Drug, Healthcare and Patient Safety

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ORIGINAL RESEARCH

Endoscopic Examination and Long-Term Use of Proton Pump Inhibitors for Gastroesophageal Reflux Disease Treatment in Japan

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Introduction: Long-term use of proton pump inhibitors (PPIs) requires careful observation with endoscopy in Japan. However, there are no studies examining whether monitoring is being properly carried out in clinical practice. Thus, we investigate the usage of PPIs by the presence or absence of endoscopic monitoring using a claims database.

Methods: This study was a retrospective observational cohort study using the nationwide claims database. We obtained data of patients diagnosed with GERD (excluding suspected cases) between April 2014 and March 2024. Inclusion criteria were patients aged 18 years or older, continuously prescribed drugs of interest (omeprazole, lansoprazole, rabeprazole, esomeprazole, and vonoprazan) for 8 weeks or more. To assess the duration of prescriptions over a one-year period, the medication possession ratio (MPR) showing the prescription days per year ratio was examined. MPR was compared between patients who underwent endoscopy [endoscopy(+) group] and those who did not [endoscopy(-) group] during the follow-up period of 12 months.

Results: A total of 398,253 patients [endoscopy(+) group: 142,653; endoscopy(-) group: 255,600] were included in the analysis. The median MPR was 0.534 in the endoscopy(+) group and 0.805 in the endoscopy(-) group; MPR was significantly higher in the endoscopy(-) group ($p < 0.0001$).

Conclusion: These findings revealed that the long-term administration of PPIs without monitoring esophageal mucosa by endoscopy in patients with GERD is a common practice in Japan. However, compliance with the package inserts suggesting adequate observation, including periodic endoscopic examinations, should be highlighted to ensure safety.

Keywords: proton pump inhibitor, gastroesophageal reflux disease, safety, post-marketing, real-world data

Introduction

Gastroesophageal reflux disease (GERD) is a gastrointestinal disorder in which the disruption of the esophagogastric junction barrier resulting in exposure of the esophagus to acidic gastric contents. It causes either esophageal mucosal injury, annoying symptoms, or both. GERD is one of the most common gastrointestinal disorders, with a prevalence of approximately 12.0% in the general population of Japan, and the prevalence is increasing.[1] Treatment for GERD is important not only in gastroenterology but also in general medicine. GERD may cause comorbidities and complications, such as hiatus hernia and Barrett's mucosa.[2] In addition, quality of life in GERD patients is often lower than that in the general population.[3]

In the Japanese population, gastric acid secretion gradually increased while *Helicobacter pylori* infection has decreased,[4] and increased gastric acid secretion has been suggested to be associated with GERD.[5] Proton pump inhibitors (PPI) are the most potent inhibitors of gastric acid secretion currently available and are recommended as an initial treatment for mild GERD.[6] When endoscopy is performed prior to the initiation of treatment, a definitive diagnosis (eg, mild GERD, severe GERD, and non-erosive reflux disease) should determine treatment. If endoscopy is not performed initially, PPIs may be initiated. Symptom improvement after 2–4 weeks allows discontinuation of therapy and follow-up

https://doi.org/10.2147/DHPS.S583501
Received: 21 November 2025
Accepted: 26 December 2025
Published: 24 January 2026

without medication. When symptoms do not improve, endoscopy is recommended. PPIs have demonstrated excellent efficacy in mild GERD and have become widely used in clinical practice in Japan. However, some patients may relapse after treatment is discontinued and require maintenance therapy. PPIs are also recommended as maintenance therapy for long-term management of mild GERD. In Japan, GERD is the only disease approved for which PPIs can be administered for more than 8 weeks, and long-term administration of PPIs requires careful observation with endoscopy.[7–12] To date, a few large-scale studies have reported its association with some adverse events, yet there is limited evidence to suggest a causal relationship between administration of these PPI and adverse events.[13,14]

PPIs are effective therapy and are widely used as first-line treatment for mild GERD in Japan, and some patients are treated for long time. In this circumstance, concerns about potential adverse events associated with long-term use of PPIs have increased. Although long-term use of PPIs requires careful observation with endoscopy in Japan, there are no studies examining whether monitoring is being properly carried out in clinical practice. Thus, we investigate the usage of PPIs by the presence or absence of endoscopic monitoring using a claims database to better understand long-term use of PPIs in real-world clinical practice.

