81.25)	
CT	1 (0.49)	1 (100)	
SQ	1 (0.49)	1 (100)	
Others	14 (6.83)	7 (50)	
Regimens			< 0.001
STT	3,550 (95.95)	2,592 (73.01)	
PBMT	33 (0.89)	27 (81.82)	
CT	31 (0.84)	28 (90.32)	
SQ	14 (0.38)	14 (100)	
Others	72 (1.95)	40 (55.56)	
Durations			< 0.001
7 day	3,310 (89.46)	2,435 (73.56)	
14 day	299 (8.08)	216 (72.24)	
Others	91 (2.46)	50 (54.95)	
Compliance			< 0.001
≥ 80%	3,608 (97.54)	2,653 (73.53)	
< 80%	42 (1.14)	22 (52.38)	
Complications			0.626
No	2,967 (80.21)	2,175 (73.31)	
Yes	612 (16.55)	437 (71.41)	
Abdominal pain	73 (11.92)	47 (64.38)	
Nausea, vomiting	126 (20.59)	74 (58.73)	
Diarrhea	215 (35.13)	159 (73.95)	
Others	343 (56.05)	249 (72.59)	
First-line therapy regimens			< 0.001
STT	3,550 (95.95)	2,592 (73.01)	
PBMT	33 (0.89)	27 (81.82)	
CT	31 (0.84)	28 (90.32)	
SQ	14 (0.38)	14 (100)	
Others	72 (1.95)	40 (55.56)	
Second-line therapy regimens	583 (100)	-	0.327
PBMT	456 (78.22)	391 (85.75)	
PAC	10 (1.72)	6 (60)	
PTM	33 (5.66)	29 (87.88)	
PLM	2 (0.34)	2 (100)	
PAM	2 (0.34)	2 (100)	
SQ	6 (1.03)	5 (83.33)	
Others	74 (12.69)	60 (81.08)	

CT: PPI+AMX+CLA+MTZ; PAC: Proton pump inhibitor+Amoxicillin+Clarithromycin; PAM: Proton pump inhibitor+Amoxicillin+Metronidazole; PBMT: Proton pump inhibitor+Denol+Metronidazole+Tetracyclin; PLM: Proton pump inhibitor+Levofloxacin+Metronidazole; PTM: Proton pump inhibitor+Tetracyclin+Metronidazole; SQ: PPI+AMX - > PPI+CLA+ MTZ; STT: Proton pump inhibitor+Amoxicillin+Clarithromycin.
BGU, benign gastric ulcer including scar; DU, duodenal ulcer including scar; BGU+DU, both benign gastric and duodenal ulcers; CT, Concomitant therapy; SQ, Sequential therapy.

Table 3. First-line *Helicobacter pylori* eradication rate according to the regimen and treatment duration

Duration, day	STT	PBMT	CT	SQ	Others	Total
7	2,371/3,214 (74%)	24/29 (83%)	3/4 (75%)	0/0 (0%)	37/63 (59%)	3,310
8-13	32/64 (50%)	1/1 (100%)	0/0 (0%)	14/14 (100%)	1/4 (25%)	83
14	188/268 (70%)	2/3 (67%)	25/26 (96%)	0/0 (0%)	1/2 (50%)	299
Other	1/4 (25%)	0/0 (0%)	0/1 (0%)	0/0 (0%)	1/3 (33%)	8
Total	3,550	33	31	14	72	3,700

STT: Proton pump inhibitor+Amoxicillin+Clarithromycin; PBMT: Proton pump inhibitor+Denol+Metronidazole+Tetracyclin; CT: PPI+AMX+CLA+MTZ; SQ: PPI+AMX - > PPI+CLA+MTZ.
CT, Concomitant therapy; SQ, Sequential therapy.

