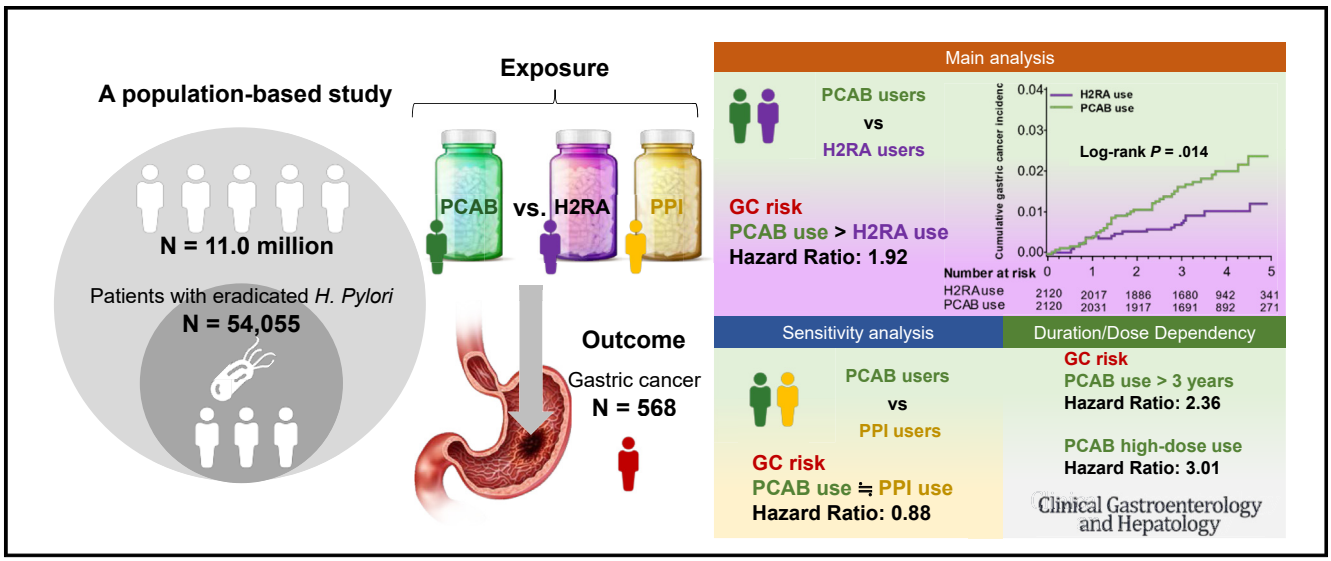
Association Between Vonoprazan and the Risk of Gastric Cancer After *Helicobacter pylori* Eradication

Junya Arai,[1,2] Atsushi Miyawaki,[3] Tomonori Aoki,[2] Ryota Niikura,[4] Yoku Hayakawa,[2] Hiroaki Fujiwara,[1] Sozaburo Ihara,[2] Mitsuhiro Fujishiro,[2] and Masato Kasuga[5]

[1]Division of Gastroenterology, The Institute of Medical Science, Asahi Life Foundation, Tokyo, Japan; [2]Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [3]Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [4]Department of Endoscopy, Graduate School of Medicine, Tokyo Medical University, Tokyo, Japan; and [5]The Institute of Medical Science, Asahi Life Foundation, Tokyo, Japan



BACKGROUND & AIMS: **Potassium-competitive acid blockers (PCABs) have been increasingly used to treat upper gastrointestinal disorders, replacing proton pump inhibitors (PPIs). Whereas PPIs are associated with an increased risk of gastric cancer (GC) after *Helicobacter pylori (Hp)* eradication, it is uncertain whether PCABs carry the same risk.**

METHODS: **Using a population-based claims database in Japan, we identified patients who were prescribed a clarithromycin-based first regimen of *Hp* eradication between 2015 and 2018. Patients who failed this regimen and those diagnosed with GC before or within 1 year after *Hp* eradication were excluded. We compared GC incidence between PCAB users and histamine type-2 receptor antagonist (H2RA) users, matching them on the basis of propensity scores calculated with considerations for age, sex, smoking, alcohol consumption, comorbidities, and co-administered medications. PCABs included only vonoprazan in this study.**

RESULTS: **Among 54,055 patients, 568 (1.05%) developed GC during the follow-up period (mean, 3.65 years). The cumulative incidence of GC was 1.64% at 3 years, 2.02% at 4 years, and 2.36% at 5 years in PCAB users and 0.71% at 3 years, 1.04% at 4 years, and 1.22% at 5 years in H2RA users. The use of PCABs was associated with a higher GC risk (matched hazard ratio, 1.92; 95%**

Abbreviations used in this paper: **CI, confidence interval; GC, gastric cancer; GERD, gastroesophageal reflux disease; *Hp*, *Helicobacter pylori*; HR, hazard ratio; H2RA, histamine 2 receptor antagonist; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; PS, propensity score.**

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2024.01.037

confidence interval, 1.13–3.25; $P = .016$). Longer PCAB use and high-dose PCAB use were significantly associated with higher incidence of GC. Sensitivity analyses showed the risk of GC incidence among PCAB users was comparable with that of PPI users.

CONCLUSIONS: **The use of PCABs was associated with an increased risk of GC among *Hp*-eradicated patients, with duration/dose response effects.**

Keywords: Gastric Cancer; *Helicobacter pylori*; Potassium-Competitive Acid Blocker; Proton Pump Inhibitor.

Gastric cancer (GC) is one of the leading causes of cancer-related mortality worldwide.[1] *Helicobacter pylori* (*Hp*) is a well-established risk factor for GC,[2] and its eradication has been shown to significantly reduce the incidence and mortality of GC.[3–7] However, even after eradication, there remains a residual risk of GC compared with *Hp* naive people.[8,9] Identifying risk factors and a high-risk group for post-eradicated GC development is important for cancer surveillance and prevention.[10]

Proton pump inhibitors (PPIs) have been commonly prescribed for acid-related upper gastrointestinal diseases, and they have been generally considered safe. However, a growing body of literature indicates that long-term use of PPIs is associated with several adverse effects including *Clostridium difficile* infection and ischemic diseases.[11–14] Furthermore, several studies have recently reported an association between PPI use and higher GC incidence rates, particularly after *Hp* eradication.[15–22] PPI use also reportedly has the potential to worsen atrophic gastritis.[23] One hypothesis suggests that the pharmacologic inhibition of gastric acid secretion leads to hypergastrinemia and alters gastric microbiota,[23–26] both of which could activate oncogenic pathways in the post-eradication gastric mucosa, as observed in experimental studies.[27–29]

Recently, a new class of acid-suppressing drugs, potassium-competitive acid blockers (PCABs), has been increasingly used in Japan and is now available in Western countries.[30,31] PCABs could provide stronger and more sustained acid suppression than PPIs, especially for healing of severe erosive esophagitis and in the management of refractory gastroesophageal reflux disease (GERD). However, this raises the concern that the intense acid suppression might increase the risk of post-eradicated GC, as suggested in PPI users. Therefore, we performed a population-based observational study to evaluate the association between PCAB use and post-*HP* eradication GC.

