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 even 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 PPIs 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 PPIs 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 PPIs use.

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

- Physicians should exercise caution when prescribing long-term PPIs 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) have been among the most commonly prescribed medications in the world since the first PPI became 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 high among 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 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 the Hong Kong Hospital Authority (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 clinical practice, as serology and stool antigen tests were not available in local public hospitals. 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.[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 also 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 *H. pylori* eardication therapy. 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 (including protopathic bias) that confound the causal relationship between PPIs and gastric cancer development.

To further control for possible confounding effects, another cohort of PPIs users (defined similarly as at least weekly use) who had not received *H. pylori* eradication therapy and fulfilled the same inclusion and exclusion criteria as in our *H. pylori* eradication cohort was recruited for comparison. These PPIs users who had not received *H. pylori* eradication therapy were then matched with the PPIs 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 PPIs use (±0.3) in a 1:4 ratio. The incidence rates of gastric cancer in the two PPIs cohorts were 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 which was categorized 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 the 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. The crude hazard ratio (HR) of gastric cancer development with PPIs use was calculated by univariate analysis using Cox proportional hazards

model. For multivariable analysis, PPIs use and other covariates (age of receiving *H. pylori* eradication therapy, sex, smoking, alcohol use, comorbidities and concomitant medications) were included in the Cox model. To better 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 aforementioned covariates. 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. To assess the balance of the continuous variable (age of receiving *H. pylori* eradication therapy) between PPIs users and non-users, the t-statistics adjusted for propensity score strata (by linear regression) and the p-value was determined.

In the primary analysis, the first and 20th 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 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 and non-PPIs use by the adjusted HR minus 1, followed by the multiplication of the crude incidence rate among non-PPIs users.[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 use 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 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 483,260 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.** Notably, both PPIs users (54.3 vs 64.1 years) and H2RA users (60.0 vs 52.0 years) were older than the corresponding non-users.

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 the public hospitals in Hong Kong during the study period (13.4% in cardia, 67.5% in non-cardia and 19.1% cases with sites unspecified).

The histology reports of 12 (7.8% out of 153) gastric cancer cases from our center were retrieved, and all cancers were verified to be adenocarcinoma. 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 five cases. For the degree of differentiation, five cases were poorly differentiated, three were moderately to poorly differentiated, one was moderately differentiated, while the degree of differentiation was unspecified for the remaining three. According to the Lauren classification, three cases were diffuse type, three were intestinal type, and the histological subtypes were unspecified for the remaining six.

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* eradication therapy 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 of PPIs users for each follow-up year is shown in **eTable 2**, which ranged from 0 to 18.5 per 10,000 person-years. Patients who developed gastric cancer within the first year of *H. pylori* eradication therapy were excluded in this study as described above.

Association of PPIs use and risk of gastric cancer

Table 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 between PPIs use and 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.

PPIs users were older than non-PPIs users by around 10 years, and the HR of gastrric cancer with increasing age was 1.06 on multivariable analysis. Therefore, the

t-statistics was used to assess the balance of age between the two groups. After adjusting for propensity score strata, the age was balanced between the two groups (t-statistics -1.42, p=0.156).

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 PPIs 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 PPIs 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 3 and 4)**. 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 ≥1 year of use; HR 6.65 [95% CI 1.62 – 27.26] for ≥2 years of use and HR 8.34 [95% CI 2.02 – 34.41] for ≥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 PPIs users (at least weekly use) who had not received *H. pylori* eradication therapy were included for comparison. Altogether, 142,460 PPIs users without prior *H. pylori* eradication therapy were identified with a total of 705,094 person-years of 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 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 ≥3 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 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 PPIs 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 use 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 large 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 generally 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, demonstrating a dose- and time-response trend to suggest 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 in the context of underlying *H. pylori*-associated chronic

