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Clinical Characteristics and Treatment Pathway of Patients Treated with *Helicobacter pylori* Infection-A Single Center Cohort Study Using Common Data Model

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Background/Aims: Changing trends in the *Helicobacter pylori* (*H. pylori*) eradication protocol have not been investigated after the publication of the third-revised Korean guideline in 2013. We aimed to analyze the clinical characteristics of *H. pylori*-infected patients alongside their treatment protocols using a common data model (CDM).
Materials and Methods: A 16-year electronic health record (of 1,689,604 patients from 2004 to 2019) was converted into a CDM in Kangdong Sacred Heart Hospital. We extracted records of patients who underwent the rapid urease test or serum anti-*H. pylori* IgG assay. The treatment protocols were visualized using a sunburst plot. We investigated the clinical characteristics and medication history of patients who underwent a urea breath test after clarithromycin-based eradication therapy.
Results: Out of 29,458 patients tested for *H. pylori* infection, 7,647 received a treatment protocol. Among them, 72.5% received a 7~14 days protocol comprising a proton pump inhibitor (PPI), amoxicillin, and clarithromycin. The proportion of patients treated with the first-line protocol (PPI, bismuth, tetracycline, and metronidazole) slightly increased from 1.9% (before 2014) to 3.3% (after 2014) ($P<0.001$). The percentages of patients with of previous exposure to macrolides (14.7% vs. 5.5%, $P<0.001$) or amoxicillin (10.6% vs. 7.3%, $P=0.006$) were higher in patients with previous clarithromycin-based eradication failure.
Conclusions: The *H. pylori* treatment protocol was not significantly modified despite the updates in the clinical guideline. There was only 1.4 percentage point increase in bismuth-based quadruple therapy as first-line eradication therapy even after the announcement of revised Korean guideline in 2013. **(Korean J *Helicobacter* Up Gastrointest Res 2022;22:214-221)**

Key Words: Common data model; *Helicobacter pylori*;Treatment

INTRODUCTION

The fourth revision of the guideline for the diagnosis and treatment of *Helicobacter pylori (H. pylori)* infection in South Korea was published in 2020, but there is a lack of research on changes in treatment patterns in response to the publication of updated versions of the protocol.[1] In South Korea, clarithromycin-based triple therapy, where a proton pump inhibitor (PPI), clarithromycin, and amoxicillin are administered twice a day for 7~14 days, has traditionally been used as the first-line *H. pylori* treatment. However, the eradication rate has continued to decline and recently fell under 80%.[2,3] Therefore, the 2013 revision of the South Korean protocol recommended that bismuth-based quadruple therapy should be used as the first-line *H. pylori* treatment when resistance to clarithromycin is suspected.[4] Since 2020, tailored treatment has been introduced; in this approach, the treatment is selected after determining resistance to clarithromycin using PCR or gene sequencing. However, it is not well understood whether this recommendation has led to any changes in treatment patterns. A recently published European registry study on *H. pylori* eradication found that the treatment patterns varied by country.[5] Although the European guideline recommends shifting from triple therapy to quadruple therapy, the report showed that actual treatment patterns did not change.[5,6]

There have been technical difficulties in synthesizing data from hospitals to be used in research since medical data is characterized by heterogeneity in the data structure and format, large data size, and a tendency to be unrefined. There have also been difficulties sharing data

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among researchers due to differences in institutions' data sharing policies and personal information privacy issues. Distributed research networks using a common data model (CDM) have recently been gaining attention to resolve these difficulties and allow easy application to research.[7] The Observational Medical Outcomes Partnership (OMOP)-CDM has been developed and operated by the Observational Health Data Sciences and Informatics (OHDSI), and has been used in various multinational studies around the world.[8-11] In South Korea, the Ministry of Trade, Industry and Energy started a CDM-based distributed bio-health big data platform project in 2018. Around 40 hospitals in South Korea converted their electronic medical records data to the OMOP-CDM, establishing a consolidated bio-health big data network.

The cohort characterization method makes it possible to analyze the prior medications and diseases easily in patients who received clarithromycin-based triple therapy. Studying the treatment pathway enables analysis and visualization of *H. pylori* treatment patterns. In this study, we aimed to analyze the characteristics and history of antibiotic exposure in patients who underwent clarithromycin-based eradication therapy using the data transformed to the CDM from a single institution. Furthermore, we aimed to determine whether there was a change in the treatment pattern after January 1, 2014 when the third revised guideline[4] was applied.