Methods

Study Design, Setting, and Participants

We conducted a retrospective cohort study using healthcare insurance claims and medical check-up data spanning from April 2014 to February 2023, sourced from DeSC Healthcare Inc in Tokyo, Japan. This database is robust and has been used in several previous studies.[32–35] This data set includes de-identified healthcare-related information from insurance claims, encompassing diagnostic codes, prescription and procedure codes, and medical check-up data. Importantly, individual healthcare information can be traced across all medical institutions in Japan as long as individuals remain part of the same health insurance plan. The 3 insurance systems providing the data consisted of the Society-managed Employment-based Health Insurance Association, serving individuals working at large companies and their family members, the National Health Insurance, serving people younger than 75 who are not covered by other public health systems such as self-employed persons, farmers, college students, and retirees, and the Latter-Stage Elderly Healthcare System, serving people aged 75 years or older[36] (Supplementary Figure 1). These insurance systems encompassed a population of more than 10 million individuals, representing approximately 10% of Japan's total population.

From the database, we extracted the data of patients who used a 7-day course of clarithromycin-based triple therapy for *Hp* infection between April 2015 and March 2018. We included patients who successfully eradicated *Hp* in the analyses. We defined the successful eradication of *Hp* as the prescription of the first regimen of clarithromycin-based triple therapy without the second regimen prescription of metronidazole-based triple therapy using a previous research definition.[15] We excluded patients who underwent gastrectomy or were diagnosed with GC before *Hp* eradication. We also excluded patients whose follow-up period was less than 1 year, as well as patients who were diagnosed with GC within 1 year after *Hp* eradication. Finally, we excluded concomitant users of histamine type-2 receptor antagonist (H2RA), PPI, and PCAB during the study period (Figure 1*A*).

Informed consent was waived because we used completely anonymous data. The data were purchased from DeSC Healthcare Inc, and permission was obtained to use them in the study and to publish the results in a scientific article.

Outcomes and Variables

The primary outcome was the development of GC more than 1 year after *Hp* eradication, as defined by the International Classification of Diseases-10th revision codes (C16.0–C16.9) according to an approach used in

previous studies.[15,17,19,20,37–40] Patients who developed GC within 1 year after *Hp* eradication were excluded from our analysis, because it was indicative that the onset of these GC cases was likely before *Hp* eradication. The date of diagnosis of GC was defined as the first date of disease registration for GC workup or treatment. The follow-up period extended from 1 year after the initiation of eradication medication until the final visit, GC development, or death.

We evaluated the following clinical factors associated with GC risk: age, sex, smoking, alcohol consumption, comorbidities, and medication use. Smoking status and alcohol consumption data were unavailable in the current database, necessitating a methodology akin to that used in previous studies.[15,41] Chronic obstructive pulmonary disease was used as a proxy for smoking. Alcohol consumption was identified by assessing for alcohol-related disorders, encompassing hepatic and gastrointestinal conditions, as well as neurologic and psychiatric ailments. The following comorbidities were included: gastric atrophy, peptic ulcer diseases, hypertension, diabetes, dyslipidemia, chronic heart failure, chronic kidney disease, stroke, ischemic heart diseases, obesity, liver cirrhosis, and atrial fibrillation, in line with previous studies.[15–20] These comorbidities were defined on the basis of International Classification of Diseases-10th revision diagnosis at baseline. Drug usage in the study period, encompassing both before and after *Hp* eradication, was assessed, including PCABs, PPIs, H2RAs, metformin, statins, aspirin, and nonsteroidal anti-inflammatory drugs. In particular, exposure to PCABs, PPIs, and H2RAs was defined as a single drug use with a duration of usage exceeding 6 months, aiming to restrict their prolonged or long-term usage. PCABs included only vonoprazan in this study, because vonoprazan has been the only PCAB that can be prescribed in Japan, and the medication lists of PCABs, PPIs, and H2RAs are shown in Supplementary Table 1. In addition, cases where the prescription was initiated within 6 months before GC development were excluded to avoid protopathic bias. The duration of PCAB use was classified into 4 groups based on prescription periods: PCAB use for less than 1 year, between 1 and 2 years, between 2 and 3 years, and for 3 years or more. The PCAB dose was also categorized into 2 groups: the high-dose group (where the duration of vonoprazan 20 mg exceeded 2 months) and the low-dose group (which includes half-dose [10 mg] users with or without 20 mg use for less than 2 months).

What You Need to Know

Background

An association between long-term use of proton pump inhibitors (PPIs) and higher gastric cancer (GC) incidence after the eradication of *Helicobacter pylori* (*Hp*) has been reported. However, the association between the use of potassium-competitive acid blockers (PCABs) and GC incidence after *Hp* eradication remains unknown.

Findings

PCAB use was associated with increased GC incidence after *Hp* eradication, compared with histamine type-2 receptor antagonist users, with duration/dose response effects.

Implications for patient care

Caution is warranted for prolonged prescription of PCABs as well as PPIs for *Hp*-eradicated patients because of the potential association with increased GC risk.

Statistical Analysis

First, we constructed propensity score (PS) matched cohorts between PCAB users and H2RA users and compared the incidence of GC analyses in line with previous studies,[15,17,19] because unobserved differences in the background gastric mucosa appear to be comparable between PCAB users and H2RA users, and the influence of H2RA on the risk of GC is estimated to be minimal.[16,19,37] Details of the matching method are shown in Supplementary Methods. The Kaplan–Meier method was used to calculate the cumulative probability of GC development at 5 years for each group. Cox models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Second, to evaluate whether the association varies by exposure duration and dose, we stratified PCAB users into subgroups based on duration and dosage dependency and repeated analyses. We estimated the HRs for GC development according to PCAB duration/dose using another Cox model that was adjusted by PS. The trend for duration/dose response of PCAB use was assessed by Cochran–Armitage trend test.

Sensitivity Analyses

First, to compare the influence of PCAB and PPI on GC risk, we constructed another PS-matched cohort between PCAB users and PPI users and compared the incidence of GC analyses. Second, to perform competing risk analysis, we used Fine and Gray's test to compute the subdistribution HR along with its corresponding 95% CI. This analysis considered death without the development of GC as a competing risk. Third, we investigated the association between PCAB/H2RA usage and GC development in the matched cohort, specifically excluding patients with a follow-up period of less than 2 years. This exclusion aimed to create a more extended lag duration between *Hp* eradication and the potential development of GC. Finally, we estimated the effects of unmeasured confounders using calculation for an E-value to formally examine how strongly unmeasured confounders would

