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ORIGINAL ARTICLE

Lifestyle- and comorbidity-related factors for the prescription of proton pump inhibitors after *Helicobacter pylori* eradication in Japan

Furitsu Shimada,*[,†,‡] Hiroyoshi Endo,* Ayako Takamori,[§] Takuya Matsunaga,* Shun Fujimoto,*[,†] Shimpei Shirai,* Toshihiko Kakiuchi,[¶] Takashi Akutagawa,[†] Yasuhisa Sakata,[†] Koichi Node,[†] Kohei Yamanouchi,[‡] Shotaro Nakamura,[‡] Kazuma Fujimoto[‡] and Motohiro Esaki[†]

*Division of Gastroenterology, Saiseikai Karatsu Hospital, Departments of [†]Internal Medicine, Faculty of Medicine, [¶]Pediatrics, Faculty of Medicine, Saga University, [§]Division of Clinical Research Center, Saga University Hospital, Saga and [‡]International University of Health and Welfare, Fukuoka, Japan

Key words
aging, clinical symptoms, hypertension, potassium-competitive acid blocker, reflux esophagitis.

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Correspondence
Furitsu Shimada, Division of Gastroenterology, Saiseikai Karatsu Hospital, Motohata 817 Karatsu, Saga 847-0852, Japan.
Email: frtz991118@yahoo.co.jp

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Abstract

Background and Aim: The aim of the present study was to examine the lifestyle- and comorbidity-related determinant factors of the prescription of proton pump inhibitors (PPIs) for patients in whom *Helicobacter pylori* has been eradicated, and to evaluate the relationship between PPI prescription and the severity of endoscopic esophagitis.
Methods: This retrospective study included patients who underwent *H. pylori* eradication from May 2012 to September 2016 at Saiseikai Karatsu Hospital. All patients received upper gastrointestinal endoscopy before *H. pylori* eradication. Patients with open peptic ulcers and/or malignant diseases were excluded, and a final total of 389 patients were evaluated. Medical records were reviewed to determine the prescription of PPIs after *H. pylori* eradication, lifestyle-related factors, and comorbidities. Lifestyle-related factors were confirmed by a questionnaire.
Results: PPIs were administered to 124 of 389 patients (31.9%). The only lifestyle-related risk factor for the prescription of PPIs after *H. pylori* eradication was older age ($P < 0.01$). Hypertension increased the prescription of PPIs ($P = 0.034$). The prescription of PPIs was not influenced by the presence of grade A esophagitis, whereas the PPI prescription rate was significantly increased in patients with grades B/C/D endoscopic esophagitis ($P < 0.01$). The grade of chronic gastritis before *H. pylori* eradication had no effect on the prescription of PPIs.
Conclusion: The lifestyle- and comorbidity-related risk factors for the prescription of PPIs after *H. pylori* eradication were older age and hypertension, while mild endoscopic esophagitis had no influence on PPI prescription.

Introduction

In East Asian countries, the main therapeutic approach for functional upper gastrointestinal diseases, including gastroesophageal reflux disease (GERD) and functional dyspepsia, is the prescription of proton pump inhibitors (PPIs) such as potassium-competitive acid blockers[1–5]; in addition, the surgical and/or endoscopic therapeutic approach is occasionally applied in GERD.[6,7] The decision to prescribe PPIs is mainly based on the clinical symptoms and the severity of endoscopic esophagitis,[1–3] although the extent of the clinical symptoms does not necessarily correspond with the grade of the endoscopic esophagitis.[1,8]

Eradication of *Helicobacter pylori* (*H. pylori*) is a widely accepted treatment in most countries, including Japan.[9–13] The major adverse events after *H. pylori* eradication therapy are GERD and related clinical symptoms.[11,14–16] The incidence of GERD after *H. pylori* eradication is lower in Japan than in Western countries,[14–16] and the prescription of PPIs is the main therapeutic approach after *H. pylori* eradication.[1,11,17] Whereas several studies demonstrated the patient-characteristics for *H. pylori* eradicated patients, the patients-characteristics and comorbidities with prescription of PPI after *H. pylori* eradication have not been clearly demonstrated.

The present study aimed to examine (i) the lifestyle- and comorbidity-related determinant factors of the prescription of PPIs after *H. pylori* eradication, and (ii) the relationship between the prescription of PPIs and the severity of endoscopic esophagitis in patients who have undergone *H. pylori* eradication.