Table 4. Association between the outcome of eradication therapy and risk factors evaluated using logistic regression model

Variables		Eradication success rates No. (%)/Total	Univariate analysis		Multivariate analysis	
			Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value
Age in years	< 30	105 (72.92)/144	Reference	0.002	Reference	0.009
	30-39	251 (77.95)/322	1.313 (0.835-2.064)		1.337 (0.792-2.257)	
	40-49	511 (76.73)/666	1.224 (0.813-1.843)		1.236 (0.764-2.000)	
	50-59	917 (73.54)/1,247	1.032 (0.700-1.522)		0.995 (0.626-1.581)	
	60-69	625 (70.7)/884	0.896 (0.604-1.331)		0.854 (0.531-1.373)	
	≥ 70	292 (66.82)/437	0.748 (0.492-1.136)		0.753 (0.456-1.243)	
Sex	Male	1,643 (73.58)/2,233	Reference	0.329	NA	
	Female	1,058 (72.12)/1,467	0.929 (0.801-1.077)		NA	
Residence	Seoul	592 (73.18)/809	Reference	< 0.001	Reference	< 0.001
	Gyeonggi	496 (71.68)/692	0.928 (0.739-1.164)		0.859 (0.660-1.116)	
	Gangwon	68 (73.12)/93	0.997 (0.614-1.618)		1.015 (0.560-1.841)	
	Chungcheong	187 (60.32)/310	0.557 (0.423-0.734)		0.570 (0.413-0.786)	
	Gyeongsang	884 (76.08)/1,162	1.166 (0.949-1.432)		1.128 (0.882-1.443)	
	Jeolla	201 (72.83)/276	0.982 (0.722-1.336)		1.000 (0.712-1.405)	
	Jeju	273 (76.26)/358	1.177 (0.882-1.572)		1.294 (0.948-1.766)	
Current smoking	No	1,486 (72.67)/2,045	Reference	0.794	NA	
	Yes	568 (71.45)/795	0.941 (0.785-1.129)		NA	
	NA	135 (72.97)/185	1.016 (0.724-1.425)		NA	
Alcohol consumption	No	1,165 (71.17)/1,637	Reference	0.264	NA	
	Yes	894 (73.95)/1,209	1.150 (0.973-1.359)		NA	
	NA	129 (72.07)/179	1.045 (0.741-1.474)		NA	
Medication	No	1,285 (73.05)/1,759	Reference	0.022	Reference	0.012
	Yes	781 (70.11)/1,114	0.865 (0.733-1.021)		0.947 (0.788-1.137)	
	NA	85 (81.73)/104	1.650 (0.993-2.744)		2.500 (1.328-4.708)	
Previous gastrointestinal disorder	No	1,697 (73.30)/2,315	Reference	0.019	Reference	0.038
	Yes	382 (67.37)/567	0.752 (0.617-0.917)		0.816 (0.659-1.012)	
	NA	83 (72.81)/114	0.975 (0.639-1.488)		0.595 (0.351-1.011)	
Comorbidity	No	1,289 (73.95)/1,743	Reference	0.021	NA	
	Yes	808 (69.54)/1,162	0.804 (0.682-0.948)		NA	
	NA	61 (77.22)/79	1.194 (0.698-2.041)		NA	
Previous *H. pylori* eradication	No	2,581 (73.85)/3,495	Reference	< 0.001	Reference	< 0.001
	Yes (within 1 yr)	33 (55.0)/60	0.433 (0.259-0.723)		0.364 (0.207-0.640)	
	Yes (before 1 yr)	87 (60.0)/145	0.531 (0.378-0.746)		0.627 (0.425-0.925)	
Duration in days	7	2,435 (73.56)/3,310	Reference	< 0.001	Reference	0.019
	14	216 (72.24)/299	0.935 (0.718-1.218)		0.918 (0.651-1.295)	
	Other	50 (54.95)/91	0.438 (0.288-0.667)		0.520 (0.329-0.821)	
Compliance	≥ 80%	2,653 (73.53)/3,608	Reference	< 0.001	Reference	< 0.001
	< 80%	22 (52.38)/42	0.396 (0.215-0.729)		0.375 (0.196-0.717)	
	NA	25 (51.02)/49	0.375 (0.213-0.660)		0.390 (0.189-0.805)	
Complication	No	2,175 (73.31)/2,967	Reference	0.626	NA	
	Yes	437 (71.41)/612	0.909 (0.749-1.103)		NA	
	NA	88 (73.33)/120	1.001 (0.663-1.513)		NA	

NA, not applicable.

tion success rate. Of the 999 patients whose first-line therapy failed, 583 (58.3%) patients tried the second-line therapy. The overall eradication rate was 84.3%. However, there was no statistically significant difference (*P* = 0.25) in the eradication rate among various treatment regimens (Table 2).