Materials and Methods

Study Design and Patients

This study was a retrospective observational cohort study using the claims database provided by JMDC, Inc. (JMDC database). The database has been accumulating claims (inpatient, outpatient, and prescription) and medical checkup data from over 200 health insurance organizations, and it has been widely used for health economics, epidemiology, and outcomes research. We obtained data of patients diagnosed with GERD (excluding suspected cases), identified using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes of K21, between April 2014 and March 2024. Inclusion criteria were patients aged 18 years or older, continuously prescribed drugs of interest (omeprazole, lansoprazole, rabeprazole, esomeprazole, and vonoprazan; Supplementary Table 1) for 8 weeks or more, and followed up for 12 months or more from the date when drugs of interest were initially prescribed (Figure 1); in these settings, individuals who died before 12 months were not included in the analysis because they did not have complete 12-month follow-up data. Vonoprazan was included in the drugs of interest because Japanese regulatory authorities approved vonoprazan as a type of PPI,[15] although it has a different mechanism of action to inhibit proton pump compared to conventional PPIs. Patients who were prescribed analgesics on the same day as the PPI prescription and in the same claim were excluded because prescribing PPIs concomitantly for gastroprotection when prescribing non-steroidal anti-inflammatory agents is suggested in the guidelines[16] and is commonly practiced in Japan. Ethics approval was not applicable to this study based on the Ethical Guidelines for Medical and Biological Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare (MHLW) because only completely encrypted data were used. This study was conducted in accordance with the Declaration of Helsinki.

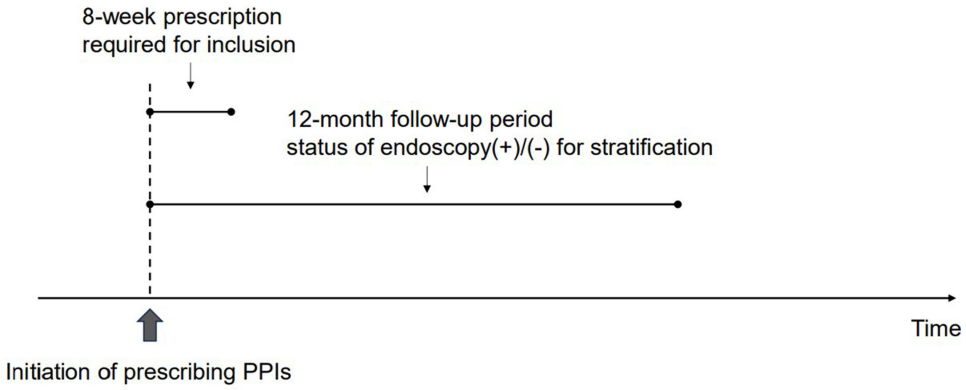

Figure 1 Study design. Patients aged 18 years or older, prescribed drugs of interest (omeprazole, lansoprazole, rabeprazole, esomeprazole, and vonoprazan; Supplementary Table 1) for 8 weeks or more, and followed up for 12 months or more from the date when drugs of interest were initially prescribed were included. Patients were stratified by the status of endoscopy during the 12-month follow-up period.

Study Outcome and Variables

The outcome of this study was the medication possession ratio (MPR), a ratio calculated as the proportion of the period where PPIs were prescribed to duration of the prescription. The numerator was the total number of days PPIs were prescribed from the initial prescription date, and the denominator was set as 365 days. MPR and duration of the prescription were compared between patients who underwent endoscopy [endoscopy(+) group] and those who did not [endoscopy(-) group] during the follow-up period of 12 months.

