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Original Article

Predictors for the Development of Hypergastrinemia in Maintenance Treatment for Mild Gastroesophageal Reflux Disease Using a Half-dose Proton Pump Inhibitor

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Background/Aims
Serum gastrin levels may be elevated following proton pump inhibitor (PPI) therapy. We aim to elucidate the predictors for the development of hypergastrinemia in maintenance treatment for mild gastroesophageal reflux disease (GERD) using a half-dose PPI.

Methods
This study analyzed data from a prospective randomized trial to compare continuous versus on-demand maintenance treatment modalities in patients with mild GERD. Age, sex, body mass index, *Helicobacter pylori* infection, serum gastrin levels, pepsinogen (PG) I/II ratios, total days of PPI intake, and weight-based PPI dosage (mg/kg) were evaluated.

Results
Data from 293 patients who completed a randomized trial were analyzed (continuous group, n = 147 vs on-demand group, n = 146). In univariate analysis, age ($P < 0.001$), *H. pylori* infection ($P = 0.012$), baseline gastrin levels ($P < 0.001$), and baseline PG ratios ($P = 0.016$) significantly correlated with post-treatment gastrin levels. In multivariate analysis, age, baseline gastrin levels, and baseline PG ratios were independently associated with final serum gastrin levels. In univariate analysis, age ($P = 0.018$), *H. pylori* infection ($P = 0.028$), baseline gastrin levels ($P = 0.011$), and baseline PG ratios ($P = 0.031$) significantly correlated with the development of hypergastrinemia. In multivariate analysis, age, baseline gastrin levels, and baseline PG ratios were independently associated with the development of hypergastrinemia.

Conclusion
Old age, high baseline serum gastrin levels, and low baseline PG ratios are significant predictors of the development of hypergastrinemia in maintenance treatment for mild GERD using a half-dose PPI.
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Key Words
Gastrin; Gastroesophageal reflux; Maintenance; Proton pump inhibitors

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Introduction

Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs worldwide and are extensively used for the treatment of acid-related disorders.[1] Acid suppression by PPIs increases gastrin production by antral G cells through the acid secretion feedback system. Gastrin is a hormone that is secreted by antral G cells, stimulates gastric acid secretion,[2] and acts as a potent cell growth factor with proliferative and trophic effects on the gastrointestinal mucosa, including the enterochromaffin-like (ECL) cells of the stomach.[3,4] The proliferation of ECL cells may lead to neoplastic transformation and result in the occurrence of gastric neuroendocrine cell tumors (NETs). Gastric NETs have been reported in the oxyntic mucosa of rats due to hypergastrinemia induced by histamine-2 receptor antagonists or PPIs.[5,6]

Serum gastrin levels can be elevated due to *Helicobacter pylori* infection and atrophic gastritis, as well as the use of PPIs.[7-10] Long-term PPI use may induce moderate hypergastrinemia that may increase the prevalence of the ECL cell hyperplasia and the risk of cell proliferation.[9,11,12] Moreover, chronic and continuous gastrin elevation is considered to be a potential factor contributing to gastric carcinogenesis.[13] Prior studies have shown significant variability in serum gastrin levels among patients on both short- and long-term PPI treatment,[14-16] with some patients developing hypergastrinemia, defined as gastrin levels exceeding the normal range. The dosage of PPIs is presumed to be an important factor in the development of gastrin elevation during PPI therapy.[17] However, in the long-term maintenance treatment of mild gastroesophageal reflux disease (GERD), the use of a half-dose PPI is usually recommended. Whether the total duration or dosage of PPIs used for the maintenance treatment of GERD is a significant predictor of serum gastrin elevation or hypergastrinemia is currently unclear yet. Therefore, the current study aims to elucidate predictors for the development of hypergastrinemia during maintenance treatment for mild GERD using a half-dose PPI.