Method

The present study comprised a retrospective review of the medical records of patients who received eradication therapy for *H. pylori* at Saiseikai Karatsu Hospital from May 2012 to

September 2016, as previously described.[10] All patients received upper gastrointestinal endoscopy before *H. pylori* eradication, and 660 patients were followed up after the eradication. All participants provided informed consent for the use of their test results and survey responses. The data were anonymized to prevent personal identification. All procedures performed in the present study were approved by the Saiseikai Karatsu Hospital Ethics Committee.

Esophageal hiatal hernia was defined as a Hill classification gastroesophageal flap valve grade of III or IV,[18] and chronic gastritis was classified in accordance with the Kimura–Takemoto classification.[19] Patients with malignant diseases and/or peptic ulcers were excluded from the study. *H. pylori* infection was diagnosed based on at least one of the following findings: (i) serum anti-*H. pylori* immunoglobulin $G \geq 10$ U/mL (E plate Eiken; Eiken Chemical, Tokyo, Japan); (ii) a positive rapid urease test (Helicocheck; Otsuka Pharmaceutical, Tokyo, Japan); (iii) a ^{13}C-urea breath test result of ≥2.5% (UBIT tablet/POC one; Otsuka Pharmaceutical). The eradication regimen consisted of 20 mg vonoprazan (Takeda Pharmaceutical, Tokyo, Japan), 30 mg lansoprazole (Takeda Pharmaceutical), 10 mg rabeprazole (Eisai, Tokyo, Japan), or 20 mg esomeprazole (AstraZeneca, Tokyo, Japan) + 750 mg amoxicillin (Astellas Pharma, Tokyo, Japan) + 200 mg clarithromycin (Taisho Toyama Pharmaceutical, Tokyo, Japan), twice daily for 1 week. The success or failure of *H. pylori* eradication was evaluated using the ^{13}C-urea breath test at least 5 weeks after the eradication therapy.

The medical records of the patients who had undergone *H. pylori* eradication were retrospectively reviewed to identify the prescription of PPIs (including potassium-competitive acid blockers) after the eradication, lifestyle-related factors including age, sex, body weight, height, smoking status, and alcohol intake, and comorbidities including hypertension, use of Ca blockers, diabetes mellitus, dyslipidemia, renal failure, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and use of antiplatelet medicines and/or anticoagulants. PPIs were prescribed by the three medical doctors (HE, SS, and KK), and the experience as the medical doctor was 20 years (HE), 7 years (SS), or 7 years (KK). The presence of comorbidities was based on the information contained in the medical records, including interviews during endoscopy, outpatient consultations, and examination history at the hospital. Lifestyle-related factors and comorbidities were confirmed by a questionnaire completed by each patient during a follow-up visit from August 2017 to July 2018, as previously described.[20] The questionnaire items were: (i) whether the patient was eating breakfast, (ii) whether the patient was eating supper within 2 h before bedtime, (iii) intake of carbonated drinks, (iv) intake of coffee, (v) whether the patient was overeating, (vi) intake of a high-fat diet, (vii) whether the patient was eating quickly, (viii) whether the patient performed light exercise (including walking activities) for more than 1 h every day, (ix) whether the patient had been working out (heavy exercise) for more than 30 min twice a week for over 1 year, (x) whether the patient was walking quickly, (xi) smoking status, (xii) alcohol intake, (xiii) hypertensive status, and (xiv) whether the patient was taking Ca blockers.

After *H. pylori* eradication, each patient was evaluated endoscopically for reflux esophagitis using the Los Angeles classification.[21] Patients with grade A or higher reflux esophagitis in accordance with the Los Angeles classification were defined as having endoscopic reflux esophagitis, and the most severe grade of esophagitis after *H. pylori* eradication was used in the evaluation.

The patients were divided into those who were prescribed PPIs after *H. pylori* eradication and those who were not prescribed PPIs after *H. pylori* eradication. Differences between the two groups in categorical variables were tested using the Chi-squared test or Fisher's exact test, while continuous data were evaluated by the Student's *t* test. Multivariable logistic regression was performed using the stepwise selection method with the same entry and removal significance levels of 0.05, except for age and sex. The estimated odds ratio (OR) and 95% confidence interval (CI) were calculated. *P* values of <0.05 were considered to indicate statistical significance. All analyses were performed using JMP Pro version 14.2.0 software (SAS Institute Inc., Cary, NC, USA).