Variables included patients' characteristics [ie, gender, age, number of medical facilities where prescriptions were received, management body of medical facilities (ie, clinic, university hospital, public hospital, other hospital), number of PPI types prescribed, and presence of the same day prescription], prescribed PPIs, duration of the prescription, and presence and absence of endoscopy monitoring during the 12-month follow-up. Patients who underwent endoscopy at least once during the 12-month follow-up were included in the endoscopy(+) group. For duration of the prescription, the longest duration of the prescription was counted if there was a record of multiple prescriptions of PPIs on the same day. No prescription for 90 days was defined as treatment discontinuation. Facility where the greatest number of PPIs was prescribed during the follow-up period was counted for type of medical facilities. Also, the most prescribed PPIs were counted within the number of PPIs prescribed.

Statistical Methods

Continuous variables were summarized as mean ± standard deviation (SD), and variables were summarized as frequency and percentage (%). MPRs were compared using the Wilcoxon rank-sum test, and the duration of the prescription was estimated using the Kaplan–Meier method and compared using the Log rank test. Probability values less than 0.05 were considered to be statistically significant. Statistical Analysis System version 9.4 was used for analysis.

Results

Patients

From 20,483,463 patient data, 398,253 patients [endoscopy(+) group: 142,653; endoscopy(-) group: 255,600] were included in the analysis (Figure 2). The mean age (±SD) was 51.6 (11.7) years in the endoscopy(+) group and 52.0 (11.5) years in the endoscopy(-) group (Table 1). The majority of patients received PPI prescription in one facility (endoscopy

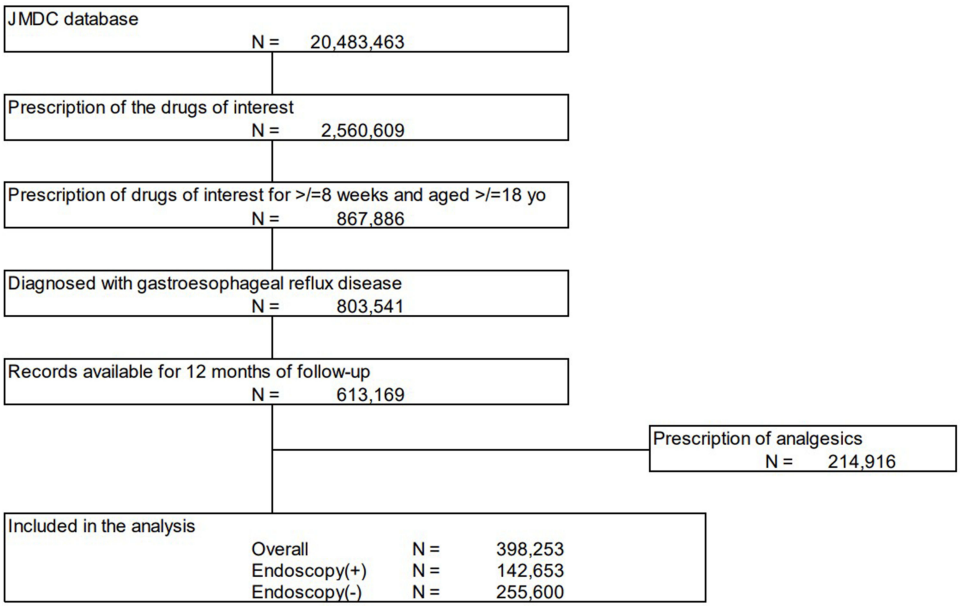

Figure 2 Patients flow. Patients who were prescribed analgesics on the same day as the PPI prescription and in the same claim were excluded because prescribing PPIs concomitantly for gastroprotection when prescribing NSAIDs is suggested in the guidelines[16] and is commonly practiced in Japan.