Materials and Methods

Study Population and Protocol

The data in the present study were collected from a prospective randomized multicenter trial performed at 25 referral hospitals between September 2020 and December 2022.[18] Figure 1 represents the protocol of the study. In that study, subjects were required to abstain from PPIs for at least 2 weeks prior to enrollment to assess baseline symptoms and laboratory findings. During the screening period, patient demographics, medical history, concomitant medications, symptom questionnaire results, and laboratory tests, including serum anti-*H. pylori* immunoglobulin G (IgG), gastrin, and pepsinogen (PG) I/II, were collected. The patients were not allowed to take any kind of anti-secretory agents at least 2 weeks before study enrollment to assess the baseline symptoms and laboratory values. After the screening period, 363 patients with non-erosive GERD or mildly erosive esophagitis (Los Angeles classification grade A or B) were enrolled in the study.

The inclusion criteria of the original study were as follows: (1) age > 19-75 years, (2) endoscopically confirmed non-erosive GERD or mild erosive esophagitis (Los Angeles classification grade A or B) within 12 weeks, and (3) symptoms of heartburn or regurgitation over 2 days within 1 week of enrollment and the presence of those reflux symptoms for the past 3 months. The study exclusion criteria were as follows: (1) endoscopically confirmed esophageal stricture, esophageal varix, long segment Barrett's esophagus, active peptic ulcer, gastrointestinal bleeding, malignancy, and eosinophilic esophagitis; (2) a history of primary esophageal motility disorder; (3) a history of gastrointestinal resection (with an exception of a history of primary repair and endoscopic resec-

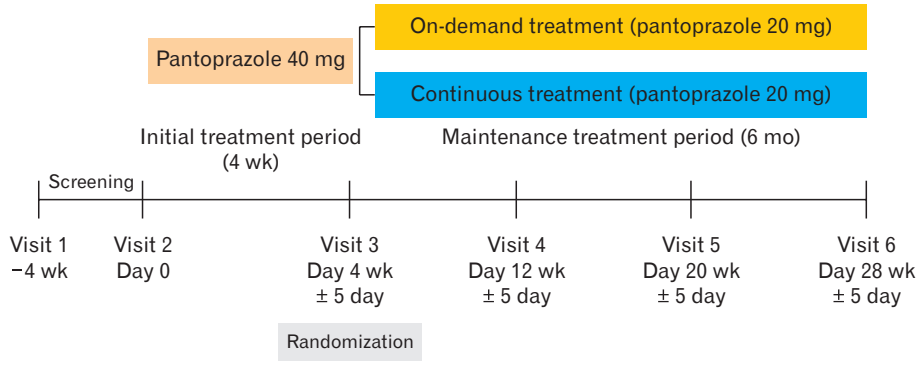

Figure 1. The study protocol in the analyzed data.

tion); (4) sensitivity to antacids or PPIs; (5) malignancy within five years of enrollment; (6) clinically significant disorders in the liver, kidney, cardiovascular, respiratory, endocrine, and central nervous systems; (7) pregnant and/or lactating individuals; (8) a history of psychological diagnosis; and (9) scheduled for surgery that required hospitalization or those who required surgical treatment while participating in the study. The patients were not permitted to take concomitant medications which could affect the results of the study. After the screening period, patients were orally administered 40 mg pantoprazole once daily for 4 weeks as an initial treatment. A total of 304 patients who symptomatically responded to the 4-week initial PPI treatment were randomized into either continuous or on-demand maintenance treatment groups (continuous, n = 151 vs on-demand, n = 153) using 20 mg of pantoprazole. After randomization, the patients were followed-up at weeks 8, 16, and 24. Patients in the continuous group received 20 mg of oral pantoprazole once daily during the maintenance treatment period. Patients in the on-demand group took 20 mg of oral pantoprazole once daily if they experienced symptoms; when symptoms improved sufficiently for at least 2 days, administration of pantoprazole was discontinued, and pantoprazole was taken again if their symptoms recurred. The patients recorded their PPI intake in a medication diary. Data from 293 of the 304 patients who were randomized to maintenance treatment were analyzed, after excluding patients with inadequate inclusion criteria (n = 4) and those lost to follow-up (n = 7) (continuous, n = 147 vs on-demand, n = 133). This study was approved by the Institutional Review Board of the Ajou University Hospital (AJOUIRB-DB-2024-240).