Results

Six-hundred-and-sixty patients underwent upper gastrointestinal endoscopy at Karatsu Saiseikai Hospital during the study period and were confirmed to be positive for *H. pylori* infection. Of

Table 1 Demographic and clinical characteristics of patients who were prescribed proton pump inhibitors (PPIs) after successful eradication of *Helicobacter pylori* infection

	PPIs ($n = 124$)	No PPIs ($n = 265$)	*P* value
Age, years, mean ± SD	66.0 ± 11.0	57.0 ± 12.0	<0.01
Gender, male	57 (46.0%)	136 (51.3%)	0.33
BMI > 25.0	23 (26.4%)	51 (22.6%)	0.47
Smoking	36 (29.5%)	70 (26.7%)	0.57
Alcohol drinking	46 (37.7%)	137 (52.7%)	<0.01
Hypertension	44 (35.5%)	36 (13.6%)	<0.01
Ca blockers	30 (68.2%)	20 (55.6%)	0.25
Diabetes mellitus	16 (13.0%)	13 (4.9%)	<0.01
Liver disease	10 (8.0%)	16 (6.0%)	0.46
Kidney disease	7 (5.5%)	10 (3.8%)	0.41
NSAIDs	7 (5.5%)	3 (1.1%)	<0.01
Dyslipidemia	49 (39.5%)	53 (20.0%)	<0.01
Antithrombotic	17 (13.7%)	8 (3.0%)	<0.01
Hiatal hernia	58 (46.8%)	98 (37.0%)	0.067
Atrophic gastritis			
C-I	18 (14.5%)	38 (14.3%)	0.31
C-II	9 (7.3%)	33 (12.5%)	
C-III	15 (12.1%)	29 (11.0%)	
O-I	16 (12.9%)	50 (18.9%)	
O-II	27 (21.8%)	46 (17.4%)	
O-III	39 (31.5%)	69 (26.0%)	
Endoscopic reflux esophagitis			
No esophagitis	102 (82.3%)	231 (87.2%)	<0.01
Grade A	10 (8.1%)	29 (10.9%)	
Grade B + C + D	12 (9.7%)	5 (1.9%)	
B/C/D	8/3/1	5/0/0	

BMI, body mass index; C, closed type; NSAIDs, nonsteroidal anti-inflammatory drugs; O, open type.

these patients, *H. pylori* was successfully eradicated using the abovementioned medication regimen in 519 patients, while the eradication therapy failed in 141 patients. Among the 519 patients with successful *H. pylori* eradication, 40 patients with gastric cancer, 90 patients with gastric ulcers, and 52 patients with duodenal ulcers were excluded from the present study. A final total of 389 patients were evaluated in the present study. PPI therapy was prescribed for 124 of 389 patients (31.9%) after successful *H. pylori* eradication. PPIs were prescribed for 22 of 56 patients (39.3%) with endoscopic reflux esophagitis, and 102 of 333 patients (30.6%) without esophagitis.

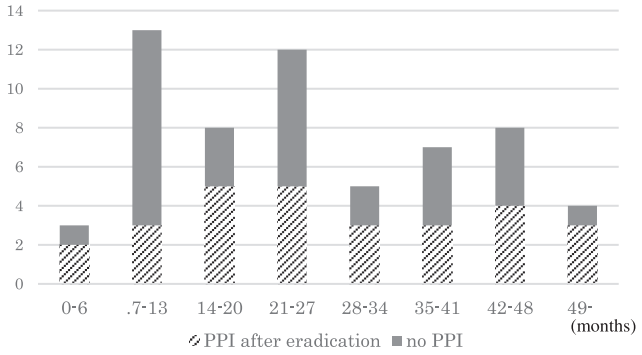

Figure 1 The time span of endoscopic reflux esophagitis after *Helicobacter pylori* eradication.