MATERIALS AND METHODS

1. Database

This study was conducted using the Kangdong Sacred Heart Hospital CDM. This database includes 16 years of treatment data (2004~2019) from 1,689,604 patients. The data were analyzed as described in our previous study.[12] It contains variables such as prescriptions, diagnoses, procedures including endoscopy, operations, blood tests, rapid urease test results (CLOtest, Pronto Dry New; Medical Instruments Co., Herford, Germany), and urea breath test results (^{13}C-UBT; UBiT-IR 300, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan).

ATLAS, developed by the OHDSI community, is a web-based open platform that supports study design, cohort sampling, prevalence calculation, large-scale propensity score matching, cohort characteristics analysis, and artificial intelligence-based predictions.[13] ATLAS version 2.7.6 was used for the study design, and the analyses were conducted using FEEDER-NET, a coordinating platform that enables data user and supplier connections and multi-institution analyses.[7] This study was approved by the Kangdong Sacred Heart Hospital Medical Research Institutional Review Board (decision No.: IRB 2021-11-001).

2. Cohort definition

To assess the *H. pylori* treatment pathway, we analyzed the patterns of antibacterial treatment among the target cohort of 29,458 adult patients over the age of 18 who underwent rapid urease test or *H. pylori* antibody test (Genedia *H. pylori* ELISA; Green Cross Medical Science Co., Seoul, Korea). The event cohort was defined as those who were prescribed clarithromycin, amoxicillin, metronidazole, bismuth subcitrate, tetracycline, or levofloxacin for 7~14 days after being included in the target cohort. The antibacterial treatment patterns before and after the announcement of the guideline were compared by dividing the cohort on January 1, 2014. We also created a cohort of patients who were prescribed clarithromycin-based triple therapy (PPI, amoxicillin, and clarithromycin) for 7~14 days as the first-line treatment and underwent a ^{13}C-UBT after a month. Differences according to patients' history of antibiotic exposure were analyzed by comparing those who were prescribed PPI, bismuth subcitrate, tetracycline, and metronidazole for 7~14 days as second-line treatment after the clarithromycin-based triple therapy and those who were not.

3. Treatment pathway analysis

Treatment pathway analysis, which is a method to summarize the events that occurred after patients entered the target cohort, can provide important evidence about the treatment status, including medication use, within a population sample.[14] In a previous international OHDSI study, the first-line medication, most frequently used medi-

cation, and subsequent treatment patterns were visualized as sunburst plots for type 2 diabetes, hypertension, and depression after analyzing the characteristics of treatment pathways using OMOP-CDM data.[15] Using the cohort pathway tab in the ATLAS platform, the target cohort and event cohort were activated, and graphs to visualize treatment pathways were created using the R statistical program. The percentages of patients in specific treatment pathways and the patterns of subsequent treatment were identified by clicking on the generated graphs.

4. Analysis of clinical characteristics

The characteristics of a target cohort can be analyzed using the characterization tab on ATLAS. This function can be applied to a multi-institution database. Characteristic analysis requires at least one cohort and at least one characteristic to be analyzed. First, the characteristic to be analyzed is defined using the feature analysis tool for the target cohort. In this study, basic sociodemographic information, prescriptions, and diagnoses during the past year before entering the cohort were analyzed. In addition, exposure to macrolides, amoxicillin, and metronidazole before cohort entry was analyzed.

5. Statistical analysis

Based on the results from ATLAS, categorical variables were analyzed using the chi-square test. The statistical software MedCalc® version 20.106 (MedCalc Software, Ostend, Belgium) was used.[16,17] Statistical significance was defined as a *P*-value below 0.05.

RESULTS

1. Changes in *H. pylori* treatment patterns

Among 29,458 patients who were tested for *H. pylori*, 15,444 received a rapid urease test, and 14,014 had the serum anti-*H. pylori* IgG test. From these patients, 7,647 (26% of all patients tested) entered the treatment pathway. The overall study flow and patient inclusion and exclusion are presented in Fig. 1. Among the 7,647 patients who entered the treatment pathway, 5,547 (72.5%) were prescribed clarithromycin and amoxicillin at the same time for 7~14 days. Meanwhile, 138 patients (1.8%) were prescribed bismuth subcitrate, metronidazole, and tetracycline for 7~14 days during the same period as the first-line treatment (Fig. 2A). Sequential therapy and concomitant therapy were not conducted in this hospital. Furthermore, 175 patients (2.3%) were treated with metronidazole and amoxicillin. The isolated use of clarithromycin was seen in 4.1%, metronidazole in 5.3%, and levofloxacin in 7.1%. It was assumed that these findings reflect antibacterial exposure unrelated to *H. pylori* treatment (Fig. 2A). When the treatment pathways before and after January 1, 2014 were analyzed, 75 out of 3,956 patients (1.9%) received first-line treatment of bismuth subcitrate, metronidazole, and tetracycline before January 1, 2014. After January 1, 2014, 63 out of 1,904 (3.3%) received this treatment, showing a statistically significant difference ($P<0.001$) (Fig. 2B). The number of patients receiving amoxicillin and metronidazole treatment increased from 31 out of 3,956 (0.8%) before 2014 to 144 out of 1,904 (7.6%) after 2014 ($P<0.001$).