Measurement of Serum Anti-Helicobacter pylori immunoglobulin G, Gastrin, and Pepsinogen I/II

Serum was obtained in the fasting state and stored at −80°C until analysis. Serum gastrin levels were measured using radioimmunoassay and are expressed in picograms per milliliter (pg/mL). The upper limit of normal was based on the data from a previously published report of gastrin assay kits (MP Biomedical, Irvine, CA, USA).[19] Hypergastrinemia in this analysis kit was defined as a gastrin value greater than 111 pg/mL.[17] The antibodies used in the kit recognized both gastrin-17 and gastrin-34.

Serum levels of PG I and II were measured using a latex-enhanced turbidimetric immunoassay (HiSens; HBI, Anyang, Korea), and PG I/II ratios were calculated. Patients with PG I/II ratios ≤ 3 were classified as having an abnormal PG ratio.[20,21] Serum gastrin and PG levels were measured at baseline and at the last follow-up during the maintenance treatment period.

Anti-*H. pylori* IgG antibodies was evaluated using an enzyme-linked immunosorbent assay (Genedia HP ELISA; Green Cross Medical Science Corp, Yongin, Korea), which had a 97.9% sensitivity and a 92.0% specificity in the Korean population.[22]

Study outcomes

The main outcomes included final serum gastrin levels defined as fasting serum gastrin levels at the last follow-up, which were recorded as log-transformed continuous variables to normalize the distribution of gastrin values, and the development of hypergastrinemia at the last follow-up. PPI exposure during the maintenance treatment period was assessed in terms of the total days of PPI intake and weight-based PPI dosage (mg/kg).

Statistical Methods

Continuous and normally distributed values are expressed as mean values with standard deviation, and non-normally distributed continuous values are expressed as median values with 25-75% percentiles. The odds ratio (OR) and 95% confidence intervals (CIs) were calculated using binomial regression analysis. Multiple linear regression analysis was performed; the evaluated covariates included age, sex, *H. pylori* infection, baseline gastrin levels, baseline PG I/II ratio, body mass index, total days of PPI intake, and weight-based PPI dosage (mg/kg). *P*-values < 0.05 were considered to be statistically significant. Statistical analyses were performed using R-Studio software (version 1.1.453) and SPSS (version 25.0) for Windows (IBM Corp, Armonk, NY, USA).

Results

Baseline Characteristics of Subjects

The inclusion process of a prospective, randomized, comparative multicenter study focusing on the comparison of 2 modalities of PPI maintenance treatment is illustrated in Figure 2. A total of 304 patients were randomized into the on-demand and continuous maintenance groups. Among them, 11 were excluded based on the exclusion criteria, and 293 patients were finally analyzed. The baseline characteristics of patients are presented in Table 1. The mean follow-up duration was 178.5 days and the mean PPI administration duration during the study period was 130.4 days. The mean serum gastrin levels were significantly higher at the end of follow-up, compared with baseline gastrin levels. Hypergastrinemia, defined as gastrin levels greater than 111 pg/mL, was observed in a total of 20 patients (7.8%) at enrollment in the study and in 37 patients (15.2%)