https://doi.org/10.2147/DHPS.S583501

Table 1 Characteristics of Patients

	All		Endoscopy(+)		Endoscopy(-)	
	N = 398,253		N = 142,653		N = 255,600	
Male, n (%)	229,446	(57.6)	79,204	(55.5)	150,242	(58.8)
Age, mean (SD), years	51.9	(11.6)	51.6	(11.7)	52.0	(11.5)
Facilities, n (%)						
1	343,090	(86.1)	115,708	(81.1)	227,382	(89.0)
2	49,005	(12.3)	23,426	(16.4)	25,579	(10.0)
3	5,380	(1.4)	3,009	(2.1)	2,371	(0.9)
4	778	(0.2)	510	(0.4)	268	(0.1)
Type of facilities, n (%)						
Clinic	250,525	(62.9)	91,327	(64.0)	159,198	(62.3)
University hospital	25,084	(6.3)	7,301	(5.1)	17,783	(7.0)
Public hospital	22,302	(5.6)	7,318	(5.1)	14,984	(5.9)
Other hospital	100,307	(25.2)	36,699	(25.7)	63,608	(24.9)
Unknown	35	(<0.1)	8	(<0.1)	27	(<0.1)
Number of PPI types prescribed, n (%)						
1	338,688	(85.0)	108,667	(76.2)	230,021	(90.0)
2	53,485	(13.4)	29,649	(20.8)	23,836	(9.3)
3	6,080	(1.5)	4,337	(3.0)	1,743	(0.7)
Multiple prescriptions on the same day, n (%)						
Yes (among those received multiple prescriptions)	2,438	(4.1)	1,625	(4.8)	813	(3.2)
Drugs of interest						
Omeprazole	17,724	(4.5)	5,122	(3.6)	12,602	(4.9)
Lansoprazole	87,675	(22.0)	22,293	(15.6)	65,382	(25.6)
Rabeprazole	71,440	(17.9)	24,787	(17.4)	46,653	(18.3)
Esomeprazole	125,809	(31.6)	47,499	(33.3)	78,310	(30.6)
Vonoprazan	97,425	(24.5)	43,893	(30.8)	53,532	(20.9)

Notes: Patients who underwent endoscopy at least once during the 12-month follow-up were included in the endoscopy(+) group, and those who did not were included in the endoscopy(-) group.
Abbreviation: SD, standard deviation.

(+): 81.1%; endoscopy(-): 89.0%) and received one PPI type (76.2%; 90.0%). In both patient groups, the most prescribed facility was "clinic" (endoscopy(+): 64.0%; endoscopy(-): 62.3%). The most prescribed PPI was esomeprazole (endoscopy(+): 33.3%; endoscopy(-): 30.6%), followed by vonoprazan (30.8%; 20.9%), and rabeprazole (17.4%; 18.3%).

Outcomes

The median MPR (range) was 0.534 (0.153–2.362) in the endoscopy(+) group and 0.805 (0.153–4.468) in the endoscopy(-) group; MPR was significantly higher in the endoscopy(-) group ($p < 0.0001$) (Table 2). In the endoscopy(-) group, more than half of patients (50.4%) had MPR of 80% or higher (Table 2 and Figure 3). The median duration of prescription (95% confidence interval) was 210.0 (207.0–212.0) days in the endoscopy(+) group and 575.0 (566.0–587.0) days in the endoscopy(-) group. The duration of PPI prescription was significantly longer in the endoscopy(-) group ($p < 0.0001$).

Among 398,253 patients, 70,592 patients (17.7%) had MPR ≥100%, indicating the excessive prescriptions (Table 2); 18,952 were in the endoscopy(+) group and 51,640 were in the endoscopy(-) group (Table 3). Most patients (endoscopy (+): 93.6%; endoscopy(-): 96.7%) had MPR less than 110%; there were 38 patients in the endoscopy(+) group and 85 in the endoscopy(-) group with MPR of 150% or higher. The majority of patients received PPI prescription in one facility (endoscopy(+): 82.5%; endoscopy(-): 88.4%) and received one PPI type (79.6%; 92.0%). In both patient groups, clinics were the facility with the most prescriptions (endoscopy(+): 47.6%; endoscopy(-): 42.1%).