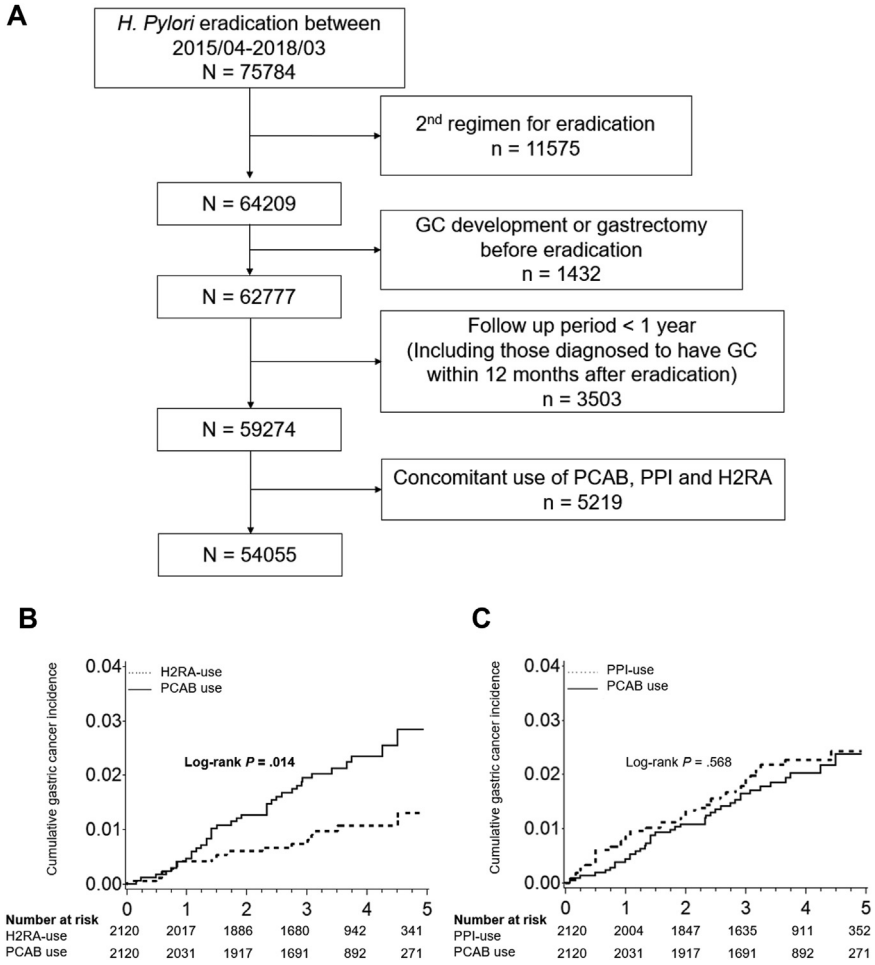


Figure 1. Association between GC incidence and use of gastric acid inhibitors. (*A*) Study flow diagram. Cumulative incidence of GC (*B*) in PCAB users vs matched H2RA users, (*C*) in PCAB users vs matched PPI users. Bold: $P < .050$.

need to be associated with PCAB use (exposure variable) and GC incidence (outcome variable) to explain the observed difference in GC incidence between PCAB users and H2RA users.[42] A P value $<.05$ was considered statistically significant, and HRs with 95% CIs were determined. All statistical analyses were performed using SAS software v. 9.4 (SAS Institute, Cary, NC).

Results

Patient Characteristics

A total of 75,784 patients received *Hp* eradication therapy. After excluding 21,729 patients, 54,055 individuals who successfully eradicated *Hp* were analyzed (Figure 1*A*). Among these 54,055, mean age was 64.65 years, 44.94% (n = 24,292) were male, and 3.92% used PCABs. The percentages of PPI and H2RA users were 16.74% and 10.82%, respectively. The baseline characteristics of the cohort are shown in Table 1.

Incidence of GC and the Factors Associated With GC in PCAB Users Compared With Matched H2RA Users

During mean follow-up period of 3.69 years, 61 patients (1.44%) developed GC in a PS matched cohort consisting of PCAB users and H2RA users after excluding 3728 H2RA users (Table 2, Supplementary Figures 2 and 3). The cumulative incidence of GC was 1.64% at 3 years, 2.02% at 4 years, and 2.36% at 5 years in PCAB users and 0.71% at 3 years, 1.04% at 4 years, and 1.22% at 5 years in H2RA users (Figure 1*B*). PCAB use was significantly associated with increased GC incidence ($P = .014$, log-rank test).

The results of a Cox model evaluating factors associated with GC are shown in Table 3. In the analyzed *Hp*-eradicated patients, PCAB users had a higher incidence of GC than H2RA users (adjusted HR, 1.92; 95% CI, 1.13–3.25; $P = .016$). This trend was consistent with the findings for GC occurring at non-cardia sites, whereas the incidence of GC at the cardia did not reach statistical significance (Supplementary Table 2).

Association Between Duration/Dose of PCAB Use Compared With H2RA Use and GC Incidence

The incidence of GC according to the duration of PCAB use was as follows: PCAB use $<$ 1 year, 2/400 (0.05%); 1 year $<$ PCAB use $<$ 2 years, 9/476 (1.89); 2 years $<$ PCAB use $<$ 3 years, 6/354 (1.69%); and PCAB use $>$ 3 years, 23/890 (2.58%). Of the 1361 low-dose PCAB users, 18 developed GC (1.32%), whereas 22 of 759 high-dose PCAB users did (2.90%). The associations between the duration and dose of PCAB use and GC incidence were assessed using a Cox model (Table 4).

Table 1. Characteristics of Patients With Successful *Hp* Eradication

Variables	No. of patients (%)
Male	24,292 (44.94)
Age, y	64.65 ± 11.60
Follow-up y	3.65 ± 1.38
Smoking	2052 (3.80)
Alcohol	970 (1.79)
Comorbidities	
Gastric atrophy	18,209 (33.69)
Peptic ulcer diseases	23,348 (43.19)
Hypertension	29,479 (54.54)
Diabetes mellitus	19,157 (35.44)
Dyslipidemia	29,656 (54.86)
Chronic heart failure	9551 (17.67)
Chronic kidney disease	2352 (4.35)
Stroke	6327 (11.70)
Ischemic heart disease	8299 (15.35)
Obesity	516 (0.95)
Liver cirrhosis	723 (1.34)
Atrial fibrillation	2642 (4.89)
Medication use	
PCAB	2120 (3.92)
PPI	9049 (16.74)
H2RA	5848 (10.82)
Metformin	3791 (7.01)
Statin	18,573 (34.36)
Aspirin	3400 (6.29)
NSAIDs	44,536 (82.39)
Gastric cancer development	568 (1.05)
Cardia	16 (0.03)
Non-cardia	552 (1.02)

NSAIDs, nonsteroidal anti-inflammatory drugs.

The adjusted HRs for PCAB use >3 years and high-dose PCAB use were 2.36 (95% CI, 1.30–4.26; $P = .004$) and 3.01 (95% CI, 1.66–5.48; $P < .001$), respectively, compared with the H2RA use group. The Cochran-Armitage trend test demonstrated a duration/dose-dependent relationship between PCAB usage and GC development ($P_{\text{trend}} = .001$ and .001, respectively).

Sensitivity Analyses

In a PS matched cohort (Table 5, Supplementary Figures 3 and 4), PCAB users had comparable incidence rates of GC with PPI users (Figure 1*C*, Table 3). In competing risk analysis, the risk of GC incidence was higher among PCAB users than H2RA users but comparable with PPI users (Supplementary Table 3). The findings from the 2-year lag duration analysis were consistent with the main analysis (Supplementary Table 4). The E-value for the observed difference in GC incidence between PCAB users and H2RA users was 3.24, indicating that an unmeasured confounder that was associated with both the exposure and outcome is unlikely to exist according to our knowledge and previous studies[15–22] (Supplementary Figure 5).