The characteristics of the patients who did or did not receive PPI therapy after successful *H. pylori* eradication are shown in Table 1. The group who were prescribed PPIs was significantly older than those who were not prescribed PPIs ($P < 0.01$). Sex, BMI, and smoking status had no influence on the prescription of PPIs. The PPI prescription rate was significantly deceased in the group of patients who drank alcohol ($P < 0.01$). Other eating styles including eating breakfast or not, eating supper within 2 h before bedtime, intake of carbonated drinks, taking coffee, overeating, high-fat diet, and eating speed had no influence on the PPI prescription. Excises including light exercise for more than 1 h every day and heavy exercise more than 30 min twice a week for over 1 year had no influence on the prescription. Hypertension, diabetes mellitus, dyslipidemia, NSAIDs use, and antithrombotic use increased the prescription rate of PPIs, whereas liver disease and kidney disease had no influence on the prescription of PPIs. Hiatal herniation and atrophic gastritis evaluated by endoscopy had no influence on the prescription of PPIs.

As indicated in Table 1, 56 patients (14.4%) had endoscopic reflux esophagitis after *H. pylori* eradication, most of whom had grade A (mild) esophagitis (39 of 56; 69.6%). The presence of endoscopic reflux esophagitis increased the prescription rate of PPIs after successful *H. pylori* eradication. Figure 1

Table 2 Univariate and multivariate analyses of the factors that increased the prescription rate of proton pump inhibitors after successful eradication of *Helicobacter pylori* infection

	Unadjusted OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Age, years	1.07	1.05–1.09	<0.01	1.06	1.03–1.08	<0.01
Gender, male	0.81	0.53–1.24	0.325	1.01	0.57–1.78	0.98
BMI > 25.0	1.04	0.97–1.11	0.285			
Smoking	1.15	0.71–1.85	0.569			
Alcohol drinking	0.54	0.35–0.84	<0.01	0.72	0.41–1.28	0.27
Hypertension	3.50	2.10–5.82	<0.01	1.95	1.05–3.60	0.034
Ca blockers	1.71	0.69–4.27	0.248			
Diabetes mellitus	2.87	1.34–6.18	<0.01	1.27	0.53–3.07	0.59
Liver disease	2.18	0.62–7.69	0.224			
Kidney disease	1.53	0.57–4.10	0.403			
NSAIDs	5.23	1.33–20.56	0.018			
Dyslipidemia	2.61	1.63–4.18	<0.01	1.38	0.78–2.43	0.27
Antithrombotic	5.10	2.14–12.18	<0.01	1.81	0.67–4.88	0.24
Hiatal hernia	1.50	0.97–2.31	0.067			
Atrophic gastritis						
C-I	Reference					
C-II	0.58	0.23–1.45	0.242			
C-III	1.09	0.47–2.53	0.837			
O-I	0.68	0.31–1.50	0.333			
O-II	1.24	0.59–2.58	0.568			
O-III	1.19	0.60–2.37	0.613			
Reflux esophagitis						
No esophagitis	Reference					
Grade A	0.78	0.37–1.66	0.521	0.78	0.33–1.84	0.58
Grade B + C + D	5.44	1.87–15.38	<0.01	6.58	2.02–21.46	<0.01

95% CI, 95% confidence interval; BMI, body mass index; C, closed type; NSAIDs, nonsteroidal anti-inflammatory drugs; O, open type; OR, odds ratio.

Table 3 Multivariate analysis of the factors affecting the prescription of proton pump inhibitors in accordance with the grade of endoscopic reflux esophagitis

Endoscopic reflux esophagitis	Adjusted OR	*P* value
No esophagitis		
Age, years	1.06	<0.01
Gender, male	1.07	0.78
Hypertension	2.12	0.011
Grade A		
Age, years	1.07	0.25
Gender, male	0.12	0.048
Hypertension	19.45	0.038
Grade B + C + D		
Age, years	1.37	0.069
Gender, male	NA	
Hypertension	NA	

NA, not available; OR, odds ratio.

shows the timing of endoscopic reflux esophagitis after *H. pylori* eradication. Reflux esophagitis mainly occurred within 2 years after *H. pylori* eradication, although several patients developed reflux esophagitis more than 4 years after the eradication.

Table 2 shows the results of univariate and multivariate analyses performed to identify the factors associated with PPI prescription after successful *H. pylori* eradication. The factors independently associated with an increased prescription rate of PPIs were older age (OR: 1.06, 95% CI: 1.03–1.08, $P < 0.01$) and hypertension (OR: 1.95, 95% CI: 1.05–3.60, $P = 0.034$). Grade A endoscopic reflux esophagitis had no influence on the prescription of PPIs, while endoscopic esophagitis of grades B/C/D significantly increased the prescription rate of PPIs (OR: 6.58, 95% CI: 2.02–21.46, $P < 0.01$).