Factors related to *H. pylori* eradication success

In univariate analysis, age, residential area, medication, previ-

ous gastrointestinal disorder, comorbidity, previous *H. pylori* eradication, PPI, duration of treatment, and compliance to treatment were related to the success of eradication (Table 4). After the adjustment for age, residential area, history of *H. pylori* eradication, duration of treatment, and compliance to treatment remained statistically significant. Older age was related to unfavorable outcome (*P* for trend = 0.0543). Chungcheong province showed a decreased success rate; eradication failure was 1.67 times more frequent than in Seoul. Previous history of *H. pylori* eradication treatment increased the failure rate almost twice compared to those without previous treatment. Lower compliance (< 80%) was related to 2.78 times more treatment failure than patients with high compliance (> 80%). Treatment duration longer than 7 days did not show any increased success in eradication treatment.

DISCUSSION

The current study reports on the establishment and interim results of a nationwide online registry in Korea aimed at tracking the eradication of *H. pylori*. This registry is unique globally. This interim analysis of the 5-year study was planned to review the completeness of the data to date and predict the results at an early stage.

The data supports the evidence that the *H. pylori* eradication rate using standard triple therapy is indeed decreasing and has become sub-optimal in Korea. The eradication rate of first-line therapy has significantly decreased to 73% since 2000, demonstrating a lower than expected efficacy of STT of *H. pylori* infection in Korea. This eradication rate is similar to that in other countries (7,10,11). This suggests that alternate regimens including sequential or concomitant therapy are required as soon as possible. This interim analysis underscores the urgency of the current situation in Korea.

Korean guidelines for *H. pylori* infection were formulated in 1998. They state that a definitive indication for *H. pylori* eradication is peptic ulcer including scarring, marginal zone B cell lymphoma (MALT type), and early gastric cancer after endoscopic resection (12). Since 1998, PPI-based triple therapy has been recommended as the first-line therapy for *H. pylori* eradication in Korea. However, since 2000, the eradication rate has been declining, falling below 80%. The Asia-Pacific Consensus Guidelines have stricter standards that re-quire a success rate of > 80% in intention-to-treat analysis and > 90% in per-protocol analysis for a regimen to be considered suitable for first-line eradication therapy (8). In the present study, the overall eradication rate was only 73% in first-line therapy. Considering the fact that the majority (89.4%) of cases were treated with STT for 7 days, a decline in the eradication rate could imply a serious problem in the management of *H. pylori* infection in Korea. Fortunately, naïve patients had a significantly higher eradica-

tion rate than those with previous *H. pylori* infection. These results strongly suggest that more effective first-line therapy is necessary to treat *H. pylori* infection.

In cases where treatment fails, the consensus treatment is one or two weeks of quadruple therapy (PPI + metronidazole + tetracycline + bismuth) (12). The overall eradication rate of 84.3% in second-line therapy was consistent with the eradication rates observed in previous studies (13).

Several factors affect the eradication of *H. pylori*. These include antibiotic resistance, geographical area, patient age, smoking status, compliance, duration of therapy, bacterial density, Cag A, gastric acid concentration, individual response to PPI, and the presence of CYP2C19 polymorphism (8). Of these factors, clarithromycin resistance has been suspected to be the main cause of eradication failure (14,15). In Korea, 5.9% of those treated were resistant to clarithromycin before 2000. However, from 2007-2009, the rate of resistance showed a sharp increase, reaching 38.5% (10,16,17). Rates of resistance in other countries are much lower. The discrepancy can be explained by wide international and regional variations in the prevalence of resistance to antibiotics (18,19). In the present study, Jeju province showed the highest eradication rate with STT as the first-line therapy, whereas STT therapy in Chungcheong province had the lowest eradication rate (76.2% vs. 60.3%). Nonetheless, the hypothesis that there are regional differences in Korea is still under debate.