Discussion

In this population-based cohort study, we found that PCAB use was associated with an increased risk of post-eradication GC incidence when compared with H2RA use and duration/dose response relationships were confirmed, whereas PPI users and PCAB users showed no significant differences in GC risk (Graphic abstract).

We recently reported the potential association between PCAB use and GC using a small sample size database analysis.[39] This population-based study provided consistent and more convincing results that PCAB use was associated with a higher incidence of GC when compared with H2RA use, and also the influence of both PPIs and PCABs on GC risk exhibited a similar profile. Both of these medications exert robust inhibitory effects on gastric acid secretion, and their respective influences on the incidence of GC appear to be quite comparable. To gain a comprehensive understanding of the causal relationship between the development of GC and the use of PPIs and PCABs, prospective cohort and/or randomized controlled studies would be required. An exhaustive analysis encompassing clinical variables, blood tests, genetic profiles, and diverse racial backgrounds would be helpful for future studies.

Recently, PCABs have been prescribed not only for *Hp* eradication or treatment of peptic ulcers but also for alleviation of several abdominal symptoms, mainly GERD-related. Because treatment for GERD often requires longer prescriptions of acid-suppressing drugs, long-term usage of PCABs may increase in various countries worldwide. According to the results of our study, longer use of PCABs was particularly associated with the increased risk of GC after *Hp* eradication. Therefore, for patients at high risk of GC such as those with a history of *Hp* infection, it might be better to switch strong acid inhibitors including PCABs and PPIs to H2RAs before reaching a lengthy prescription period (eg, more than 3 years).

This is a population-based, large-scale cohort study to evaluate the association between PCAB use and the incidence of GC after *Hp* eradication. Nevertheless, our study has several limitations. First, this study was retrospective, introducing several inherent challenges, notably selection bias and confounding. Although we used PS matching and conducted multivariable analyses to mitigate these biases to some extent, it is imperative to emphasize the necessity for future prospective observational studies to provide more robust evidence. Second, information on some potential confounders, including diet, body mass index, and family history, was unavailable in our database. However, the E-value of the adjusted HR for PCAB use was high enough that the

Table 2. Baseline Characteristics of PCAB/H2RA Users Before and After Propensity Score Matching

	Before matching			After matching		
	H2RA users (n = 5848)	PCAB users (n = 2120)	SMD	H2RA users (n = 2120)	PCAB users (n = 2120)	SMD
Male	2443 (41.77)	972 (45.85)	0.082	971 (45.80)	972 (45.85)	0.001
Age, y	65.88±11.83	66.88±11.06	0.087	66.88±11.13	66.88±11.06	–.0002
Smoking	265 (4.53)	123 (5.80)	0.057	130 (6.13)	123 (5.80)	–0.015
Alcohol	138 (2.36)	40 (1.89)	–0.033	53 (2.50)	40 (1.89)	–0.043
Comorbidities						
Gastric atrophy	1668 (28.52)	728 (34.34)	0.125	733 (34.58)	728 (34.34)	–0.005
PUD	3706 (63.37)	1337 (63.07)	–0.006	1345 (63.44)	1337 (63.07)	–0.008
HT	3643 (62.29)	1389 (65.52)	0.067	1419 (66.93)	1389 (65.52)	–0.029
DM	2314 (39.57)	921 (43.44)	0.079	949 (44.76)	921 (43.44)	–0.027
DL	3536 (60.47)	1345 (63.44)	0.061	1344 (63.40)	1345 (63.44)	0.001
CHF	1244 (21.27)	600 (28.30)	0.163	613 (28.92)	600 (28.30)	–0.014
CKD	316 (5.40)	148 (6.98)	0.065	144 (6.79)	148 (6.98)	0.008
Stroke	910 (15.56)	409 (19.29)	0.098	402 (18.96)	409 (19.29)	0.009
IHD	1110 (18.98)	519 (24.48)	0.134	507 (23.92)	519 (24.48)	0.014
Obesity	71 (1.21)	31 (1.46)	0.022	30 (1.42)	31 (1.46)	0.004
LC	90 (1.54)	38 (1.79)	0.020	43 (2.03)	38 (1.79)	–0.018
Af	318 (5.44)	170 (8.02)	0.103	173 (8.16)	170 (8.02)	–0.006
Medication use						
Metformin	432 (7.39)	186 (8.77)	0.051	195 (9.20)	186 (8.77)	–0.016
Statin	2233 (38.18)	902 (42.55)	0.089	901 (42.50)	902 (42.55)	0.001
Aspirin	459 (7.85)	249 (11.75)	0.131	241 (11.37)	249 (11.75)	0.013
NSAIDs	5110 (87.38)	1851 (87.31)	–0.002	1852 (87.36)	1851 (87.31)	–0.001

Af, atrial fibrillation; CHF, chronic heart failure; CKD, chronic kidney disease; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension; IHD, ischemic heart disease; LC, liver cirrhosis; NSAIDs, nonsteroidal anti-inflammatory drugs; PUD, peptic ulcer disease; SMD, standard mean difference.

effect of unmeasured confounders is estimated to be quite low. Third, it is important to note that our study exclusively focused on an almost single racial background in Japan, which may restrict the broader applicability of our findings. The pathogenesis of *Hp* infection, as well as the responsiveness to PPIs and PCABs, can vary among different countries. Therefore, further validation using data from diverse racial backgrounds across different countries is necessary to substantiate the generalizability of our study's outcomes. Fourth, the drug prescription data before the study periods were unavailable, and the study periods were relatively short. Future studies with extended observation periods are warranted. Fifth, it is noteworthy that this study exclusively incorporated vonoprazan among PCABs, which may constrain its generalizability because other PCABs such as linaprazan, soraprazan, revaprazan, tegoprazan, and fexuprazan exist. Consequently, further

Table 3. Association Between PCAB/H2RA/PPI Use and GC Development in the Matched Cohort

H2RA and PCAB matched cohort	Non-GC (n = 4179)	GC (n = 61)	Matched HR	*P* value
H2RA use	2099 (99.01)	21 (0.99)	1	
PCAB use	2080 (98.11)	40 (1.89)	1.92 (1.13–3.25)	**.016**
PPI and PCAB matched cohort	**Non-GC (n = 4155)**	**GC (n = 85)**	**Matched HR**	***P* value**
PPI use	2075 (97.88)	45 (2.12)	1	
PCAB use	2080 (98.11)	40 (1.89)	0.88 (0.58–1.35)	.569

NOTE. Bold font indicates $P < .050$.