2. Characteristics of patients who underwent clarithromycin-based triple therapy

Among the 5,547 patients who received PPI, clarithromycin, and amoxicillin for 7~14 days as first-line therapy, 3,138 received a ^{13}C-UBT (Fig. 1). The average age of these patients was 53.10±13.34 years, and the proportion of men was 60.6% (Table 1). The proportion of patients with peptic ulcers, an indication for eradication treatment, was 83.2% (n=2,612), while 178 patients (5.7%) had stomach cancer and 348 (11.1%) had other conditions. When patients' prescription history of medication related to peptic ulcers before eradication treatment was analyzed, 16% had been prescribed nonsteroidal anti-inflammatory drugs, 14.3% had been prescribed antithrombotics, and 7.5% had been prescribed steroids. Among the antithrombotics, 8.5% of the prescriptions were for aspirin, and 3.2% were for clopidogrel. Patients' history of antibiotic prescriptions before eradication treatment was analyzed, including all ingredients

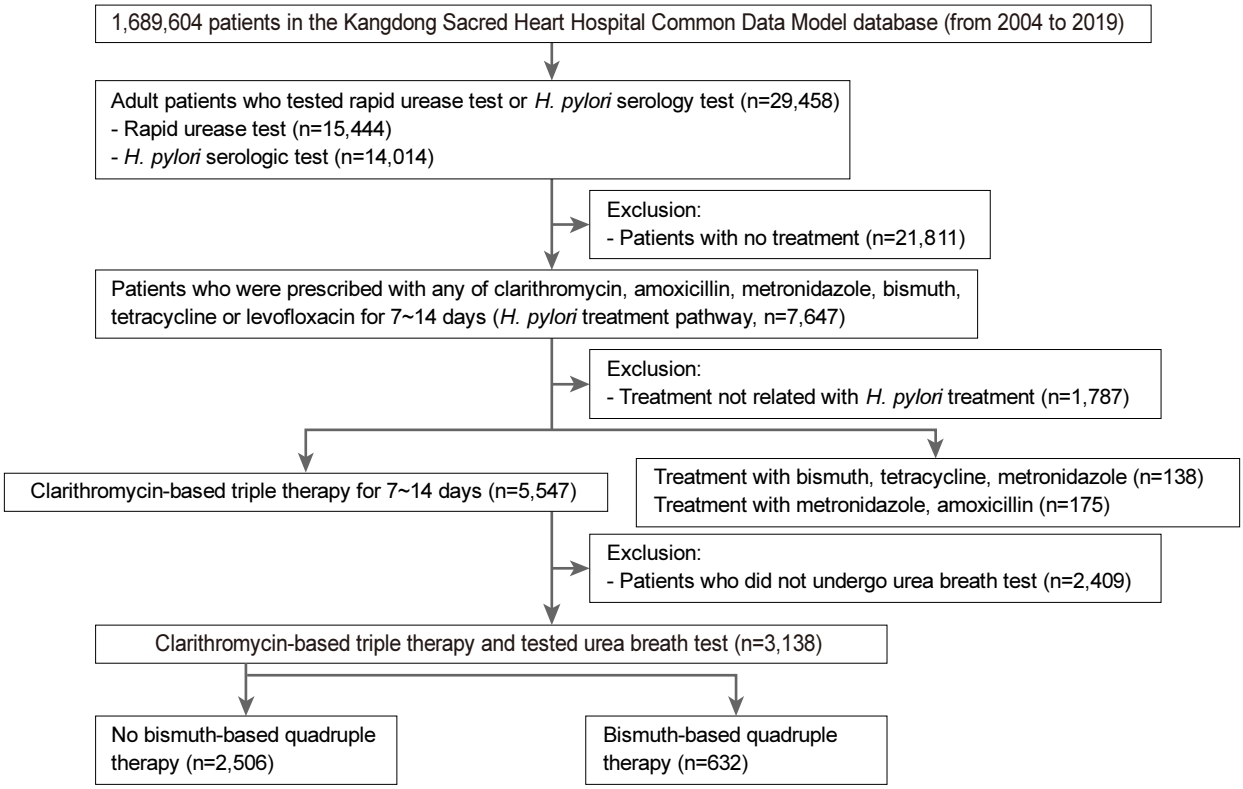

Fig. 1. Study flow chart. *H. pylori, Helicobacter pylori*.