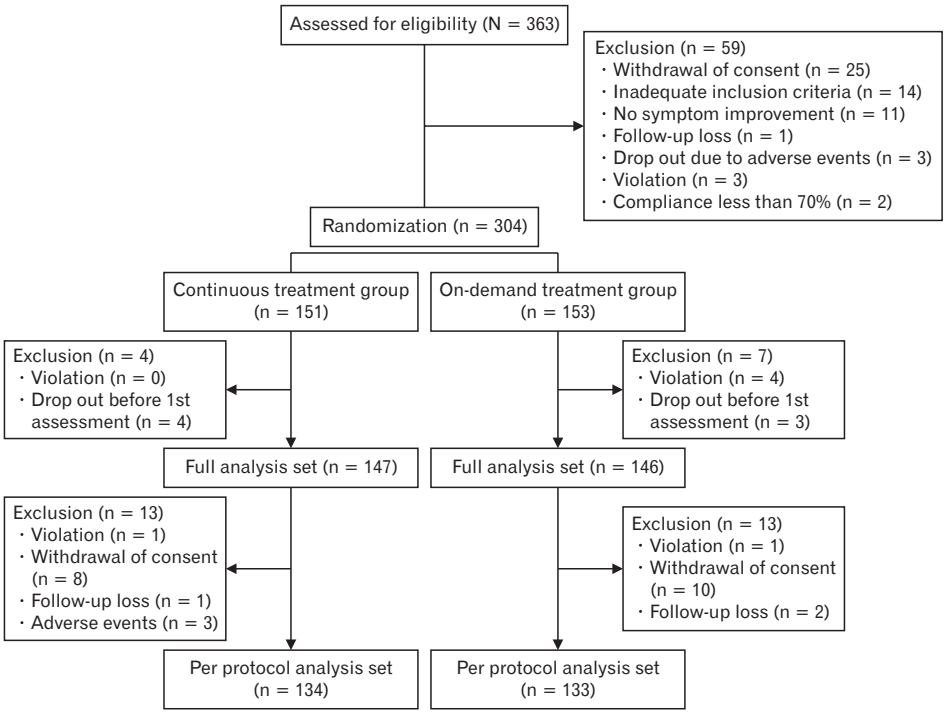

Figure 2. The inclusion process of a prospective, randomized, multicenter trial for the comparison of 2 modalities of proton pump inhibitor maintenance treatment for mild gastroesophageal reflux disease.

Table 1. Baseline Characteristics of the Study Subjects

Variables	
Group	
On-demand therapy	146 (49.8)
Continuous therapy	147 (50.2)
Age (yr)	51.8 ± 13.6
Sex	
Male	163 (55.6)
Female	130 (44.4)
H. pylori infection	
Positive	58 (19.8)
Negative	199 (67.9)
Unknown	36 (12.3)
BMI (kg/m^2)	24.6 ± 4.3
Dosage over weight (mg/kg)	48.9 ± 21.4
Baseline gastrin levels (pg/mL)	57.5 ± 71.8
Last visit gastrin levels (pg/mL)	74.1 ± 68.4
Pepsinogen I/II	5.1 ± 1.7
Hypergastrinemia (last visit)	
< 112 pg/mL	207 (84.8)
≥ 112 pg/mL	37 (15.2)
Days of PPI intake (day)	130.4 ± 57.3

H. pylori, *Helicobacter pylori*; BMI, body mass index; PPI, proton pump inhibitor.
Data are presented as n (%) or mean ± SD.

Table 2. Comparisons Between On-demand and Continuous Groups

Variables	On-demand group (n = 146)	Continuous group (n = 147)	*P*-value[a]
Age (yr)	52.4 ± 13.0	51.2 ± 14.1	0.447
Sex			0.219
Male	76 (52.1)	87 (59.2)	
Female	70 (47.9)	60 (40.8)	
BMI (kg/m^2)	24.9 ± 5.0	24.3 ± 3.6	0.220
Duration of GERD symptoms			
Heartburn (mo)	30.7 ± 41.3	27.1 ± 37.9	0.443
Regurgitation (mo)	24.2 ± 34.2	23.4 ± 30.1	0.862
Endoscopic findings			0.961
Non-erosive	86 (58.9)	87 (59.2)	
Erosive (LA-A/B)	60 (41.1)	60 (40.8)	
Baseline gastrin levels (pg/mL)	62.9 ± 86.6	52.1 ± 52.7	0.228
Baseline pepsinogen I/II	8.10 ± 14.0	8.2 ± 13.0	0.939

[a]*P*-value was calculated by independent *t* test for continuous variables and Pearson chi-square test for categorical variables.
BMI, body mass index; GERD, gastroesophageal reflux disease; LA, Los Angeles classification.
Data are presented as mean ± SD or n (%).

at the final visit. Positive serology for *H. pylori* infection was observed in 22.6%. The mean PG I/II ratio was 5.12. The data set used in the present study came from the already published paper.[18]

There were no significant differences in the baseline characteristics, including the mean age, sex ratio, baseline gastrin levels, and PG I/II ratios, between the continuous and on-demand groups (Table 2).

Factors Related to Log-transformed Final Serum Gastrin Levels

The univariate analysis revealed that age ($P = 0.001$), *H. pylori* infection ($P = 0.012$), baseline gastrin levels ($P < 0.001$), and the baseline PG I/II ratio ($P = 0.016$) significantly correlated with the log-transformed serum gastrin levels of last visit. Sex, total days of PPI intake, and weight-based PPI dosage were not significantly correlated with the log-transformed serum gastrin levels of last visit (Table 3). In the multivariate analysis, age ($P = 0.001$), baseline gastrin levels ($P < 0.001$), and the baseline PG ratio ($P = 0.020$) were independently associated with the log-transformed serum gastrin levels of last visit (Fig. 3).