Table 2 Medication Possession Ratio

	All		Endoscopy(+)		Endoscopy(-)	
	N = 398,253		N = 142,653		N = 255,600	
MPR*, median (min-max)	0.712	(0.153–4.468)	0.534	(0.153–2.362)	0.805	(0.153–4.468)
MPR category, n (%)						
0%–<20%	58,049	(14.6)	25,580	(17.9)	32,469	(12.7)
20%–<40%	76,751	(19.3)	33,581	(23.5)	43,170	(16.9)
40%–<60%	43,497	(10.9)	16,911	(11.9)	26,586	(10.4)
60%–<80%	38,495	(9.7)	13,894	(9.7)	24,601	(9.6)
80%–<100%	110,869	(27.8)	33,735	(23.6)	77,134	(30.2)
≥100%	70,592	(17.7)	18,952	(13.3)	51,640	(20.2)

Notes: *MPR was significantly higher in the endoscopy(-) group than that in the endoscopy(+) group ($p < 0.0001$; Wilcoxon rank-sum test).
Abbreviation: MPR, medication possession ratio.

Discussion

We investigated the trends of long-term prescribing of PPIs using the JMDC database. Endoscopy was not performed in 64.2% of patients with a diagnosis of GERD and prescribed PPIs during the one-year follow-up period. Compared to those patients who underwent endoscopy, patients who did not had significantly higher MPR. Moreover, the duration of prescription was also significantly longer in patients who did not undergo endoscopy. These findings suggest that it is common practice in Japan to continue long-term administration of PPIs without monitoring esophageal mucosa by endoscopy in patients with GERD.

The Japanese guidelines do not set an explicit limit on the duration of PPI administration,[6] which could be a reason long-term prescribing of PPIs was observed. Moreover, the guidelines allow for PPI prescription as initial treatment without endoscopy though, endoscopy needs to be performed in cases in which symptomatic resolution was not obtained after a few weeks of PPI treatment.[6] We found almost two-thirds of patients with a diagnosis of GERD did not undergo endoscopy within 12 months after initial PPI prescription, despite the package inserts of PPIs suggesting adequate observation as shown in Supplementary Table 1, including periodic endoscopic examinations, during maintenance therapy.[7–12] This clearly shows that PPIs are continuously prescribed to patients diagnosed with GERD even without adequate follow-up with endoscopy.

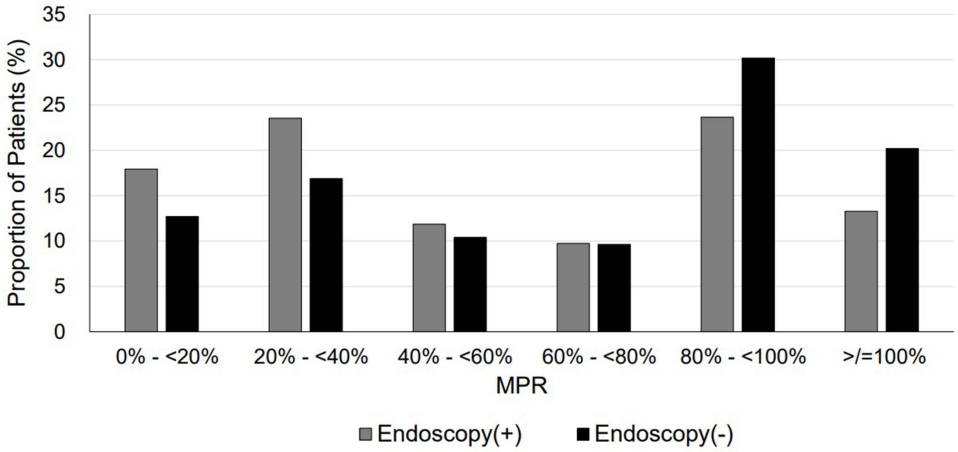

Figure 3 Proportion of patients by medication possession ratio category. Medication possession ratio was calculated as the proportion of the period where PPIs were prescribed to duration of the prescription. The numerator was the total number of days PPIs were prescribed from the initial prescription date, and the denominator was set as 365 days.
Abbreviation: MPR, medical possession ratio.