Studies have shown conflicting results in the eradication rate of elderly patients (20,21). In this study, advanced age was positively associated with treatment failure, whereas gender was not associated with treatment failure or eradication rates, which supported the results of a previous study (22). Some reports assert that smoking can increase treatment failure in *H. pylori* eradication as gastric blood flow and mucus secretion decrease, and as acid secretion increases (23). However, no significant association between smoking and treatment failure was observed in the present study. A previous report demonstrated an inverse relationship between alcohol consumption and *H. pylori* infection, which indicated alcohol consumption might facilitate eradication (24). However, no significant relationship between alcohol consumption and eradication failure was observed in this study.

Underlying chronic diseases, such as diabetes mellitus, hypertension, chronic kidney disease, chronic liver disease, and chronic lung disease, have been periodically reported to influence the outcome of *H. pylori* eradication therapy. However, the evidence is limited and the results are inconsistent (25). In the present study, eradication rates were significantly lower in patients with a history of peptic ulcer and other comorbidities, particularly liver cirrhosis and chronic renal failure. Therefore, this study demonstrates that eradication success is determined by various clinical factors as well as bacterial factors.

Most of recently recommended therapy regimens for *H. pylori* eradication are 7 days in duration. This period is associated with higher compliance and lower medical costs, while maintaining a similar eradication rate to that of longer regimens. Currently, the Korean College of Helicobacter and Upper Gastrointestinal Research group recommend a 7-day or 14-day STT. Previous studies in Korea reported that a 7-day STT was not inferior to a 10-day or a 14-day therapy. Recently, more diverse treatment regimens have being administered, including sequential and concomitant therapy, whose satisfactory eradication rates are higher than STT (26,27). Therefore, new strategies to achieve higher *H. pylori* eradication rates are required. Potential approaches in overcoming this problem are patient-tailored sequential or concomitant therapies coupled with prolonged treatment duration in Korea.

Although the number of cases in this study is small, the eradication success with SQ (100%) and CT (90.3%) were significantly ($P < 0.001$) higher when compared to STT (73.0%). PBMT for 14 days had an eradication success of 81.8%. International guidelines have not incorporated such emerging first-line therapies so far (5,28). However, more recent recommendations suggest that change is likely in the immediate future. A lot of work in developing and validating novel regimens needs to be done before recommending new therapies as first-line therapy against *H. pylori* infection (27,29). Adverse events were reported in 16.5% of patients, mainly mild diarrhea, nausea, and mild vomiting. The types of adverse events or severity were not in particular affected by the differences in the patients' background.

To date, this is the most comprehensive, systematic, and easily accessible online registration database tracking *H. pylori* eradication in Korea. This registration database will serve as a valuable resource in monitoring antibiotic resistance, *H. pylori* reinfection, and association of *H. pylori* infection with gastric carcinogenesis. This database makes it possible to construct a global network for those working in the field of *H. pylori* control in the future.

In conclusion, our data support the evidence that *H. pylori* eradication rate using STT is decreasing and has become suboptimal in Korea, suggesting the need for alternate regimens including sequential or concomitant therapy to improve the efficacy of first-line therapy for *H. pylori* infection in Korea.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and design of the study: Kim JG, Lee JH. Performing the study: Kim HS, Song HJ, Chung IK, Kim GH, Kim BW, Shim KN, Jeon SW, Jung YJ, Yang CH, Kim JH, Kim TH, Kim SG, Shin WG, Kim SM, Han SW, Kim KH, Kim BJ, Lee JH, Kim JG. Analysis of the data: Park SK, Park BJ, Lee J. Writing the first draft: Kim BJ. Revision of manuscript: Kim BJ, Kim JG. Approval of the final version of the manuscript: all authors.