Table 4. Association Between Duration/Dose of PCAB Use and GC Development in the H2RA/PCAB Matched Cohort

	Non-GC (n = 4179)	GC (n = 61)	HR adjusted with PS	*P* value	P_{trend}
H2RA use	2099 (99.01)	21 (0.99)	1		
PCAB use < 1y	398 (99.50)	2 (0.05)	0.54 (0.13–2.31)	.542	**.001**
1 y < PCAB use < 2 y	467 (98.11)	9 (1.89)	2.13 (0.98–4.65)	.058	
2 y < PCAB use < 3 y	348 (98.31)	6 (1.69)	1.81 (0.73–4.50)	.199	
3 y < PCAB use	867 (97.42)	23 (2.58)	2.36 (1.30–4.26)	**.005**	
H2RA use	2099 (99.01)	21 (0.99)	1		
Low-dose PCAB use	1343 (98.68)	18 (1.32)	1.32 (0.70–2.47)	.395	**.001**
High-dose PCAB use	737 (97.10)	22 (2.90)	3.01 (1.66–5.48)	**<.001**	

NOTE. Bold font indicates $P < .050$.

investigations are warranted to evaluate the class effect of PCABs in future research. Finally, the determination of successful *Hp* eradication may not be completely accurate because of the lack of laboratory data including *Hp* antigen in stool, antibody, and urea breath test. However, Japanese public insurance covered second regimens for all patients who failed to first regimens. Furthermore, the ratio of second regimen prescriptions compared with the first regimen in our database is approximately 15%, aligning with the rate of unsuccessful *Hp* eradication in Japan.[30] Hence, the majority of patients who do not successfully eradicate *Hp* with the initial regimen undergo a second regimen. Consequently, our criteria for successful *Hp* eradication should have reasonable reliability. However, further studies incorporating comprehensive laboratory data for detailed *Hp* profiles are necessary to validate these findings.

In conclusion, PCABs were associated with an increased risk for GC in *Hp*-eradicated patients, with duration/dose response effects. Although the effects of PCABs on GC risk in general population remains to be elucidated, greater attention should be given to long-term prescription of PCABs in patients after *Hp* eradication.

Table 5. Baseline Characteristics of PCAB/PPI Users Before and After Propensity Score Matching

	Before matching			After matching		
	PPI users (n = 9049)	PCAB users (n = 2120)	SMD	PPI users (n = 2120)	PCAB users (n = 2120)	SMD
Male	4116 (45.49)	972 (45.85)	0.007	969 (45.71)	972 (45.85)	0.003
Age, y	65.88±11.83	66.88±11.06	–0.119	66.88±11.13	66.88±11.06	0.027
Smoking	265 (4.53)	123 (5.80)	–0.016	129 (6.08)	123 (5.80)	–0.012
Alcohol	138 (2.36)	40 (1.89)	–0.040	42 (1.98)	40 (1.89)	–0.006
Comorbidities						
Gastric atrophy	3193 (35.29)	728 (34.34)	–0.020	723 (34.10)	728 (34.34)	0.005
PUD	5132 (56.71)	1337 (63.07)	0.130	1333 (62.88)	1337 (63.07)	0.004
HT	6426 (71.01)	1389 (65.52)	–0.118	1364 (64.34)	1389 (65.52)	0.025
DM	4349 (48.06)	921 (43.44)	–0.093	935 (44.10)	921 (43.44)	–0.013
DL	5998 (66.28)	1345 (63.44)	–0.060	1353 (63.82)	1345 (63.44)	–0.008
CHF	2831 (31.29)	600 (28.30)	–0.065	568 (26.79)	600 (28.30)	0.033
CKD	672 (7.43)	148 (6.98)	–0.017	133 (6.27)	148 (6.98)	0.027
Stroke	1875 (20.72)	409 (19.29)	–0.036	397 (18.73)	409 (19.29)	0.014
IHD	2593 (28.66)	519 (24.48)	–0.095	532 (25.09)	519 (24.48)	–0.014
Obesity	106 (1.17)	31 (1.46)	0.026	29 (1.37)	31 (1.46)	0.008
LC	198 (2.19)	38 (1.79)	–0.028	42 (1.98)	38 (1.79)	–0.014
Af	911 (10.07)	170 (8.02)	–0.072	177 (8.35)	170 (8.02)	–0.012
Medication use						
Metformin	863 (9.54)	186 (8.77)	–0.026	181 (8.54)	186 (8.77)	0.008
Statin	4133 (45.67)	902 (42.55)	–0.063	910 (42.92)	902 (42.55)	–0.008
Aspirin	1462 (16.16)	249 (11.75)	–0.128	242 (11.42)	249 (11.75)	0.010
NSAIDs	7933 (87.67)	1851 (87.31)	–0.011	1852 (87.36)	1851 (87.31)	–0.001

Af, atrial fibrillation; CHF, chronic heart failure; CKD, chronic kidney disease; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension; IHD, ischemic heart disease; LC, liver cirrhosis; NSAIDs, nonsteroidal anti-inflammatory drugs; PUD, peptic ulcer disease; SMD, standard mean difference.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2024.01.037.