Factors Related to the Development of Hypergastrinemia

The univariate analysis revealed that age ($P = 0.018$), *H. pylori* infection ($P = 0.028$), baseline gastrin levels ($P = 0.011$), and the baseline PG ratio ($P = 0.024$) significantly correlated with

Table 3. Univariate and Multivariate Analysis for Risk Factors Associated With the Log Transformed Gastrin Levels of Last Visit

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (yr) ≥ 60	0.146	0.064-0.228	0.001	0.132	0.054-0.211	0.001
Sex (female)	−0.014	−0.095-0.067	0.729	−0.008	−0.094-0.079	0.862
H. pylori	0.122	0.027-0.216	0.012	0.083	−0.010-0.176	0.082
Baseline gastrin levels	0.001	0.001-0.002	< 0.001	0.001	0.001-0.002	< 0.001
Baseline pepsinogen I/II	−0.030	−0.533-−0.006	0.016	−0.028	−0.051-−0.005	0.020
Days of PPI intake (day)						
< 90	ref					
≥ 90 and < 150	0.056	−0.059-0.171	0.340	0.102	−0.021-0.224	0.104
≥ 150	0.077	−0.017-0.170	0.108	0.125	−0.036-0.286	0.130
Dosage over weight (mg/kg)	0.001	−0.000-0.003	0.136	−0.001	−0.004-0.003	0.779

H. pylori, *Helicobacter pylori*; PPI, proton pump inhibitor.

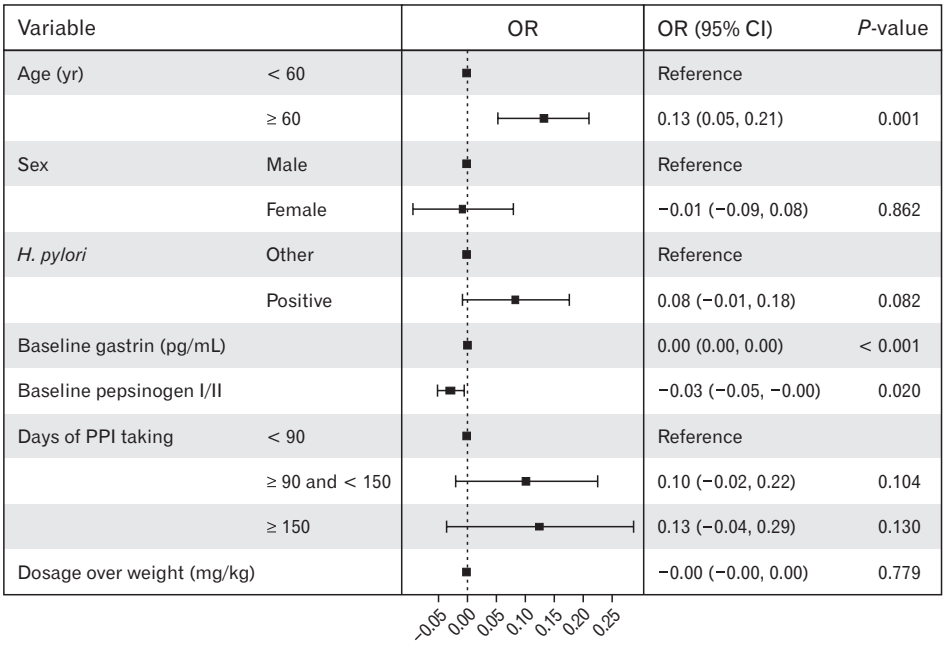

Figure 3. The multivariate analysis for risk factors associated with the log transformed gastrin levels of last visit during the maintenance treatment. *H. pylori*, *Helicobacter pylori*; PPI, proton pump inhibitor.