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REFERENCES

1. Gisbert JP, Calvet X. Review article: the effectiveness of standard triple therapy for *Helicobacter pylori* has not changed over the last decade, but it is not good enough. *Aliment Pharmacol Ther* 2011; 34: 1255-68.
2. Suerbaum S, Michetti P. *Helicobacter pylori* infection. *N Engl J Med* 2002; 347: 1175-86.
3. McColl KE. Clinical practice. *Helicobacter pylori* infection. *N Engl J Med* 2010; 362: 1597-604.
4. Kim MS, Kim N, Kim SE, Jo HJ, Shin CM, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, et al. Long-term follow-up *Helicobacter pylori* reinfection rate and its associated factors in Korea. *Helicobacter* 2013; 18: 135-42.
5. Fock KM, Talley N, Moayyedi P, Hunt R, Azuma T, Sugano K, Xiao SD, Lam SK, Goh KL, Chiba T, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. *J Gastroenterol Hepatol* 2008; 23: 351-65.
6. Lim SH, Kwon JW, Kim N, Kim GH, Kang JM, Park MJ, Yim JY, Kim HU, Baik GH, Seo GS, et al. Prevalence and risk factors of *Helicobacter pylori* infection in Korea: nationwide multicenter study over 13 years. *BMC Gastroenterol* 2013; 13: 104.
7. Kim N, Kim JJ, Choe YH, Kim HS, Kim JI, Chung IS; Korean College of Helicobacter and Upper Gastrointestinal Research; Korean Association of Gastroenterology. Diagnosis and treatment guidelines for *Helicobacter*

pylori infection in Korea. *Korean J Gastroenterol* 2009; 54: 269-78.

8. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 2007; 102: 1808-25.

9. Kim JM, Kim JS, Jung HC, Kim N, Kim YJ, Song IS. Distribution of antibiotic MICs for *Helicobacter pylori* strains over a 16-year period in patients from Seoul, South Korea. *Antimicrob Agents Chemother* 2004; 48: 4843-7.

10. Cho DK, Park SY, Kee WJ, Lee JH, Ki HS, Yoon KW, Cho SB, Lee WS, Joo YE, Kim HS, et al. The trend of eradication rate of *Helicobacter pylori* infection and clinical factors that affect the eradication of first-line therapy. *Korean J Gastroenterol* 2010; 55: 368-75.

11. Choi YS, Cheon JH, Lee JY, Kim SG, Kim JS, Kim N, Lee DH, Kim JM, Jung HC, Song IS. The trend of eradication rates of first-line triple therapy for *Helicobacter pylori* infection: single center experience for recent eight years. *Korean J Gastroenterol* 2006; 48: 156-61.

12. Gong EJ, Yun SC, Jung HY, Lim H, Choi KS, Ahn JY, Lee JH, Kim DH, Choi KD, Song HJ, et al. Meta-analysis of first-line triple therapy for *Helicobacter pylori* eradication in Korea: is it time to change? *J Korean Med Sci* 2014; 29: 704-13.

13. Georgopoulos SD, Papastergiou V, Karatapanis S. *Helicobacter pylori* eradication therapies in the era of increasing antibiotic resistance: a paradigm shift to improved efficacy. *Gastroenterol Res Pract* 2012; 2012: 757926.

14. Graham DY, Shiotani A. New concepts of resistance in the treatment of *Helicobacter pylori* infections. *Nat Clin Pract Gastroenterol Hepatol* 2008; 5: 321-31.

15. Chung JW, Lee GH, Han JH, Jeong JY, Choi KS, Kim DH, Jung KW, Choi KD, Song HJ, Jung HY, et al. The trends of one-week first-line and second-line eradication therapy for *Helicobacter pylori* infection in Korea. *Hepatogastroenterology* 2011; 58: 246-50.

16. Park JM, Hahm KB. The Korean perspective of *Helicobacter pylori* infection: lessons from the Japanese government's policy to prevent gastric cancer. *Dig Dis* 2014; 32: 290-4.

17. Kim SY, Jung SW. *Helicobacter pylori* eradication therapy in Korea. *Korean J Gastroenterol* 2011; 58: 67-73.

18. Saracino IM, Zullo A, Holton J, Castelli V, Fiorini G, Zaccaro C, Ridola L, Ricci C, Gatta L, Vaira D. High prevalence of primary antibiotic resistance in *Helicobacter pylori* isolates in Italy. *J Gastrointestin Liver Dis* 2012; 21: 363-5.