https://doi.org/10.2147/DHPS.S583501

Table 3 Characteristics of Patients with MPR ≥1

	All		Endoscopy(+)		Endoscopy(-)	
	70,592		18,952		51,640	
Male, n (%)	40,961	(58.0)	10,778	(56.9)	30,183	(58.4)
Age, mean (SD), years	55.0	(10.9)	56.2	(10.3)	54.6	(11.1)
MPR, median (min-max)	1.008	(1.000–4.468)	1.011	(1.000–2.362)	1.008	(1.000–4.468)
MPR category, n (%)	1.01		1.01		1.01	
100%–<110%	67,672	(95.9)	17,744	(93.6)	49,928	(96.7)
110%–<120%	2,197	(3.1)	915	(4.8)	1,282	(2.5)
120%–<130%	422	(0.6)	186	(1.0)	236	(0.5)
130%–<140%	124	(0.2)	53	(0.3)	71	(0.1)
140%–<150%	54	(0.1)	16	(0.1)	38	(0.1)
150%–<200%	112	(0.2)	35	(0.2)	77	(0.1)
≥200%	11	(<0.1)	3	(<0.1)	8	(<0.1)
Facilities, n (%)						
1	61,276	(86.8)	15,639	(82.5)	45,637	(88.4)
2	8,272	(11.7)	2,873	(15.2)	5,399	(10.5)
3	914	(1.3)	369	(1.9)	545	(1.1)
4	130	(0.2)	71	(0.4)	59	(0.1)
Type of facilities, n (%)						
Clinic	30,790	(43.6)	9,027	(47.6)	21,763	(42.1)
University hospital	8,755	(12.4)	1,937	(10.2)	6,818	(13.2)
Public hospital	6,877	(9.7)	1,617	(8.5)	5,260	(10.2)
Other hospital	24,166	(34.2)	6,370	(33.6)	17,796	(34.5)
Unknown	4	(<0.1)	1	(<0.1)	3	(<0.1)
Number of PPI types prescribed, n (%)						
1	62,610	(88.7)	15,081	(79.6)	47,529	(92.0)
2	7,193	(10.2)	3,355	(17.7)	3,838	(7.4)
3	789	(1.1)	516	(2.7)	273	(0.5)
Multiple prescriptions on the same day, n (%)	364	(4.6)	186	(4.8)	178	(4.3)
Yes (among those received multiple prescriptions)	364	(4.6)	186	(4.8)	178	(4.3)
Drugs of interest						
Omeprazole	3,173	(4.5)	778	(4.1)	2,395	(4.6)
Lansoprazole	21,056	(29.8)	4,080	(21.5)	16,976	(32.9)
Rabeprazole	13,515	(19.1)	3,692	(19.5)	9,823	(19.0)
Esomeprazole	19,835	(28.1)	5,730	(30.2)	14,105	(27.3)
Vonoprazan	13,016	(18.4)	4,672	(24.7)	8,344	(16.2)
Median duration of prescription, days (min-max)	966.0	(85–3653)	959.5	(85–3653)	969.0	(213–3653)

Abbreviations: MPR, medication possession ratio; SD, standard deviation.

Similar to the Japanese guidelines, the American College of Gastroenterology (ACG) guidelines do not set an explicit limit on the duration of PPI administration.[17] However, the ACG guidelines state that patients should be informed regarding the long-term use of PPIs and the risk of developing adverse events, such as gastric cancer, osteoporosis-related bone fractures, deficiencies of certain vitamins and minerals, and even early death. The guidelines published by the American Society for Gastrointestinal Endoscopy suggest management at the lowest dose for the shortest duration and further recommend optimization and de-escalation of medical management for patients who have been on long-term PPI administration with >6 months.[18] Overall, there is a consensus that maintenance therapy with PPIs is effective and safe, however the risk-benefit balance should be considered for patients with certain risk factors.

