# LONG-TERM PROTON PUMP INHIBITORS AND RISK OF GASTRIC CANCER DEVELOPMENT AFTER TREATMENT FOR *H. PYLORI*: A POPULATION-BASED STUDY

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AF | Atrial fibrillation |
| CDARS | Clinical Data Analysis and Reporting System |
| CHF | Congestive heart failure |
| COX-2 | Cyclooxygenase-2 |
| CRF | Chronic renal failure |
| DM | Diabetes mellitus |
| DU | Duodenal ulcer |
| GC | Gastric cancer |
| GERD | Gastroesophageal reflux disease |
| GU | Gastric ulcer |
| HR | Hazard ratio |
| H2RA | Histamine 2-receptor antagonist |
| *H. pylori* | *Helicobacter pylori* |
| ICD-9 | International Classification of Diseases, Ninth Revision |
| IHD | Ischemic heart disease |
| IQR | Interquartile range |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| PPIs | Proton pump inhibitors |

## ABSTRACT

**Objective:** Proton pump inhibitors (PPIs) is associated with worsening of gastric atrophy, particularly in *H. pylori* (HP)-infected subjects. We determined the association between PPIs use and gastric cancer (GC) among HP-infected subjects who had received HP therapy.

**Designs:** This study was based on a territory-wide health database of Hong Kong. We identified adults who had received an outpatient prescription of clarithromycin-based triple therapy between year 2003 and 2012. Patients who failed this regimen, and those diagnosed to have GC within 12 months after HP therapy, or gastric ulcer after therapy were excluded. Prescriptions of PPIs or histamine-2 receptor antagonists (H2RA) started within 6 months before GC were excluded to avoid protopathic bias. We evaluated GC risk with PPIs by Cox proportional hazards model with propensity score adjustment. H2RA was used as a negative control exposure.

**Result:** Among the 63,397 eligible subjects, 153 (0.24%) developed GC during a median follow-up of 7.6 years. PPIs use was associated with an increased GC risk (HR 2.44; 95% CI 1.42–4.20), while H2RA was not (HR 0.72; 95% CI:0.48–1.07). The risk increased with duration of PPIs use (HR 5.04 [95% CI:1.23–20.61], 6.65 [95% CI:1.62–27.26] and 8.34 [95% CI:2.02–34.41] for ≥1 year, ≥ 2 years and ≥ 3

years, respectively). The adjusted absolute risk difference for PPIs versus non-PPIs use was 4.29 excess GC (95%:CI 1.25 to 9.54) per 10,000 person-years.

**Conclusion:** Long-term use of PPIs was still associated with an increased GC risk in subjects after HP eradication therapy.

## SIGNIFICANCE OF THIS STUDY

### What is already known on this subject?

- Although *Helicobacter pylori* (*H. pylori)* eradication has been shown to reduce the risk of gastric cancer development, a considerable proportion of these individuals continues to progress to gastric cancer even after successful eradication of *H. pylori.*
- Previous studies have shown that the risk of gastric cancer was increased by 43% among PPI users but the major confounding factor, *H. pylori,* was not adjusted in these analyses and the causal relationship may be biased.

### What are the new findings?

- Long-term PPI use was associated with a 2.4-fold increase in gastric cancer risk in *H. pylori*-infected subjects who had received eradication therapy.
- The risk of gastric cancer increases with the dose and duration of PPI use.

### How might it impact on clinical practice in the foreseeable future?

- Physicians should exercise cautions when prescribing long-term PPI to *H. pylori*-infected individuals even after successful eradication of *H. pylori*.

## INTRODUCTION

Gastric cancer is the third leading cause of cancer related mortality in the world.[1] Although *Helicobacter pylori* (*H. pylori)* eradication has been shown to reduce the risk of gastric cancer development by 33-47%[2, 3], a considerable proportion of these individuals continues to progress to gastric cancer even after eradication of *H. pylori*. Apart from baseline gastric histology at the time of eradication[4], data are sparse on other modifiable risks of gastric cancer development, particularly on the role of concurrent medications.

Proton pump inhibitors (PPIs) are among the most commonly prescribed medications in the world since the first PPI has become available in the 1980s.[5] Although PPIs are generally considered safe, recent data have demonstrated various adverse effects associated with long-term use of PPIs including bone fracture,[6] *Clostridium difficile* infection,[7] pneumonia,[8] myocardial infarction and even stroke.[9] Apart from the systemic adverse effects, there are also concerns on the long-term safety profile of PPIs in the stomach. The use of PPIs is associated with profound acid suppression, which could worsen atrophic gastritis.[10] The risk is considerably higher in individuals infected with *H. pylori* who are susceptible to the development of corpus atrophy.[11] Moreover, PPIs stimulate the production of gastrin, which is a potent growth factor,

and hypergastrinemia has been shown to induce hyperplasia of enterochromaffin-like cells.[11] A recent meta-analysis showed that the risk of gastric cancer is increased by 43% among PPI users.[12] However, these studies included both *H. pylori*-infected and *H. pylori*-negative subjects. Although previous short-term studies had suggested the resolution of corpus atrophy with *H. pylori* eradication therapy in patients with gastroesophageal reflux disease[13, 14], it remains uncertain whether the potential risk of PPIs on gastric cancer development could be eliminated by clearance of *H. pylori*.