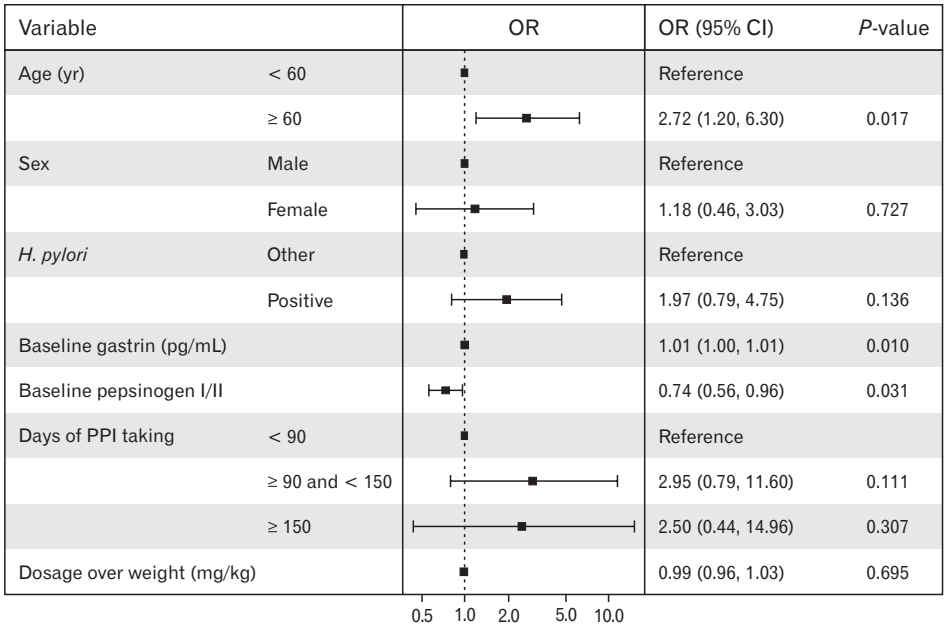

Figure 4. The multivariate analysis for risk factors associated with the development of hypergastrinemia. *H. pylori*, *Helicobacter pylori*; PPI, proton pump inhibitor.

Table 4. Univariate and Multivariate Analysis for Risk Factors Associated With the Development of Hypergastrinemia

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (yr) ≥ 60	2.353	1.160-4.825	0.018	2.722	1.204-6.303	0.017
Sex (female)	1.002	0.492-2.022	0.995	1.183	0.456-3.029	0.727
H. pylori	2.364	1.077-5.042	0.028	1.966	0.794-4.751	0.136
Baseline gastrin	1.006	1.002-1.011	0.011	1.006	1.002-1.011	0.010
Baseline pepsinogen I/II	0.753	0.583-0.954	0.024	0.741	0.558-0.962	0.031
Days of PPI intake (day)						
< 90	ref					
≥ 90 and < 150	1.585	0.574-4.384	0.368	2.949	0.791-11.600	0.111
≥ 150	1.359	0.593-3.322	0.481	2.497	0.439-14.959	0.307
Dosage over weight (mg/kg)	1.006	0.989-1.022	0.504	0.993	0.956-1.028	0.695

H. pylori, *Helicobacter pylori*; PPI, proton pump inhibitor.

the development of hypergastrinemia. Sex, total days of PPI intake, and weight-based PPI dosage were not significantly correlated with the development of hypergastrinemia (Table 4). In the multivariate analysis, age ($P = 0.017$), baseline gastrin levels ($P = 0.010$), and the baseline PG ratio ($P = 0.031$) were independently associated with the development of hypergastrinemia (Fig. 4).

Discussion

The results of the present study revealed that the development of hypergastrinemia in patients with GERD who received maintenance treatment using a half-dose PPI were more strongly associated with age, baseline gastrin levels, and baseline PG I/II ratios rather than the total days of PPI intake and weight-based PPI dosage. A previous study reported that fasting serum gastrin levels showed a dose-dependent increase with the PPI dosage, when divided by the patient's weight and body surface area.[17] However, in real world situations, clinical guidelines recommend the use of a half-dose PPI for the maintenance treatment of non-erosive GERD or mild erosive esophagitis.[23-25] Actually, a half-dose PPI is commonly used for the maintenance treatment of GERD in continuous or on-demand modalities. A previous study revealed that PPI dosage and female sex were important predictors related to the development of hypergastrinemia after PPI therapy.[17] Fasting serum gastrin levels were

found to be significantly correlated with the dosage of PPIs relative to body weight.[17] Unlike the results of a previous study, our findings of the present study indicate that the patients' baseline conditions such as old age, high baseline gastrin levels and low baseline PG I/II ratios referring to the degree of atrophic gastritis are crucial in the development of hypergastrinemia following maintenance treatment using a half-dose PPI. The advantage of the data set used in the present study over a previous report[17] is that they were obtained from a well-controlled, randomized study and included an accurate evaluation of PPI intake and patient compliance for PPI administration.