References

1. Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2019;5:1749–1768.
2. Correa P, Piazuelo MB, Camargo MC. The future of gastric cancer prevention. Gastric Cancer 2004;7:9–16.
3. Ford AC, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut 2020;69:2113–2121.
4. Lee YC, Chiang TH, Chou CK, et al. Association between *Helicobacter pylori* eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology 2016; 150:1113–1124.
5. Choi IJ, Kook MC, Kim YI, et al. Helicobacter pylori therapy for the prevention of metachronous gastric cancer. N Engl J Med 2018;378:1085–1095.
6. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008;372:392–397.
7. Yan L, Chen Y, Chen F, et al. Effect of Helicobacter pylori eradication on gastric cancer prevention: updated report from a randomized controlled trial with 26.5 years of follow-up. Gastroenterology 2022;163:154–162.
8. Tan MC, Graham DY. Gastric cancer risk stratification and surveillance after Helicobacter pylori eradication: 2020. Gastrointest Endosc 2019;90:457–460.
9. Usui Y, Taniyama Y, Endo M, et al. Helicobacter pylori, homologous-recombination genes, and gastric cancer. N Engl J Med 2023;388:1181–1190.
10. Arai J, Aoki T, Sato M, et al. Machine learning-based personalized prediction of gastric cancer incidence using the endoscopic and histologic findings at the initial endoscopy. Gastrointest Endosc 2022;95:864–872.
11. Janarthanan S, Ditah I, Adler DG, et al. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol 2012;107:1001–1010.
12. Zhou B, Huang Y, Li H, et al. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 2016; 27:339–347.
13. Xie Y, Bowe B, Yan Y, et al. Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study. BMJ 2019;29:l1580.
14. Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia. JAMA Neurol 2016;73:410.
15. Cheung KS, Chan EW, Wong AYS, et al. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. Gut 2018;67:28–35.
16. Niikura R, Hayakawa Y, Hirata Y, et al. Long-term proton pump inhibitor use is a risk factor for gastric cancer after treatment for *Helicobacter pylori*: a retrospective cohort analysis. Gut 2018; 67:1908–1910.
17. Seo SI, Park CH, You SC, et al. Association between proton pump inhibitor use and gastric cancer: a population-based cohort study using two different types of nationwide databases in Korea. Gut 2021;70:2066–2075.
18. Arai J, Niikura R, Hayakawa Y, et al. OLGIM staging and proton pump inhibitor use predict the risk of gastric cancer. Gut 2022; 71:1043–1044.
19. Abrahami D, McDonald EG, Schnitzer ME, et al. Proton pump inhibitors and risk of gastric cancer: population-based cohort study. Gut 2022;71:16–24.
20. Arai J, Niikura R, Hayakawa Y, et al. Nonsteroidal anti-inflammatory drugs prevent gastric cancer associated with the use of proton pump inhibitors after *Helicobacter pylori* eradication. JGH Open 2021;5:770–777.
21. Gong EJ, Jung HK, Lee B, et al. Proton pump inhibitor use and the risk of metachronous gastric cancer after H. pylori eradication in patients who underwent endoscopic resection for gastric neoplasms: a population-based cohort study. Aliment Pharmacol Ther 2023;58:668–677.
22. Cheung KS, Leung WK. Long-term use of proton-pump inhibitors and risk of gastric cancer: a review of the current evidence. Therap Adv Gastroenterol 2019;12:1756284819834511.
23. Niikura R, Hayakawa Y, Hirata Y, et al. The reduction in gastric atrophy after Helicobacter pylori eradication is reduced by treatment with inhibitors of gastric acid secretion. Int J Mol Sci 2019;20:1913.
24. Waldum HL, Rehfeld JF. Gastric cancer and gastrin: on the interaction of *Helicobacter pylori* gastritis and acid inhibitory induced hypergastrinemia. Scand J Gastroenterol 2019;54:1118–1123.
25. Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, et al. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. Gut 2018;67:226–236.
26. Jackson MA, Goodrich JK, Maxan ME, et al. Proton pump inhibitors alter the composition of the gut microbiota. Gut 2016; 65:749–756.
27. Abuduwaili M, Boda T, Ito M, et al. Serum gastrin and pepsinogen levels after administration of acid secretion inhibitors for ulcers due to endoscopic submucosal dissection in patients with early gastric cancer. Gastroenterol Res Pract 2022;2022:2830227.
28. Hayakawa Y, Chang W, Jin G, et al. Gastrin and upper GI cancers. Curr Opin Pharmacol 2016;31:31–37.
29. Niikura R, Hayakawa Y, Nagata N, et al. Non-*Helicobacter pylori* gastric microbiome modulates prooncogenic responses and is associated with gastric cancer risk. Gastro Hep Advances 2023; 2:684–700.
30. Shichijo S, Hirata Y, Niikura R, et al. Vonoprazan versus conventional proton pump inhibitor-based triple therapy as first-line treatment against *Helicobacter pylori*: a multicenter retrospective study in clinical practice. J Dig Dis 2016;17:670–675.
31. Niikura R, Yamada A, Hirata Y, et al. Efficacy of vonoprazan for gastroesophageal reflux symptoms in patients with proton pump inhibitor-resistant nonerosive reflux disease. Intern Med 2018;57:2443–2450.
32. Okada Y, Inada K, Akazawa M. Comparative effectiveness of long-acting injectable antipsychotics in patients with schizophrenia in Japan. Schizophr Res 2023;252:300–308.
33. Ohbe H, Goto T, Okada A, et al. Association between COVID-19 pandemic and mental disorders in spouses of intensive care unit patients. Intensive Care Med 2023;49:112–114.

34. Konish T, Ono S, Okada A, et al. Comparison of bleeding following gastrointestinal endoscopic biopsy in patients treated with and without direct oral anticoagulants. Endosc Int Open 2023;11:E52–E59.
35. Okada A, Yasunag H. Prevalence of noncommunicable diseases in Japan using a newly developed administrative claims database covering young, middle-aged, and elderly people. JMA J 2022;5:190–198.
36. Ministry of Health, Labour and Welfare. An outline of the Japanese medical system. Available at: https://www.mhlw.go.jp/english/policy/health-medical/health-insurance/index.html. Accessed April 2, 2021.
37. Arai J, Hayakawa Y, Niikura R, et al. Letter: potassium-competitive acid blockers may increase the risk of gastric cancer after Helicobacter pylori eradication a retrospective multicentre-cohort analysis. Aliment Pharmacol Ther 2023;57:1196–1198.
38. Arai J, Niikura R, Hayakawa Y, et al. Association of probiotic use with nivolumab effectiveness against various cancers: a multicenter retrospective cohort study. Cancer Med 2023;12:16876–16880.
39. Arai J, Niikura R, Hayakawa Y, et al. Use of antibiotics and probiotics reduces the risk of metachronous gastric cancer after endoscopic resection. Biology (Basel) 2021;10:455.
40. Luise C, Sugiyama N, Morishima T, et al. Validity of claims-based algorithms for selected cancers in Japan: results from the VALIDATE-J study. Pharmacoepidemiol Drug Saf 2021;30:1153–1161.
41. Poulsen AH, Christensen S, McLaughlin JK, et al. Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. Br J Cancer 2009;100:1503–1507.
42. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–274.

Correspondence
Address correspondence to: Yoku Hayakawa, MD, PhD, Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. e-mail: yhayakawa-tky@umin.ac.jp. or Ryota Niikura, MD, PhD, Department of Endoscopy, Graduate School of Medicine, Tokyo Medical University, Shinjuku, Shinjuku-ku, Tokyo 160-8402, Japan. e-mail: niikura-dky@umin.ac.jp.

CRediT Authorship Contributions

Junya Arai, PhD, MD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Funding acquisition: Lead; Methodology: Lead; Visualization: Lead; Writing – original draft: Lead)

Atsushi Miyawaki (Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Equal)

Tomonori Aoki (Conceptualization: Equal; Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Equal)

Ryota Niikura (Conceptualization: Lead; Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Equal)

Yoku Hayakawa (Conceptualization: Equal; Formal analysis: Equal; Methodology: Equal; Supervision: Lead; Writing – review & editing: Equal)

Hiroaki Fujiwara (Writing – review & editing: Equal)

Sozaburo Ihara (Writing – review & editing: Equal)

Mitsuhiro Fujishiro (Writing – review & editing: Equal)

Masato Kasuga (Writing – review & editing: Equal)

Conflicts of interest
The authors disclose no conflicts.

Funding
Supported by Daiwa Securities Foundation (Junya Arai), KAKENHI Grants-in-Aid for Scientific Research (grant numbers 23H02744 (Yoku Hayakawa), 23K07448 (Ryota Niikura), Yakult Bio-Science Foundation, Mochida Memorial Foundation for Medical and Pharmaceutical Research, Yasuda Memorial Foundation, Ono Pharmaceutical Foundation for Oncology, Immunology, and Neurology, Eli Lilly Japan KK Inovation Research Grant 2023, Princess Takamatsu Cancer Research Fund, P-CREATE from AMED, and the Advanced Research and Development Programs for Medical Innovation (PRIME) (Yoku Hayakawa). The funding agencies had no role in the design of the study, data collection or analyses, decision to publish, or preparation of the manuscript.

Data Availability
Data supporting the findings of this study are available from the corresponding author upon reasonable request.