This population-based study aimed to determine the risk of gastric cancer development among individuals who had received treatment for *H. pylori* with focus on the role of long-term PPIs.

## METHODS

### Data source

Data were retrieved from Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The Hospital Authority is the sole public healthcare provider for primary, secondary and tertiary health services through 7 hospital clusters and covers 87-94 % of all secondary and tertiary care in Hong Kong with a population of around 7.3 million.[15] Under this system, there are altogether 42 public hospitals, 47 specialist out-patient clinics and 73 general out-patient clinics. All essential clinical information including patients' demographics, hospitalization, visits to outpatient clinics and emergency departments, diagnoses, laboratory results, procedures, prescriptions, dispensing of medications and death are recorded in CDARS, which is an electronic database managed by the HA. This database was established in 1995 for both audit and research purposes. To protect patient's confidentiality, each patient is assigned a unique, anonymous patient identifier, which is linked to all the clinical data contained in CDARS. A number of high-quality, population-based studies[16-18] and multinational pharmacovigilance studies[19, 20] have been conducted based on the data retrieved from CDARS. The International Classification of Diseases, Ninth Revision (ICD-9) was used for disease coding and previous studies have verified the accuracy of the coding in CDARS with high

positive and negative predictive values of more than 90%.[17, 21] The study protocol was approved by the Institutional Review Board of the University of Hong Kong and the West Cluster of Hospital Authority, Hong Kong (reference no: UW 16-545).

**Study Subjects**

We identified all adult patients who were aged 18 years or above and had been prescribed a minimum of 7-day course of clarithromycin-based triple therapy for *H. pylori* infection in outpatient clinics between 1 January 2003 and 31 December 2012. *H. pylori* infection was diagnosed by either upper endoscopy with biopsy based tests or urea breath test in this study, as serology and stool antigen tests were not available in the public hospitals in Hong Kong. The prescription of clarithromycin-based triple therapy was identified by the co-prescription of one of the proton pump inhibitors (PPIs) with clarithromycin and either amoxicillin or metronidazole, with doses as described previously.[22] The start date of the prescriptions should be the same, with an overlapping duration of seven to 14 days. Clarithromycin-based triple therapy was the first-line therapy for *H. pylori* in Hong Kong during the study period due to the low clarithromycin resistance rate (8%)[23] and overall high eradication rate (> 90%).[24] To remove the confounding effects of symptoms from gastric cancer leading to the use of PPIs or histamine 2-receptor antagonist (H2RA) (i.e. protopathic bias), prescriptions

of these agents started within six months prior to the gastric cancer diagnosis were excluded from analyses.[25, 26]

Since gastric cancer can masquerade as non-healing ulcer, all patients with gastric ulcer diagnosed at the time of or any time after receiving triple therapy were excluded. As there may be a delay in the diagnosis of gastric cancer, patients who developed gastric cancer within the first year of *H. pylori* eradication therapy were excluded. Patients with history of gastric cancer, previous gastrectomy or those who failed triple therapy were also excluded to ensure homogeneity of our study cohort. We defined failure of *H. pylori* eradication therapy as the requirement of subsequent prescriptions of (a) repeated course of clarithromycin-based triple therapy; (b) a second-line therapy (bismuth-based quadruple therapy or PPI-levofloxacin-amoxycillin); or (c) a third-line therapy (rifabutin-based therapy). **Figure 1** illustrates the inclusion and exclusion process of patients in this study. The time frame of the study is shown in **eFigure 1**.

**Outcomes**

The primary outcome was the development of gastric adenocarcinoma. The observation period commenced from the date of first triple therapy prescription (i.e.

index date) and was censored at the date of diagnosis of gastric cancer, death, or end of the study (31 December 2015). The date of diagnosis of gastric cancer was defined as the first date of hospitalization for gastric cancer workup or treatment. Follow-up duration of individual patient was defined as the duration of observation between the index date and the censored date. All cases of gastric adenocarcinoma were identified in accordance with the ICD-9 (International Classification of Diseases, ninth revisions) (**eTable 1**). We excluded patients with diagnosis of gastric lymphoma in this study. In order to ensure the validity of the case definition, a list of diagnostic codes was reviewed and finalized by a group of gastroenterologists.

**Study variables**

The primary exposure of interest was the subsequent prescription of PPIs after receiving the triple therapy for *H. pylori*. Potential confounders for gastric cancer development were also evaluated including the age of receiving triple therapy, sex, smoking status, alcohol consumption, past history of gastric ulcer, past history of duodenal ulcer, other comorbidities (including diabetes mellitus, hypertension, dyslipidemia, obesity, ischemic heart disease, atrial fibrillation, congestive heart failure, stroke, chronic renal failure and cirrhosis) and uses of various medications

including statin, metformin, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, clopidogrel and H2RA.