Population-based epidemiological studies have suggested that the long-term use of PPIs is associated with an increased risk of gastric cancer.[26-28] PPIs reduce gastric acid production and consequently stimulate the secretion of gastrin. Gastrin is suggested to induce cell proliferation and increase the risk of gastric neoplasms.[9,11,12] The development of gastric adenocarcinoma is also found to be associated with a significant elevation in serum gastrin levels when compared with control patients.[29] Moreover, it is proposed that gastrin may play a role in gastric carcinogenesis in patients with hypergastrinemia, particularly in the setting of *H. pylori* infection.[30] *H. pylori* is known to be the main cause of gastric cancer. Persistent *H. pylori* infection causes oxyntic atrophy and gastric hypoacidity, which may lead to hypergastrinemia. It is presumed that gastrin can be a pathogenetic factor for gastric cancer associated with *H. pylori*, autoimmune gastritis, and long-term inhibition of gastric acid secretion.[31] As gastrin has potent trophic action on ECL cells, hypergastrinemia is presumed to induce ECL cell hyperplasia and cause NETs or neuroendocrine carcinomas, that was observed in rodents.[6,32] Although the development of neoplastic lesions in ECL cells is not yet documented in humans,[33] hypergastrinemia is suggested to be the most likely explanation for the association of the long-term use of PPIs with the development of gastric cancer.[9,34] Actually, studies have shown that hypergastrinemia may play a role in the development of gastric tumors.[35-38] Tumorigenic effects of elevated serum gastrin is also suggested in the long-term PPI use for Barrett's esophagus.[39] Prospective studies are required to determine whether patients with elevated serum gastrin or hypergastrinemia associated with long-term PPI therapy are at increased risk for gastric neoplasia development in humans.

In the present study, 7.8% of the patients exhibited hypergastrinemia in the basal state, which may be explained by several factors. First, atrophic gastritis is prevalent in the general adult population of Korea. Second, the prevalence of *H. pylori* infection is still high in Korea. Third, since GERD is a chronically recurrent disorder, GERD patients included in the data set usually had a history of repeated administration of a PPI due to chronically recurrent GERD symptoms. In order to minimize the influence of a previous intake of PPIs on serum gastrin levels, participants were asked to stop PPI therapy for at least 2 weeks before enrollment, after which basal serum gastrin levels were measured. At the last follow-up in the maintenance treatment using a half-dose PPI, hypergastrinemia was observed in 15.2% of the patients. Studies have shown that there is a significant individual variation in the effect of long-term PPI use on serum gastrin levels.[7,40] The results of the current study suggest that patients' baseline factors including age, baseline serum gastrin levels and the basal PG I/II ratio may be more implicated in the development of hypergastrinemia during long-term use of a half-dose PPI rather than the duration of PPI treatment. In real-world clinical situations where the use of a half-dose PPI is recommended for the maintenance treatment of mild GERD including NERD and mild erosive esophagitis, total days of PPI intake and weight-based PPI dosage do not seem to be important predictors for the development of hypergastrinemia. In keeping with our findings, a previous study reported that there was no significant correlation between the duration of PPI treatment and serum gastrin levels.[41]