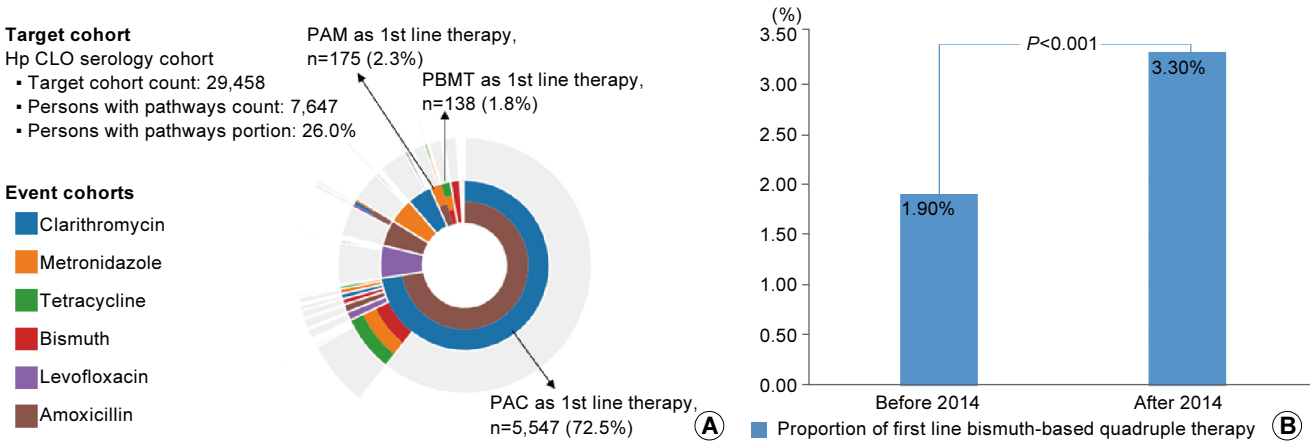

Fig. 2. (A) Sunburst plot of *H. pylori* treatment pathway in the KDH-CDM database and (B) difference in the proportion of first line bismuth-based quadruple therapy between before 2014 and after 2014. Hp CLO serology cohort refers to patients who underwent the rapid urease test (CLOtest, Pronto Dry New; Medical Instruments Co., Herford, Germany) or serum anti-*H. pylori* IgG test. PAM, proton pump inhibitor, amoxicillin, metronidazole; PBMT, proton pump inhibitor, bismuth subcitrate, metronidazole, tetracycline; PAC, proton pump inhibitor, amoxicillin, clarithromycin; *H. pylori, Helicobacter pylori*; KDH-CDM, Kangdong Sacred Heart Hospital Common Data Model.

of medications, and exposure to amoxicillin was most frequent, with 7.4% of patients having received macrolide antibiotics (clarithromycin: 3.3%; roxithromycin: 1.9%; azithromycin: 1.8%), 3.7% having received metronidazole, and 7.9% having received amoxicillin (Table 1).

Among the 3,138 patients who had a ^{13}C-UBT after clarithromycin-based triple therapy, 632 received bismuth-based quadruple therapy, while 2,506 did not re-

ceive bismuth-based quadruple therapy. Based on these findings, the presumed eradication rate of clarithromycin-based triple therapy was calculated as 79.8%.