PPIs are much more potent than H2RA in terms of gastric acid suppression,[27] and previous studies did not reveal any association between gastric cancer development and H2RA.[25, 28, 29] Hence, H2RA was selected as a negative control exposure in our study. If there is a positive association between H2RA and gastric cancer, this will suggest some unmeasured factors that confound the causal relationship between PPIs and gastric cancer development including protopathic bias.

To further control for possible confounding effects, another cohort of PPIs users (at least weekly use) who had not received *H. pylori* eradication therapy and fulfilled the same inclusion and exclusion criteria as our *H. pylori* eradication cohort was recruited for comparison. These PPI users who had not received *H. pylori* eradication therapy were then matched with the PPI users who had received *H. pylori* eradication therapy (n = 3,271) by age (+/- 5 years), sex, duration of follow-up (+/- 2 years) and frequency of PPI use (+/- 0.3) in a 1:4 ratio. The incidence rates of gastric cancer in the two PPI cohorts were then compared.

We used similar approaches as adopted by Poulsen et al[28] to ascertain smoking status and alcohol consumption as these data was not available in the CDRAS. Smoking was identified by the ICD-9 code of V15.82 while chronic obstructive pulmonary disease (COPD) (ICD-9 codes: 491, 492, 496) was also used as proxy of heavy smoking. Heavy alcohol consumption was identified by alcohol-related diseases, including hepatic and gastrointestinal diseases, neurological and psychiatric diseases (ICD-9: 291, 303, 305.0, 571, 980). The diagnostic codes of other variables are listed in **eTable 1**.

In the primary analysis, the exposure categories of various medications were categorized similarly into non-regular use (<weekly use; reference group) and regular use (at least weekly use) as described by Thrift et al.[30] The treatment duration of each prescription of a particular medication was defined as the difference between the prescription start date and end date within the observation period. The total treatment duration of that particular medication was then calculated by summing up the treatment duration of each prescription.

To study the dose-response relationship of PPIs on gastric cancer, the frequency of PPIs use was classified into three groups: (i) <weekly use, (ii) weekly to <daily use

and (iii) daily use. The frequency of PPIs use was calculated by dividing the total treatment duration by the duration of follow-up. The effect of PPIs was also studied with regard to the duration of therapy into ≥ 1 year, ≥ 2 years and ≥ 3 years as defined in a recent meta-analysis.[12]

**Data validation**

As individual's identification is anonymized in the electronic database (CDARS), we could only retrieve detailed information of individual gastric cancer cases who were managed in our centre (Queen Mary Hospital), which is a tertiary referral centre and a university teaching hospital. Of the 153 gastric cancer cases, 12 cases were managed in our centre and were reviewed in details for gastric histology.

**Statistical analyses**

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing) statistical software. Continuous variables were expressed as median and interquartile range (IQR). Mann-Whitney U-test was used to compare continuous variables of two groups. Chi-square test or Fisher's exact test was applied for categorical variables. Cox proportional hazards model was used to estimate the crude and adjusted hazard ratio (HR) of gastric cancer development with PPIs use. To

control for the confounders, propensity score adjustment was performed. Propensity scores were derived from logistic regression to represent the conditional probability of PPIs use given the other variables (age, sex, comorbidities and concomitant medications). To further reduce the bias from unmeasured confounding, individuals with extreme scores in the upper and lower tails of the propensity score distribution were excluded.[31] In order to establish the cut-points for trimming, we constructed 20 categories of 5% each for the distribution of scores.

In the primary analysis, the first and 20$^{th}$ propensity score strata were trimmed, and the estimated propensity score was then used as an adjustment variable in the Cox proportional hazards model to derive the HR (propensity score adjustment with trimming). A sensitivity analysis was also performed without trimming the extreme propensity score strata (propensity score adjustment without trimming). In addition, the HR by univariate and multivariable analyses (with all covariates included) from Cox proportional hazards model were presented. For subgroup analysis, the risk of gastric cancer with PPIs use was stratified according to the tumour sites (cardia and non-cardia regions). Moreover, we estimated the propensity score adjusted absolute difference in gastric cancer risk for PPIs vs non-PPIs use by the adjusted HR minus 1, followed by the multiplication of the crude incidence rates among patients who did

not use PPIs.[32] As H2RA was selected as a negative control exposure, propensity scores were also derived from logistic regression to represent the conditional probability of H2RA use given the other variables. The HR of gastric cancer with H2RA was determined by propensity score adjustment after trimming. All statistical tests were two-sided, and a p-value of <0.05 was used to define statistical significance.