19. Liu G, Xu X, He L, Ding Z, Gu Y, Zhang J, Zhou L. Primary antibiotic resistance of *Helicobacter pylori* isolated from Beijing children. *Helicobacter* 2011; 16: 356-62.

20. Kim JJ, Reddy R, Lee M, Kim JG, El-Zaatari FA, Osato MS, Graham DY, Kwon DH. Analysis of metronidazole, clarithromycin and tetracycline resistance of *Helicobacter pylori* isolates from Korea. *J Antimicrob Chemother* 2001; 47: 459-61.

21. Hwang TJ, Kim N, Kim HB, Lee BH, Nam RH, Park JH, Lee MK, Park YS, Lee DH, Jung HC, et al. Change in antibiotic resistance of *Helicobacter pylori* strains and the effect of A2143G point mutation of 23S rRNA on the eradication of *H. pylori* in a single center of Korea. *J Clin Gastroenterol* 2010; 44: 536-43.

22. Kim JY, Kim NY, Kim SJ, Baik GH, Kim GH, Kim JM, Nam RH, Kim HB, Lee DH, Jung HC, et al. Regional difference of antibiotic resistance of *Helicobacter pylori* strains in Korea. *Korean J Gastroenterol* 2011; 57: 221-9.

23. Kim N, Kim JM, Kim CH, Park YS, Lee DH, Kim JS, Jung HC, Song IS. Institutional difference of antibiotic resistance of *Helicobacter pylori* strains in Korea. *J Clin Gastroenterol* 2006; 40: 683-7.

24. Treiber G, Ammon S, Klotz U. Age-dependent eradication of *Helicobacter pylori* with dual therapy. *Aliment Pharmacol Ther* 1997; 11: 711-8.

25. Labenz J, Leverkus F, Börsch G. Omeprazole plus amoxicillin for cure of *Helicobacter pylori* infection. Factors influencing the treatment success. *Scand J Gastroenterol* 1994; 29: 1070-5.

26. Moayyedi P, Chalmers DM, Axon AT. Patient factors that predict failure of omeprazole, clarithromycin, and tinidazole to eradicate *Helicobacter pylori*. *J Gastroenterol* 1997; 32: 24-7.

27. Suzuki T, Matsuo K, Sawaki A, Ito H, Hirose K, Wakai K, Sato S, Nakamura T, Yamao K, Ueda R, et al. Systematic review and meta-analysis: importance of CagA status for successful eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2006; 24: 273-80.

28. Kuepper-Nybelen J, Rothenbacher D, Brenner H. Relationship between lifetime alcohol consumption and *Helicobacter pylori* infection. *Ann Epidemiol* 2005; 15: 607-13.

29. Lee JY, Kim N, Kim MS, Choi YJ, Lee JW, Yoon H, Shin CM, Park YS, Lee DH, Jung HC. Factors affecting first-line triple therapy of *Helicobacter pylori* including CYP2C19 genotype and antibiotic resistance. *Dig Dis Sci* 2014; 59: 1235-43.

30. Papastergiou V, Georgopoulos SD, Karatapanis S. Treatment of *Helicobacter pylori* infection: past, present and future. *World J Gastrointest Pathophysiol* 2014; 5: 392-9.

31. Lee HJ, Kim JI, Lee JS, Jun EJ, Oh JH, Cheung DY, Chung WC, Kim BW, Kim SS. Concomitant therapy achieved the best eradication rate for *Helicobacter pylori* among various treatment strategies. *World J Gastroenterol* 2015; 21: 351-9.

32. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, et al. Management of *Helicobacter pylori* infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; 61: 646-64.

33. Yoon H, Lee DH, Kim N, Park YS, Shin CM, Kang KK, Oh DH, Jang DK, Chung JW. Meta-analysis: is sequential therapy superior to standard triple therapy for *Helicobacter pylori* infection in Asian adults? *J Gastroenterol Hepatol* 2013; 28: 1801-9.