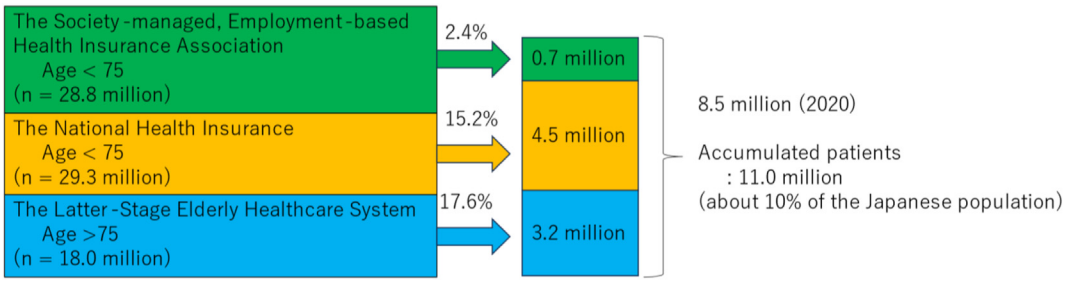
Supplementary Methods

Propensity Score Matching

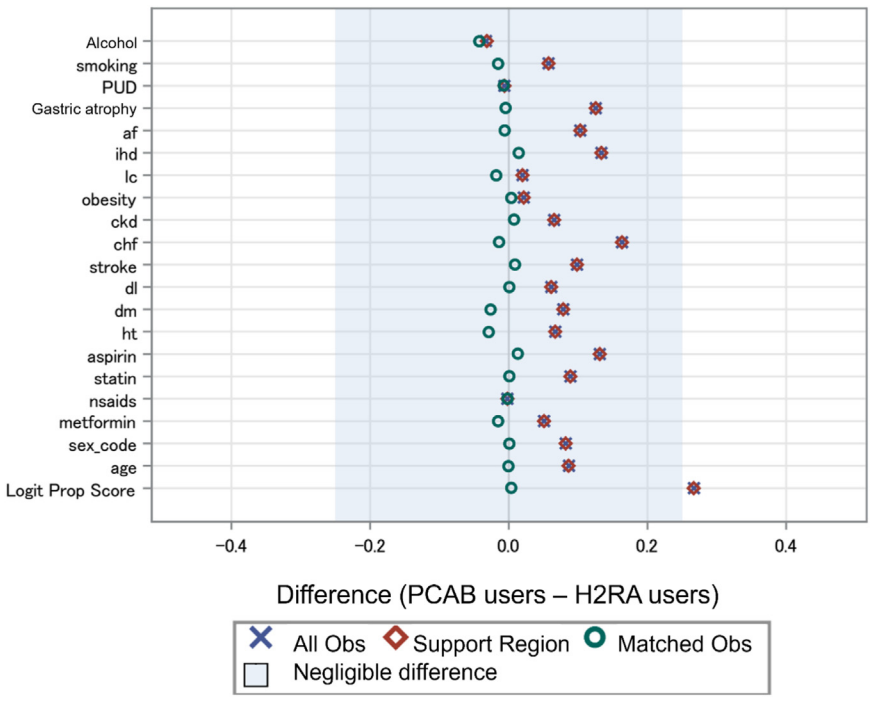
We conducted a one-to-one PS score matching analysis based on estimated PSs for each patient, pairing PCAB users with H2RA users and PPI users. This approach was conducted to achieve covariate balance between the 2 groups and avoid the problem of off-support inference, ie, the method focuses on common support regions (in contrast to multivariate adjustment) and does not depend on unreliable extrapolations in regions where the treatment and control groups have very different covariate distributions. To calculate the PS, we used a logistic regression model that considered patient demographic factors, including age, gender, smoking, alcohol consumption, 12 comorbidities, and 5 medications, to predict PCAB use as opposed to H2RA use and PPI use. For each PCAB user, an appropriate match from the H2RA and PPI user groups was identified. This matching process aimed to pair patients with the most similar estimated PSs on the logit scale, with the calliper widths set at $\leq$0.2 of the pooled standard deviation of estimated logits.[1] The distribution of PSs before and after matching is shown in Supplementary Figure 3.

Reference

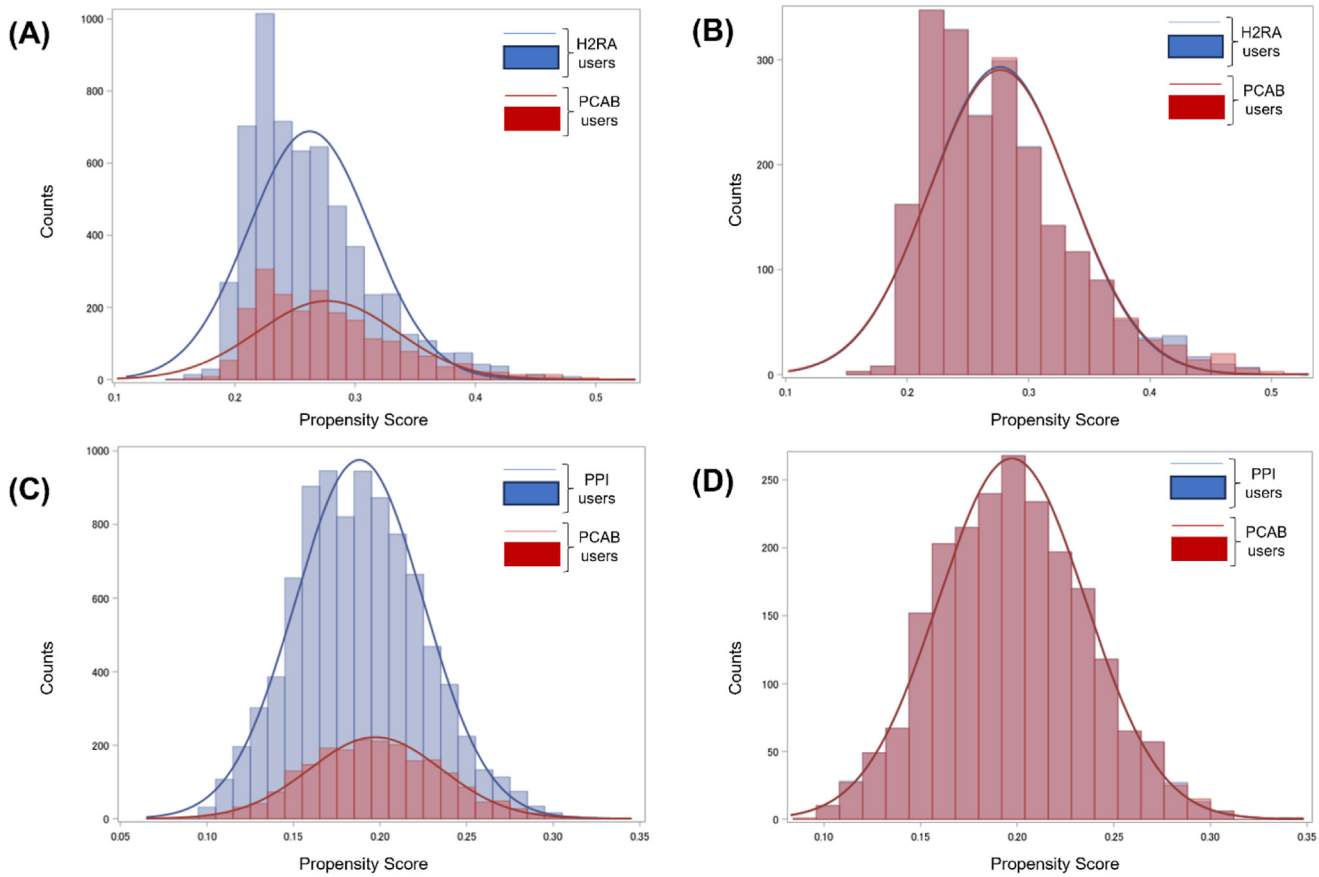
1. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharmaceut Stat 2011;10:150–161.