## RESULTS

### Patient Characteristics

A total of 74,612 subjects had received clarithromycin-based triple therapy during the 10-year period. After excluding patients who did not fulfil our inclusion criteria (**Figure 1**), 63,397 subjects were included in the final analysis. The median age of this cohort at the time of *H. pylori* eradication therapy was 54.7 years (IQR: 46.0 – 65.4 years) and 46.5% were men. The median follow-up was 7.6 years (IQR: 5.1 – 10.3 yeas) and the total follow-up duration was 483,259 person-years. The baseline characteristics of the whole cohort and the subgroups according to PPIs and H2RA use are shown in **Tables 1 and 2** .

### Risk of Gastric Cancer Development

One hundred and fifty-three (0.24%) subjects developed gastric cancer after *H. pylori* eradication therapy. Among them, 31 (20.3 %) cancer were in the cardia and 95 (62.1 %) in the non-cardia regions. The sites were not specified in the remaining 27 (17.6%) cases (ICD-9: 151.9). Similar ratio were observed for all the stomach cancer cases (n=12,898) diagnosed in Hong Kong during the study period (13.4% in cardia, 67.5% in non-cardia and 19.1% cases with sites unspecified).

Twelve out of 153 patients (7.8%) with gastric cancer who fulfilled the inclusion and exclusion criteria from our centre were verified for histological findings. All patients were negative for *H. pylori* on gastric biopsies at the time of diagnosis and had underlying chronic gastritis, while intestinal metaplasia was reported in 5 cases.

The median age at cancer diagnosis was 71.4 years (IQR 61.1 – 81.5 years). Patients who developed gastric cancer received *H. pylori* eradication therapy at a median age of 65.4 years (IQR 56.4 – 76.2 years), and the median time from *H. pylori* treatment to cancer development was 4.9 years (IQR: 2.7 – 7.2 years). The overall incidence rate of gastric cancer in this cohort was 3.2 per 10,000 person-years. The incidence rate of gastric cancer for each year is shown in **eTable 2**, which ranged from 2.5 to 5.8 per 10,000 person-years. Notably, there were no gastric cancer cases within the first year of follow-up, as these cases were excluded.

**Association of PPIs use and risk of gastric cancer**

**Table 3** and **eTable 3** show the associations between PPIs use and gastric cancer development after *H. pylori* therapy. PPIs users (at least weekly use) were found to have a higher risk of gastric cancer (HR 2.44, 95% CI 1.42 – 4.20) after propensity score adjustment with trimming. Sensitivity analysis confirms the association of PPIs

use with gastric cancer development by either multivariable analysis (HR 2.19, 95% CI 1.31 – 3.66) or propensity score adjustment without trimming (HR 2.14, 95% CI 1.27 – 3.58).

The propensity score adjusted absolute risk difference for PPIs use compared with non-PPIs use was 4.29 excess gastric cancer (95% CI 1.25 to 9.54) per 10,000 person-years.

After stratification by the site of tumour, PPIs use was only found to be significantly associated with an increased risk of non-cardia gastric cancer (HR 2.59, 95% CI 1.42 – 4.72) but not cardia cancer (HR 1.97, 95% CI 0.57 – 6.82). Sensitivity analysis yielded similar results.

**Frequency and duration of PPIs use on risk of gastric cancer**

A total of 3,271 (5.2%) patients in this cohort had used PPIs and the median duration of PPI use was 2.7 years (IQR: 1.5 – 5.1 years). Among them, 19 (0.6%) developed gastric cancer (8.1 per 10,000 person-years). We further determined the frequency and duration of PPIs use on gastric cancer development. Patients were first stratified according to the frequency of PPI use (**Table 4**) into three groups as described in the Method section. When compared with the reference group (< weekly use), there was a

progressive increase in the risk of gastric cancer with more frequent use of PPIs (HR 2.43 [95% CI 1.37 – 4.31] for "weekly to < daily use", and HR 4.55 [95% CI 1.12 – 18.52] for "daily use"). Sensitivity analysis yielded similar results **(eTables 2 and 3)**. Furthermore, the effect of long-term PPIs on gastric cancer development was studied with regard to the duration of PPIs therapy (≥ 1 year, ≥ 2 years and ≥ 3 years). As shown in **Table 4**, the risk increased with longer duration of PPIs use (HR 5.04 [95% CI 1.23 – 20.61] for at least 1 year of use; HR 6.65 [95% CI 1.62 – 27.26] for at least 2 years of use and HR 8.34 [95% CI 2.02 – 34.41] for at least 3 years of use).

**Association of H2RA use and risk of gastric cancer**

To test for potential confounding, H2RA was used as a negative control exposure. The HR of gastric cancer with H2RA use on univariate analysis was 0.95 (95% CI 0.67 – 1.33), while the HR from propensity score adjustment with trimming was 0.72 (95% CI 0.48 – 1.07).

**Comparison of the incidence rates of gastric cancer with a matched cohort of PPIs users who had not received *H. pylori* eradication therapy**

To further check for potential confounding, another cohort of PPI users (at least weekly use) who had not received *H. pylori* eradication therapy were included for

comparison. Altogether, 142,460 PPI users without *H. pylori* eradication therapy were identified with a total of 705,094 person-years follow-up. Among them, there were 59 gastric cancer cases making a crude incidence rate of 0.8 cases per 10,000 person-years. After matching, the incidence rate was 8.1 case per 10,000 person-years and 1.0 cases per 10,000 person-years in the two cohorts of PPIs users with and without *H. pylori* eradication therapy, respectively (incidence rate ratio 0.12; 95% CI 0.05 – 0.26) (**Table 5**).