Table 3 shows the factors that influenced the prescription of PPIs in accordance with the grade of endoscopic reflux esophagitis. In the group of patients without endoscopic reflux esophagitis, the prescription of PPIs was associated with older age (OR: 1.06, $P < 0.01$) and hypertension (OR: 2.12, $P = 0.011$). In the group of patients with grade A reflux esophagitis, the prescription of PPIs was associated with the female sex (OR: 0.12, $P = 0.048$) and hypertension (OR: 19.45, $P = 0.038$). The lifestyle- and comorbidity-related factors had no influence on the prescription of PPIs in the group of patients with grades B/C/D endoscopic reflux esophagitis after successful *H. pylori* eradication.

Discussion

The main results of the present study are: (i) the only lifestyle-related risk factor for the prescription of PPIs after *H. pylori* eradication was older age, while other lifestyle- and/or eating style-related factors had no influence on the prescription of PPIs; (ii) hypertension increased the frequency of PPI prescription after *H. pylori* eradication; (iii) the prescription rate of PPI did not differ between those with or without grade A endoscopic reflux esophagitis after *H. pylori* eradication, whereas the PPI prescription rate was increased in those with grades B/C/D endoscopic esophagitis after *H. pylori* eradication; (iv) there was no association between the severity of chronic gastritis before *H. pylori* eradication and the prescription of PPIs.

It is well known that GERD and related upper gastrointestinal symptoms are common adverse complications after *H. pylori* eradication.[11,12,22] Furthermore, several studies have indicated that lifestyle-related factors affect the onset and exacerbation of GERD and functional disease.[1,2,23–25] The prescription of PPIs is closely related to the deterioration of clinical upper gastrointestinal symptoms, which are related to lifestyle and eating style.[1–3,23–25] The present study indicated that PPIs were prescribed for 124 of 389 patients (31.9%) with or without endoscopic esophagitis, and that the prescription of PPIs after *H. pylori* eradication was not influenced by lifestyle-related factors, except for aging. Our previous study indicated that the lifestyle related factors of eating styles and excises as detected in the present study had no influence on the prescription of the gastric secretion inhibitors for the *Helicobacter pylori* negative GERD patients.[20] Although the present study did not evaluate the relationships between lifestyle-related factors and the clinical symptoms of GERD, the prescription of PPIs might be affected by factors other than lifestyle-related factors; this issue warrants further exploration.

The prescription rate of PPIs after *H. pylori* eradication was increased in the group of patients with hypertension. Several hypertensive medications (including Ca blockers) exacerbate GERD, causing an increase in gastroesophageal reflux.[1,15,26–29] Therefore, the increased prescription rate of PPIs after *H. pylori* eradication in hypertensive patients might be because of the increased risk of GERD due to the condition of hypertension itself and/or because of the hypertensive medications combined with hypertension.[26,30] The present study did not find a significant influence of Ca blockers on the prescription of PPIs, which suggested that other hypertensive medications than Ca blockers and/or hypertension itself might facilitate PPIs medication.

Previous research in Japan has indicated that endoscopic reflux esophagitis and the clinical symptoms of GERD are not equivalent.[1,8,17] In the present study, grade A endoscopic reflux esophagitis had no influence on the prescription rate of PPIs, whereas the prescription rate was increased in the group of patients with grades B/C/D endoscopic esophagitis. This suggests that mild endoscopic esophagitis might not affect the prescription of PPIs after *H. pylori* eradication. The presence of endoscopic chronic gastritis before the *H. pylori* eradication had no influence on the use of PPIs in the present study, whereas several studies have reported that the presence of mucosal atrophy before the eradication affects the development of GERD.[11,31]The present study had several limitations, including the retrospective research design with the single hospital setting, variations in the PPI prescription and endoscopic criteria between the different physicians, and the lack of accurate data regarding the clinical symptoms at the time of PPI prescription.

In conclusion, of the lifestyle- and eating style-related factors, only aging affected the prescription of PPIs after *H. pylori* eradication. The PPIs prescription rate after *H. pylori* eradication was high in the group of patients with hypertension, whereas the presence of mild endoscopic esophagitis (grade A) had no influence on the prescription of PPIs.

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