Prolonged suppression of gastric acid secretion by PPIs may lead to a variety of adverse events. A series of serious adverse events, including chronic kidney disease, cognitive decline, myocardial infarction, stroke, bone fractures, and

even death, are reported to be related to PPIs.[19] Thus, when PPIs are prescribed long-term, the needs for their use periodically reassessed. The association between PPIs and the development of gastric cancer has received particular attention, and in fact, several reports indicate that suppression of gastric acid secretion by PPIs increases the risk of gastric cancer.[20–28] Recently, a population-based study has shown that vonoprazan also has a similar risk of developing gastric cancer relative to duration and dose response effects;[29] the safety should not be underestimated. Upon discontinuation after long-term PPI therapy, rebound acid hypersecretion (RAHS) may occur often due to a compensatory increase in gastric acid production after PPI discontinuation. Thus, unnecessary continuation of PPI therapy leading to long-term PPI use should be avoided, and PPIs should be discontinued to prevent potential RAHS.

This study used a large database with relatively high population coverage and a wide range of hospitals and clinics, which provided informative results of PPI prescribing. However, there are limitations of this data set that should be noted when interpreting the results. The database contains claims from health insurance associations and therefore includes primarily the working population; the population of elderly is relatively low compared to the general population in Japan. The database does not include data on other health insurance enrollees, such as national health insurance, limiting generalization. The diagnosis was based on the name of the disease as listed on the claim and may not reflect the actual health status of the patient. Furthermore, even if PPIs were prescribed, confirmation of actual medication use could not be obtained from the database. The possibility of selection bias cannot be ruled out since patients without 12-month follow-up data were excluded. Moreover, data on the association between long-term PPI prescription and safety issues was not obtained in this study, and longitudinal relationship between endoscopy and PPI use was not assessed since patients were stratified based on the presence and absence of endoscopy monitoring at any timepoint during the 12-month follow-up. Given those limitations, further studies using different databases are warranted.

In conclusion, 64.2% of patients with a diagnosis of GERD and PPI prescription did not undergo endoscopy within 12 months since the initial prescription of PPIs, although adequate follow-up with endoscopy is recommended. In such patients, MPR was higher and duration of PPI prescription was longer than in patients who underwent endoscopy within 12 months since the initial prescription of PPIs. Further research is warranted to evaluate whether inadequate endoscopic follow-up is associated with adverse outcomes. In clinical practice settings, compliance with the package inserts should be highlighted to ensure safety when prescribing PPIs. Consideration from a medical economic perspective is also warranted, taking into account the reality of long-term prescriptions and excessive prescriptions.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

Ethics approval was not applicable to this study and informed consent was not required based on the Ethical Guidelines for Medical and Biological Research Involving Human Subjects issued by the MHLW since only completely anonymized data were used. This study was conducted in accordance with the Declaration of Helsinki.

Acknowledgments

The authors acknowledge Professor Jeanette Dennisson of St. Marianna University School of Medicine for editing of the manuscript.

Funding

No funding was received for the conduct of this study or the preparation of this article.

Disclosure

Akina Takami and Ataru Igarashi are members of the Department of Health Policy and Public Health. Gen Terashima and Yuichi Shiotsuki are employees of JMDC, Inc. Koki Yamashita is the president of Maxwell International, Inc., wherein he provides medical writing and clinical study consultation services to academic, pharmaceutical, biotechnology, and medical device entities. Ataru Igarashi reports receiving remuneration from AstraZeneca K.K., Eisai Co., Ltd., Daiichi Sankyo Co., Ltd., Takeda

Pharmaceuticals, and Mitsubishi Tanabe Pharma Co. He also reports grants and/or personal fees from Moderna Inc., GSK Inc., Lilly Inc., and illumina Inc., outside the submitted work. The authors report no other conflicts of interest in this work.

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