## DISCUSSION

In this population-based study that addressed the risk of gastric cancer development in *H. pylori*-infected individuals after receiving eradication treatment, we found that long-term use of PPIs increased the risk of gastric cancer development. Our results showed that even after apparent successful *H. pylori* eradication therapy, those who used long term PPIs had a 2.4-fold increase in risk of gastric cancer development than non-users. This increase in risk was not observed among H2RA users. Further analysis demonstrated a dose- and time-dependent increase in the HRs of gastric cancer with PPIs use, with the highest risk observed in daily users of PPIs (HR 4.55). Patients who took PPIs daily for at least three years were at the highest risk (HR 8.34). Notably, the increase in HR was limited to non-cardia cancer, although this result should be interpreted with caution as this subgroup analysis has a relatively small number of cardia cancers.

Gastric atrophy is generally considered to be a precursor of gastric cancer, which is usually associated with chronic *H. pylori* infection. While PPIs are potent acid suppressors, there have been concerns on the possible worsening of gastric atrophy by long term PPIs and the associated increase in gastric cancer risk.[10, 12] Most published data supported that long term PPIs could worsen corpus gastritis and atrophy, particularly in *H. pylori*-positive subjects.[10, 33] Although the long-term use of PPIs for

more than 12 months was shown to be associated with an increased risk of gastric cancer,[12] these results are largely confounded by the unknown prevalence of *H. pylori* in the study population.[25, 28, 29] On the other hand, treatment of *H. pylori* in patients with reflux esophagitis requiring long-term PPIs was found to eliminate gastric mucosal inflammation and possibly induce regression of corpus glandular atrophy.[13] Hence, current guideline recommends eradication of *H. pylori* prior to the initiation of long-term PPIs.[34] Whilst gastroesophageal reflux is related to over-production of gastric acid and hence a lower prevalence of corpus atrophy, these patients may not be the ideal population to study relationship between PPI use and worsening of corpus atrophy and gastric cancer. There is so far no long-term data to support that *H. pylori* eradication is sufficient in preventing cancer development in these individuals who use long-term PPIs.

To our knowledge, this is the first study to demonstrate that long-term PPIs use, even after *H. pylori* eradication therapy, is still associated with an increased risk of gastric cancer. This is likely related to the profound acid suppression of PPIs that worsens atrophic gastritis, particularly in those patients with established gastric atrophy as a result of chronic *H. pylori*-induced inflammation. The lack of association between H2RA uses and gastric cancer development further supports the specific role of PPIs

on gastric cancer development. One of the strengths of our study is the use of data from population-based database with complete information on subsequent diagnoses and drug prescriptions, thus minimizing the selection, information and recall biases. As all medications are dispensed by the hospital pharmacy at a very low cost to patients (i.e. £1 per item for 16 weeks), the prescription records are expected to be identical to dispensing records. The large sample size and the relatively long duration of follow-up (median 7.6 years) allow for more precise effect estimation of gastric cancer risk attributed to various factors, and enable subgroup analysis. The association was also consistent in both the frequency and duration of PPIs treatment which demonstrated a dose- and time-response trend suggestive of a cause-effect relationship.

Another strength of this study was the use of a strict exclusion criteria as well as propensity score adjustment to control for potential confounders in determining the causal relationship between PPIs use and gastric cancer development. The results remained significant by various sensitivity analyses. In addition, we recruited patients with successful *H. pylori* eradication only. In fact, failure to adjust for *H. pylori* infection is one of the major concerns in studying the effect of PPIs on gastric cancer risk in previous studies.[25, 28, 29] The indication bias and protopathic bias was another

major concern that leads to the undetermined conclusion of the causal relationship between PPIs use and gastric cancer development in previous studies.[25, 28, 29] First, as gastric cancer can present with dyspepsia leading to an increase use of PPIs, all prescriptions of PPIs in the six months preceding the diagnosis of gastric cancer were excluded to avoid protopathic bias in this study. We used six months as the priori cut-off because previous study that specifically addressed the issue of protopathic bias showed that this was the most appropriate lag-time to be applied for the assessment of PPIs exposure on gastric cancer risk in pharmaco-epidemiological studies.[26] Moreover, PPIs are not approved as first-line therapy for dyspepsia in the Hong Kong Hospital Authority, and H2RAs are usually the recommended treatment for this indication. One would anticipate a similar increase in gastric cancer risk among those taking H2RAs (negative control exposure) if there was significant indication bias in this cohort. The minimization of protopathic bias and indication bias was further supported by the findings that the matched cohort of PPIs users without *H. pylori* eradication therapy had the lowest incidence rate when compared to the two post-*H. pylori* eradicated cohorts **(Table 5)**. By comparing the incidence rate of gastric cancer of a matched cohort of PPIs users who had not received *H. pylori* eradication therapy, we showed that *H. pylori* infection, even prior infection, was a more important factor than PPIs use in determining gastric cancer risk. PPIs increase the risk of gastric

cancer development likely only in the context of underlying H. pylori-associated chronic gastritis and atrophy only. Second, we excluded patients who had active gastric ulcer diagnosed at the time of *H. pylori* eradication therapy or during surveillance intervals as gastric cancer may masquerade as non-healing gastric ulcer.