Table 1. Baseline Characteristics of Patients Who Underwent a Urea Breath Test after the Clarithromycin-based Triple Therapy (n=3,138)

	Value
Age (years)	53.10±13.34
Age ≥65 years	512 (16.3)
Male	1,903 (60.6)
Past medical history	
Peptic ulcer	2,612 (83.2)
Gastric ulcer	1,625 (51.7)
Duodenal ulcer	1,485 (47.3)
Hypertensive disorder	232 (7.4)
Diabetes mellitus	106 (3.4)
Hyperlipidemia	125 (4.0)
Ischemic heart disease	110 (3.5)
Chronic kidney disease	30 (1.0)
Chronic liver disease	51 (1.6)
Acute respiratory disease	70 (2.2)
Medication	
NSAIDs	502 (16.0)
Steroid	237 (7.5)
Antithrombotic agents	450 (14.3)
Aspirin	268 (8.5)
Clopidogrel	101 (3.2)
Others	81 (2.6)
Antibiotics	
Macrolide	232 (7.4)
Clarithromycin	104 (3.3)
Roxithromycin	60 (1.9)
Azithromycin	56 (1.8)
Erythromycin	8 (0.3)
Telithromycin	4 (0.1)
Amoxicillin	250 (7.9)
Metronidazole	118 (3.7)

Values are presented as mean±standard deviation or number (%).
NSAIDs, non-steroidal anti-inflammatory drugs.

3. Comparison of the history of antibiotic exposure by second-line treatment status among patients who received clarithromycin-based triple therapy

The history of antibiotic exposure was compared based on bismuth-based quadruple therapy status among patients who had a ^{13}C-UBT after clarithromycinbased triple therapy as their first-line treatment. A history of macrolide antibiotic exposure was present in 14.7% of patients who received bismuth-based quadruple therapy. Therefore, the patients can be assumed to have had an unsuccessful first-line eradication therapy (n=632). In comparison, previous exposure to macrollde antibiotics was found in 5.5% among those who did not receive bismuth-based quadruple therapy and therefore had successful eradication treatment (n=2,506) (P<0.001). The corresponding percentages for amoxicillin exposure were 10.6% and 7.3%, respectively (P=0.006). Previous exposure to macrolide antibiotics and amoxicillin was significantly more common among patients who received bismuthbased quadruple therapy (P<0.001). However, the two groups did not demonstrate a statistically significant difference regarding their history of metronidazole exposure (Table 2).

DISCUSSION

In the South Korean *H. pylori* treatment guideline announced in July 2013, bismuth-based quadruple therapy was recommended as the first-line eradication therapy when resistance to clarithromycin is suspected. However, studies have not examined the changes in actual treat-

Table 2. Variation in the Proportion of Patients with Previous Exposure to Antibiotics According to the Presence of Second Line Therapy in Patients Who Received the Clarithromycin-based Triple Therapy

Antibiotic exposure	Patients with BQT (n=632)	Patients without BQT (n=2,506)	*P*-value
Macrolide	94 (14.7)	138 (5.5)	<0.001
Metronidazole	27 (4.2)	91 (3.6)	0.449
Amoxicillin	67 (10.6)	183 (7.3)	0.006

Values are presented as number (%).
BQT, bismuth-based quadruple therapy.

ment patterns. This study used data from a single institution converted to the CDM to analyze changes in treatment patterns after January 1, 2014 among patients who had received *H. pylori* tests and the clinical characteristics and history of antibiotic exposure among first-line eradication treatment patients. Before January 1, 2014, 1.9% (75/3,956) received bismuth-based quadruple therapy as the first-line eradication therapy. After January 1, 2014, 3.3% (63/1,904) received bismuth-based quadruple therapy as first-line eradication therapy, indicating that the proportion increased to a statistically significant degree after the revision in the treatment protocol. However, this proportion remained low. There is a possibility that doctors prefer triple therapy due to concerns about the side effects of bismuth-based quadruple therapy. Another possibility is that doctors had difficulty interpreting the vague language in the revised treatment protocol, which stated that bismuth-based quadruple therapy is recommended when clarithromycin resistance is suspected.[4] Another effect of the revised protocol could have been the significant increase in treatment using PPI, amoxicillin, and metronidazole triple therapy when the clarithromycin resistance test demonstrated patients' resistance to clarithromycin.

According to the results of a recent European registry study that reported the treatment patterns of *H. pylori* for 5 years from 2013 to 2018 among 30,394 patients in 27 countries, 78% of patients received empirical therapy. Clarithromycin-based triple therapy was most common (39%), but the treatment patterns and durations differed significantly by region.[5] Quadruple therapy (including concomitant therapy) was performed in southwestern and central Europe, accounting for 63~82% of cases, while in most other parts of Europe, clarithromycin-based triple therapy was used.[5] The European guidelines recommend quadruple therapy in regions where clarithromycin resistance exceeds 15%. However, quadruple therapy is not commonly used in actual treatment, and eradication failure rate might increase when the protocol is not followed.[5,6]

This study used CDM-based big data, which can be utilized to analyze the treatment patterns of all medications prescribed during a certain period. A strength of this study is that the CDM data could reflect better actual clinical practice. OMOP-CDM transferred data are anonymized and have a minimal risk of privacy violation. Sharing the same data structure across hospitals facilitates multicenter studies, and the reliability can be improved by sharing the code for analysis with other researchers and correcting errors.[7] In addition, we tried to minimize selection bias by creating a cohort that received *H. pylori* diagnostic tests, including all patients who had undergone rapid urease tests and serum *H. pylori* antibody tests.