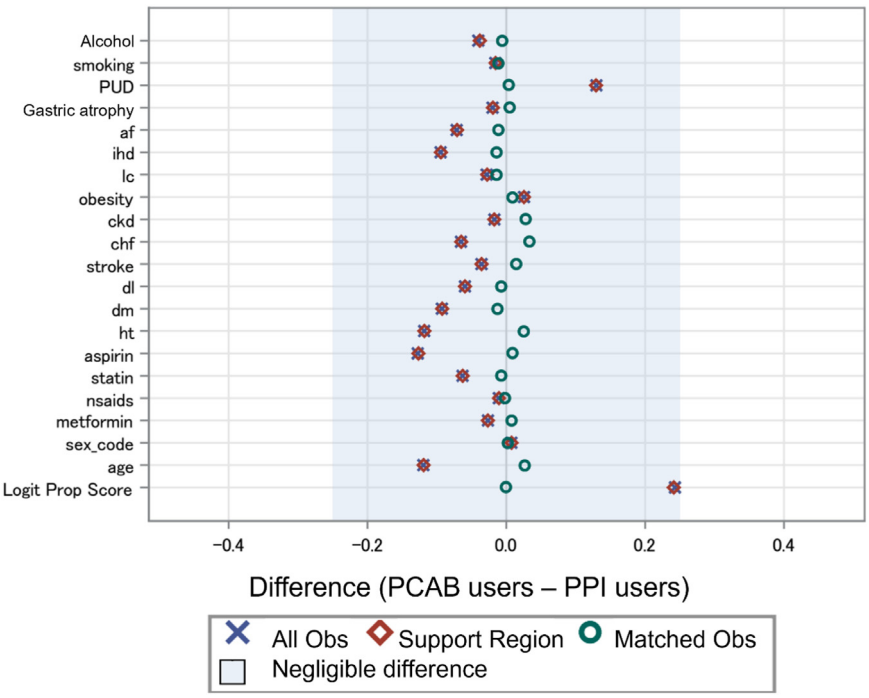
Supplementary Figure 1. The construction scheme of the database.



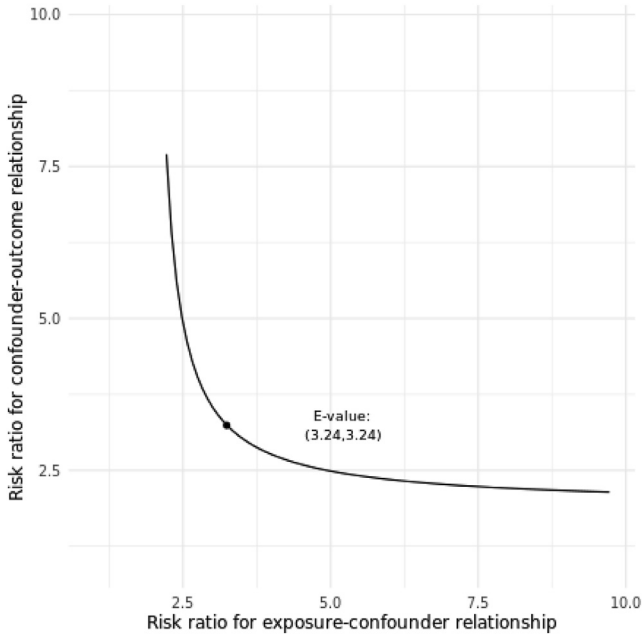
Supplementary Figure 2. Standardized differences plot for PCAB users and H2RA users before and after propensity score matching. af, atrial fibrillation; chf, chronic heart failure; ckd, chronic kidney disease; dl, dyslipidemia; dm, diabetes mellitus; ht, hypertension; ihd, ischemic heart disease; lc, liver cirrhosis; nsaids, nonsteroidal anti-inflammatory drugs; PUD, peptic ulcer disease.



Supplementary Figure 3. Distribution of propensity score for PCAB/H2RA users (*A*) before and (*B*) after matching and PCAB/PPI users (*C*) before and (*D*) after matching.



Supplementary Figure 4. Standardized differences plot for PCAB users and PPI users before and after propensity score matching. af, atrial fibrillation; chf, chronic heart failure; ckd, chronic kidney disease; dl, dyslipidemia; dm, diabetes mellitus; ht, hypertension; ihd, ischemic heart disease; lc, liver cirrhosis; nsaids, nonsteroidal anti-inflammatory drugs; PUD, peptic ulcer disease.



Supplementary Figure 5. Calculation of the E-value for the adjusted hazard ratio of PCAB use compared with H2RA use for gastric cancer incidence.

Supplementary Table 1. Specific Medication Lists That Are Included Under the PCAB, PPI, and H2RA Categories

Categories	Medication lists
PCAB	Vonoprazan
PPI	Esomeprazole, lansoprazole, omeprazole, rabeprazole
H2RA	Famotidine, ranitidine, cimetidine, roxatidine, nizatidine, lafutidine

Supplementary Table 2. Association Between PCAB Use and GC Development According to the Site of GC

	Non-GC at cardia (n = 4236)	GC at cardia (n = 4)	Matched HR	*P* value
H2RA use	2119 (99.95)	1 (0.05)	1	
PCAB use	2117 (99.86)	3 (0.14)	2.97 (0.31–28.57)	.346
	Non-GC at non-cardia (n = 4183)	GC at non-cardia (n = 57)	Matched HR	*P* value
H2RA use	2100 (99.06)	20 (0.94)	1	
PCAB use	2083 (98.25)	37 (1.75)	1.86 (1.08–3.21)	**.025**

NOTE. Bold font indicates $P < .050$.

Supplementary Table 3. Association Between PCAB and H2RA/PPI Use and GC Development in the Matched Cohort

H2RA and PCAB matched cohort	Non-GC (n = 4179)	GC (n = 61)	Death (n = 110)	Fine-Gray subdistribution HR	*P* value
H2RA use	2049 (96.65)	21 (0.99)	50 (2.36)	1	
PCAB use	2020 (95.28)	40 (1.89)	60 (2.83)	1.92 (1.13–3.25)	**.016**
PPI and PCAB matched cohort	Non-GC (n = 4155)	GC (n = 85)	Death (n = 149)	Fine-Gray subdistribution HR	*P* value
PPI use	1986 (93.68)	45 (2.12)	89 (4.20)	1	
PCAB use	2020 (95.28)	40 (1.89)	60 (2.83)	0.89 (0.58–1.36)	.586

NOTE. Bold font indicates $P < .050$.

Supplementary Table 4. Association Between PCAB/H2RA and GC Development in the Matched Cohort After Excluding Patients Whose Follow-up Period Was Less Than 2 Years

H2RA and PCAB matched cohort	Non-GC (n = 4042)	GC (n = 45)	Matched HR	*P* value
H2RA use	2007 (99.31)	14 (0.69)	1	
PCAB use	1990 (98.47)	31 (1.53)	2.25 (1.20–4.23)	**.012**

NOTE. Bold font indicates $P < .050$.