Our study has several limitations. First, the information of some risk factors (e.g. diet, family history and socioeconomic status) could not be obtained from the electronic database. Second, the identification of certain parameters (smoking, alcohol use and obesity) via coding may underestimate their true prevalence, as only patients who had heavy consumption of smoking and alcohol or who were morbidly obese would be coded. Third, although patients who failed triple therapy were identified by the repeated prescription of clarithromycin-based triple therapy or prescription of second and third line therapies, it remained possible that a small proportion of patients who failed *H. pylori* eradication therapy might be missed. In this study, about 13.2% of patients had received a second course of eradication therapy which was compatible with the observed success rate of clarithromycin-based triple therapy in our population with relatively low prevalence of clarithromycin resistance during the study period.[23] In addition, we have validated the negative *H. pylori* status of all 12 gastric cancer cases from our hospital. Fourth, although we included more than

63,000 *H. pylori*-infected subjects, the small number of gastric cancer cases did not allow for any meaningful evaluation of the dosage effect and role of different PPIs. However, it was recently shown that there was no difference in the gastric cancer risk between longer and shorter-acting PPIs.[35] Fourth, PPIs users may have a higher chance to undergo endoscopy than non-PPI users, and therefore surveillance bias may lead to a higher risk of gastric cancer as observed in current study. However, as shown in eTable

Lastly, the detailed histological findings of gastric biopsies at baseline and at the time of gastric cancer development were not available in the CDARS, precluding more in-depth analysis between the association of PPIs and baseline histology on gastric cancer development.

## CONCLUSION

Long-term use of PPIs in subjects with prior *H. pylori* eradication was still associated with an increased risk of gastric cancer development, particularly for non-cardia cancer. There was also a clear dose- and time-response trend of PPI uses and gastric cancer risk. Physicians should therefore exercise cautions when prescribing long-term PPIs to these patients even after successful eradication of *H. pylori*.

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**FIGURE LEGEND**

**Figure 1: Study patient selection flow diagram**

Abbreviations: GC, gastric cancer; GU, gastric ulcer

**Table 1. Characteristics of PPI and non-PPI users**

| | All (n=63,397) | PPI users (n=3,271) | Non-PPI users (n=60,126) |
|---|---|---|---|
| Age at triple therapy (years)* | 54.7 (46.0 – 65.4) | 64.1 (53.6 – 75.3) | 54.3 (45.7 – 64.7) |
| Male sex (n, %) | 29499 (46.5%) | 1641 (50.2%) | 27858 (46.3%) |
| Duration of follow-up (years)* | 7.6 (5.1 – 10.3) | 7.4 (4.5 – 10.0) | 7.6 (5.2 – 10.3) |
| Smoking (n, %) | 1629 (2.6%) | 162 (5.0%) | 1467 (2.4%) |
| Alcohol (n, %) | 552 (0.9%) | 50 (1.5%) | 502 (0.8%) |
| Dyspepsia (n, %) | 4145 (6.5%) | 262 (8.0%) | 3883 (6.5%) |
| GERD (n, %) | 3278 (5.2%) | 593 (18.1%) | 2685 (4.5%) |
| History of GU (n, %) | 1268 (2.0%) | 153 (4.7%) | 1115 (1.9%) |
| History of DU (n, %) | 1897 (3.0%) | 139 (4.2%) | 1758 (2.9%) |
| DM (n, %) | 7383 (11.6%) | 772 (23.6%) | 6611 (11.0%) |
| Hypertension (n, %) | 13065 (20.6%) | 1334 (40.8%) | 11731 (19.5%) |
| Dyslipidemia (n, %) | 5045 (8.0%) | 579 (17.7%) | 4466 (7.4%) |
| Obesity | 637 (1.0%) | 61 (1.9%) | 576 (1.0%) |
| IHD (n, %) | 5701 (9.0%) | 906 (27.7%) | 4795 (8.0%) |
| AF (n, %) | 2404 (3.8%) | 371 (11.3%) | 2033 (3.4%) |
| CHF (n, %) | 2512 (4.0%) | 463 (14.2%) | 2049 (3.4%) |
| Stroke (n, %) | 3965 (6.3%) | 561 (17.2%) | 3404 (5.7%) |
| CRF (n, %) | 1388 (2.2%) | 236 (7.2%) | 1152 (1.9%) |
| Cirrhosis (n, %) | 1037 (1.6%) | 98 (3.0%) | 939 (1.6%) |
| Statins (n, %) | 13180 (20.8%) | 1351 (41.3%) | 11829 (19.7%) |
| Metformin (n, %) | 7935 (12.5%) | 605 (18.5%) | 7330 (12.2%) |
| Aspirin (n, %) | 8965 (14.1%) | 1358 (41.5%) | 7607 (12.7%) |
| NSAIDs/ COX-2 inhibitors (n, %) | 3556 (5.6%) | 391 (12.0%) | 3165 (5.3%) |
| Clopidogrel (n, %) | 980 (1.5%) | 200 (6.1%) | 780 (1.3%) |
| H2RA (n, %) | 21729 (34.3%) | 1499 (45.8%) | 20230 (33.6%) |