The present study showed that older age was associated with higher serum gastrin levels and the development of hypergastrinemia. The older age group may exhibit more atrophic changes in parietal cell masses. Additionally, the prevalence of *H. pylori* infection is known to be higher in the older age population of Korea. Actually, a previous study reported that the increase in fasting serum gastrin levels observed with increasing age was associated with an increased incidence of *H. pylori* infection.[42] The findings of the present study revealed that a low PG I/II ratio, which can indicate the degree of atrophic gastritis, was an independent predictor for the development of hypergastrinemia. The use of PPIs to suppress gastric acid secretion is known to cause an increase in serum PG and gastrin levels.[43] Both PG I/II ratios and serum gastrin levels are found to be associated with the *H. pylori* infection status.[44] The risk of gastric cancer can be assessed by measuring the PG I level and the PG I/II ratio.[45] PG I is primarily secreted by mucosal cells in the fundus, whereas PG II is mainly secreted by chief cells, the proximal duodenal mucosa and the pyloric glands.[46] Decreased PG I/II ratios are suggested to be associated with the grade of atrophic gastritis.[47,48] Gastrin levels are further increased by oxyntic atrophy, and hypergastrinemia may eventually be an important predisposing factor for gastric carcinoma or neoplasia.[49,50] The threshold concentration for the trophic effect of gastrin on ECL cells has not been

determined. However, a previous study in patients with sporadic Zollinger-Ellison syndrome reported that even mid hypergastrinemia had a trophic effect on ECL cells.[51] The probability for the development of gastric neoplasia appears to be affected by the gastrin value multiplied with time.

This study has several strengths. First, the data of the present study were obtained from a well-controlled prospective randomized multicenter trial, and the participants were followed-up regularly during the maintenance treatment period. Second, the dose used for maintenance treatment was fixed for all patients; however, the maintenance modalities were randomly divided into continuous and on-demand groups. Thus, the duration of PPI exposure was variable. Third, mild GERD such as non-erosive GERD or mild erosive esophagitis was diagnosed using endoscopy and a positive symptomatic response to an initial PPI treatment.

However, this study has limitations that should be noted when interpreting our findings. It cannot be completely excluded that previous PPI use before enrollment could influence on basal serum gastrin levels. Although most of enrolled patients had a past history of medication intake for their GERD symptoms, the duration of previous intake of anti-secretory agents was very variable and could not be determined just by history taking. There was no information on the duration of previous anti-secretory agent intake, which is difficult to collect because of several reasons as follows: first, the duration of medication intake cannot be recalled accurately by patients; second, their GERD symptoms may occur irregularly and medication intake also may be non-continuous; third, many patients do not know what type and dose of anti-secretory agents are prescribed for them among diverse commercially available drugs; and fourth, the aim of the original trial was to compare on-demand versus continuous maintenance treatment modalities using a half-dose PPI for patients with non-erosive GERD or mild erosive esophagitis. In that trial, there was an at least 2-week wash-out period for basal screening, which may reduce the effect of previous medications. Although PG I/II ratios reflect the grade of atrophic gastritis, the histological or morphological grade of atrophic gastritis was not evaluated in the current study. Addition of endoscopic findings indicating the degree of gastric atrophy may strengthen the study results regarding the PG I/II ratio, which warrants further investigation. The maintenance treatment period in the current study was within 6 months, that may not be enough to reflect the long-term effect of PPI use. In addition, *H. pylori* infection status was evaluated only by measurement of serum anti-*H. pylori* IgG antibodies. Information regarding the eradication history and other *H. pylori* tests was not collected. So, the positive serology of *H. pylori* in our data cannot differentiate whether it is a current or past infection. In the current study, univariate analysis showed significant correlation of positive *H. pylori* infection with post-treatment gastrin levels or hypergastrinemia, whereas multivariate analysis failed to prove this significant correlation. It cannot be completely excluded that this negative finding may be affected by the inability to differentiate whether positive *H. pylori* is a current or past infection.

Old age, high baseline serum gastrin levels, and low baseline PG ratios are important predictors for the development of hypergastrinemia during maintenance treatment using a half-dose PPI for patients with mild GERD. Those factors need to be considered when selecting an appropriate maintenance treatment modality for GERD patients.

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Conflicts of interest: None.

Author contributions: Conception and design of the study: Kwang Jae Lee; acquisition of data: Da Hyun Jung, Young Hoon Youn, Hye-Kyung Jung, and Kwang Jae Lee; data analysis and drafting of the manuscript: Kwang Jae Lee and Da Hyun Jung; and editing the manuscript critically: Kwang Jae Lee and Da Hyun Jung.

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