In our hospital, ^{13}C-UBT status was converted to the CDM, but the text data about results were not converted. Therefore, the eradication rate was inferred by checking whether patients completed bismuth-based quadruple therapy after clarithromycin-based triple therapy and a ^{13}C-UBT. The presumed eradication rate of clarithromycin-based triple therapy conducted in this hospital from 2004 to 2019 was 79.8%, which was lower than the results (84.9~87.5%) from a study of the national eradication rate from 2001 to 2010.[3] Nonetheless, the results were similar to the per-protocol eradication rate of 79.6% presented in the South Korean treatment protocol revised in 2020 based on the analysis of randomized clinical trials reported after 2007.[1] Notably, the eradication rate of clarithromycin-based triple therapy in this study includes the results of both empirical and tailored treatment based on clarithromycin resistance tests; therefore, the actual eradication rate of empirical treatment would be lower. Of particular note, according to a recent multicenter randomized controlled trial, the eradication rate of amoxicillin and metronidazole treatment was lower than that of bismuth-based triple therapy when there was clarithromycin resistance (bismuth quadruple therapy vs. metronidazole-intensified therapy: 95.1% vs. 76.4%, P=0.001).[18] In this study, amoxicillin and metronidazole were administered as a tailored treatment to the patients with clarithromycin resistance; hence, the overall eradication rate of first-line therapy might have been relatively low.

The decrease in the eradication rate of clarithromycin-based triple therapy is related to an increase in antibiotic resistance, which is closely connected to a history of antibiotic exposure before eradication treatment.[3,19-21] As hypothesized, previous exposure to macrolide antibiotics was more common among patients who had unsuccessful

first-line treatment than among those whose first-line treatment was successful in this study (14.7% vs. 5.5%, $P<0.001$). Therefore, tailored treatment based on clarithromycin resistance testing, instead of empirical treatment, is particularly necessary for patients with a history of macrolide antibiotic exposure. A history of amoxicillin exposure was also more common in the initial treatment failure group (10.6% vs. 7.3%, $P=0.006$). An association between amoxicillin resistance and eradication failure was found in a previous study.[22] However, the resistance rate of amoxicillin in South Korea is around 9.5%,[3] and it has not been identified as the main antibiotic that influences the success of eradication treatment. Therefore, the clinical significance of differences in amoxicillin exposure seems to be low in this study.

This study analyzed a CDM database at a single institution and has limitations as follow. First, it is difficult to confirm the diagnoses and prescriptions received from other institutions in the same patient. Future studies should verify the results using CDM data from the National Health Insurance Service or Health Insurance Review and Assessment Service. Second, data such as ^{13}C-UBT results, Giemsa staining findings, and clarithromycin-resistant mutation test were not converted to the CDM, making it difficult to confirm the exact eradication rate or analyze information about tailored treatment. Third, some patients who failed in first-line eradication therapy could have refused second-line eradication therapy; however, some might have erroneously classified as eradicated patients. Fourth, there is also a possibility of false-negative results of the ^{13}C-UBT since the analysis did not include data on PPI intake before the ^{13}C-UBT. The eradication rate of first-line treatment could therefore have been exaggerated.

Despite these limitations, this is the first study using CDM data that analyzed the treatment patterns and clinical characteristics of patients with *H. pylori* infection. The analysis code developed for this study can be easily applied to multicenter or public health data. Furthermore, the code can facilitate comparisons of antibiotic exposure history by region.

In summary, there was a 1.4 percentage point increase in bismuth-based quadruple therapy as first-line eradication treatment after announcing the 2013 treatment protocol. According to the present analysis of *H. pylori* treatment patterns in the past 16 years using CDM data from a single institution in South Korea, eradication protocol was not significantly modified despite the updated clinical guideline. Our analytic code could be applied to nationwide CDM-converted hospital databases to analyze real world changing trends in *H. pylori* treatment.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY MATERIAL

Supplementary material 1. Korean translation of the article is available from https://doi.org/10.7704/kjhugr.2022.0010.

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