* Age was expressed as median (years) with interquartile range
Categorical variables were expressed as number (%)
Drug use was defined as at least weekly use, and expressed as number (%)
PPIs, proton pump inhibitors; GERD, gastroesophageal reflux disease; GU, gastric ulcer; DU, duodenal ulcer; DM, diabetes mellitus; IHD, ischemic heart disease; AF, atrial fibrillation; CHF, congestive heart failure; CRF, chronic renal failure; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; H2RA, histamine 2 receptor antagonist

**Table 2. Characteristics of H2RA and non-H2RA users**

| | All (n=63,397) | H2RA users (n=21,729) | Non- H2RA users (n=41,668) |
|---|---|---|---|
| Age at triple therapy (years)* | 54.7 (46.0 – 65.4) | 60.0 (51.6 – 71.0) | 52.0 (43.4 – 61.6) |
| Male sex (n, %) | 29499 (46.5%) | 9454 (43.5%) | 20045 (48.1%) |
| Duration of follow-up (years)* | 7.6 (5.1 – 10.3) | 7.2 (4.8 – 9.8) | 7.8 (5.3 – 10.5) |
| Smoking (n, %) | 1629 (2.6%) | 863 (4.0%) | 766 (1.8%) |
| Alcohol (n, %) | 552 (0.9%) | 232 (1.1%) | 320 (0.8%) |
| Dyspepsia (n, %) | 4145 (6.5%) | 1826 (8.4%) | 2319 (5.6%) |
| GERD (n, %) | 3278 (5.2%) | 1629 (7.5%) | 1649 (4.0%) |
| History of GU (n, %) | 1268 (2.0%) | 446 (2.1%) | 822 (2.0%) |
| History of DU (n, %) | 1897 (3.0%) | 503 (2.3%) | 1394 (3.3%) |
| DM (n, %) | 7383 (11.6%) | 3885 (17.9%) | 3498 (8.4%) |
| Hypertension (n, %) | 13065 (20.6%) | 7137 (32.8%) | 5928 (14.2%) |
| Dyslipidemia (n, %) | 5045 (8.0%) | 2939 (13.5%) | 2106 (5.1%) |
| Obesity | 637 (1.0%) | 351 (1.6%) | 286 (0.7%) |
| IHD (n, %) | 5701 (9.0%) | 3560 (16.4%) | 2141 (5.1%) |
| AF (n, %) | 2404 (3.8%) | 1468 (6.8%) | 936 (2.2%) |
| CHF (n, %) | 2512 (4.0%) | 1512 (7.0%) | 1000 (2.4%) |
| Stroke (n, %) | 3965 (6.3%) | 2466 (11.3%) | 1499 (3.6%) |
| CRF (n, %) | 1388 (2.2%) | 814 (3.7%) | 574 (1.4%) |
| Cirrhosis (n, %) | 1037 (1.6%) | 425 (2.0%) | 612 (1.5%) |
| Statins (n, %) | 13180 (20.8%) | 7401 (34.1%) | 5779 (13.9%) |
| Metformin (n, %) | 7935 (12.5%) | 3899 (17.9%) | 4036 (9.7%) |
| Aspirin (n, %) | 8965 (14.1%) | 6376 (29.3%) | 2589 (6.2%) |
| NSAIDs/ COX-2 inhibitors (n, %) | 3556 (5.6%) | 3092 (14.2%) | 464 (1.1%) |
| Clopidogrel (n, %) | 980 (1.5%) | 602 (2.8%) | 378 (0.9%) |
| PPIs (n, %) | 3271 (5.2%) | 1499 (6.9%) | 1772 (4.3%) |

* Age was expressed as median (years) with interquartile range
Categorical variables were expressed as number (%)
Drug use was defined as at least weekly use, and expressed as number (%)
H2RA, histamine 2 receptor antagonist; GERD, gastroesophageal reflux disease; GU, gastric ulcer; DU, duodenal ulcer; DM, diabetes mellitus; IHD, ischemic heart disease; AF, atrial fibrillation; CHF, congestive heart failure; CRF, chronic renal failure; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; PPIs, proton pump inhibitors;

**Table 3. Association between PPI use and risk of gastric cancer for the whole cohort and according to gastric cancer sites (non-cardia and cardia regions)**

| PPI frequency | Univariate analysis | | | Multivariable analysis | | | PS adjustment without trimming | | | PS adjustment with trimming | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **All GC** | **(n=63,397, GC=153)** | | | **(n=63,397, GC=153)** | | | **(n=63,397, GC=153)** | | | **(n=57,057, GC=139)** | | |
| | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** |
| Non-user (<weekly use) | Ref | - | - | Ref | - | - | Ref | - | - | Ref | - | - |
| At least weekly | 2.80 | 1.73 – 4.52 | **0.003** | 2.19 | 1.31 – 3.66 | **0.003** | 2.14 | 1.27 – 3.58 | **0.004** | 2.44 | 1.42 – 4.20 | **0.002** |
| **Non-cardia GC** | **(n=63,366, GC=122)** | | | **(n=63,366, GC=122)** | | | **(n=63,366, GC=122)** | | | **(n=57,028, GC=112)** | | |
| | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** |
| Non-user (<weekly use) | Ref | - | - | Ref | - | - | Ref | - | - | Ref | - | - |
| At least weekly | 2.98 | 1.76 – 5.05 | **0.001** | 2.56 | 1.46 – 4.49 | **0.001** | 2.43 | 1.38 – 4.28 | **0.002** | 2.59 | 1.42 – 4.72 | **0.002** |
| **Cardia GC** | **(n=63,275, GC=31)** | | | **(n=63,275, GC=31)** | | | **(n=63,275, GC=31)** | | | **(n=56,947, GC=27)** | | |
| | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** |
| Non-user (<weekly use) | Ref | - | - | Ref | - | - | Ref | - | - | Ref | - | - |
| At least weekly | 2.10 | 0.64 – 6.90 | 0.222 | 1.24 | 0.35 – 4.34 | 0.736 | 1.26 | 0.35 – 4.52 | 0.722 | 1.97 | 0.57 – 6.82 | 0.286 |

Significant p-values were highlighted in bold
HR, hazard ratio; 95% CI, 95% confidence interval; PPI, proton pump inhibitor; PS, propensity score; GC, gastric cancer

**Table 4 . HRs and 95% CIs for the association between frequency and duration of PPI use and risk of gastric cancer (propensity score adjustment with trimming)**

| | Dose-response relationship (n=57,057, GC=139) | | |
|---|---|---|---|
| **PPI frequency** | **HR** | **95% CI** | **p-value** |
| Non-user (<weekly use) | Ref | - | - |
| Weekly to <daily | 2.43 | 1.37 – 4.31 | **0.002** |
| Daily | 4.55 | 1.12 – 18.52 | **0.034** |

| **PPI frequency** | **PPI use ≥ 1 year (n=50,932, GC=112)** | | | **PPI use ≥ 2 years (n=49,462, GC=88)** | | | **PPI use ≥ 3 years (n=48,511, GC=69)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** |
| Non-user (<weekly use) | Ref | - | - | Ref | - | - | Ref | - | - |
| Weekly to <daily | 1.81 | 0.90 – 3.64 | 0.098 | 0.98 | 0.31 – 3.17 | 0.979 | 0.58 | 0.08 – 4.23 | 0.590 |
| Daily | 5.04 | 1.23 – 20.61 | **0.024** | 6.65 | 1.62 – 27.26 | **0.009** | 8.34 | 2.02 – 34.41 | **0.004** |

Significant p-values were highlighted in bold
HR, hazard ratio; 95% CI, 95% confidence interval; PPI, proton pump inhibitors; GC, gastric cancer

**Table 5. Comparison of incidence rates of gastric cancer in different cohorts according to PPI uses and prior *H. pylori* eradication therapy**

| **Before matching** | **Number of patients** | **Number of person-years** | **Number of GC cases** | **Incidence rate (per 10,000 person-years)** | **Incidence rate ratio with 95% CI** |
|---|---|---|---|---|---|
| non-PPI users with prior HP therapy | 60,126 | 459,864 | 134 | 2.9 | Ref |
| PPI users with prior HP therapy | 3,271 | 23,395 | 19 | 8.1 | 2.81 (1.68 – 4.43) |
| PPI users without prior HP therapy | 142,460 | 705,094 | 59 | 0.8 | 0.29 (0.21 – 0.39) |
| **After matching** | **Number of patients** | **Number of person-years** | **Number of GC cases** | **Incidence rate (per 10,000 person-years)** | **Incidence rate ratio with 95% CI** |
| PPI users with prior HP therapy | 3,270 | 23,384 | 19 | 8.1 | Ref |
| PPI users without prior HP therapy * | 13,080 | 93,500 | 9 | 1.0 | 0.12 (0.05 – 0.26) |

* matched with age (+/- 5 years), sex, duration of follow-up (+/- 2 years) and frequency of PPI use (+/- 0.3) in a 1:4 ratio
PPI, proton pump inhibitor; HP, *Helicobacter pylori*; GC, gastric cancer; 95% CI, 95% confidence interval