gastritis and atrophy. In addition, 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. Moreover, 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. Second, 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 remains possible that a small proportion of patients who failed *H. pylori* eradication therapy might be missed. In this study, about 13% of patients received a second course of eradication therapy, which is 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. Third, 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 have endoscopy than non-PPIs users resulting in discovery of more gastric cancers due to surveillance bias. However, as shown in **eTable 2**, the incidence rate of gastric cancer remained relatively stable throughout the follow-up period rather than an early peak in the first few years followed by a rapid drop in the ensuing years. Fifth, PPIs users were older than non-users in our cohort. Age was shown to be a significant risk factor for gastric cancer development (HR 1.06) on multivariable analysis. The comparability of the two groups may therefore be a concern, but this issue has been addressed by the use of propensity score adjustment with trimming and various sensitivity analyses. The non-significance of t-statistics between the PPIs users and non-users after adjusting for the propensity score strata further supports the robustness of this adjustment. Moreover, H2RA users were also significantly older than non-users (**Table 2**) but a similar increase in gastric cancer risk was not observed among H2RA users. Sixth, our patients are mainly Chinese, and hence our results may not be generizable to other ethnic groups, as Asians are at a higher gastric cancer risk than the western population.[1] 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 PPIs uses and gastric cancer risk. Physicians should therefore exercise caution 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 PPIs and non-PPIs users

	All (n=63,397)	PPIs users (n=3,271)	Non-PPIs 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 PPIs use and risk of gastric cancer for the whole cohort and according to gastric cancer sites (non-cardia and cardia regions)

PPIs frequency	Univariate analysis (n=63,397, GC=153)			Multivariable analysis (n=63,397, GC=153)			PS adjustment without trimming (n=63,397, GC=153)			PS adjustment with trimming (n=57,057, GC=139)		
All GC	**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; PPIs, proton pump inhibitors; PS, propensity score; GC, gastric cancer

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

	Dose-response relationship (n=57,057, GC=139)		
PPIs 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**

PPIs frequency	**PPIs use ≥ 1 year (n=50,932, GC=112)**			**PPIs use ≥ 2 years (n=49,462, GC=88)**			**PPIs 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; PPIs, proton pump inhibitors; GC, gastric cancer

Table 5. Comparison of incidence rates of gastric cancer in different cohorts according to PPIs uses and prior *Helicobacter 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-PPIs users with prior HP therapy	60,126	459,864	134	2.9	Ref
PPIs users with prior HP therapy	3,271	23,395	19	8.1	2.81 (1.68 – 4.43)
PPIs 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**
PPIs users with prior HP therapy	3,270	23,384	19	8.1	Ref
PPIs 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 PPIs use (+/- 0.3) in a 1:4 ratio

PPIs, proton pump inhibitors; HP, *Helicobacter pylori*; GC, gastric cancer; 95% CI, 95% confidence interval

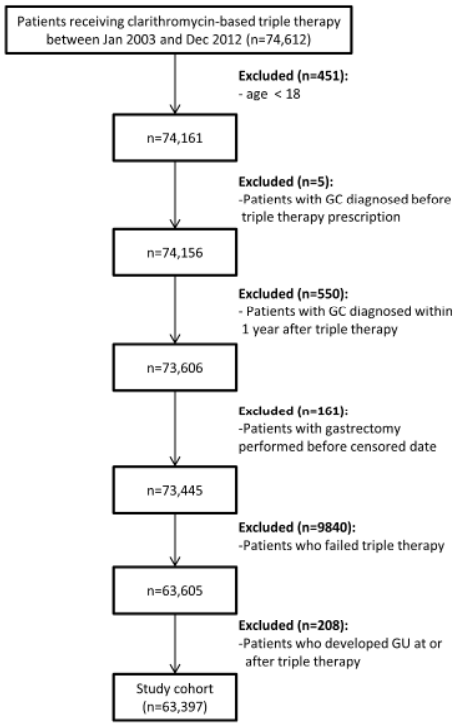

Figure 1: Study patient selection flow diagram
Abbreviations: GC, gastric cancer; GU, gastric ulcer

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eTable 1. ICD-9 codes for outcome and covariates

Outcome	
Gastric carcinoma	151, 151.0, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, 151.8, 151.9, 230.2
Covariates	
Smoking	491, 492, 496, V15.82
Alcohol	291, 303, 305.0, 571.0, 571.1, 571.2, 571.3, 980.8, 980.9
Gastric ulcer	531
Duodenal ulcer	532
Diabetes mellitus	249, 250
Hypertension	401-405
Dysplipidemia	272.0-272.4
Obesity	278.0, 278.1
Ischemic heart disease	410-413, 414.0, 414.8, 414.9, 429.7
Atrial fibrillation	427.3
Congestive heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Stroke	430-432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 437.0, 437.1
Chronic renal failure	585
Cirrhosis	571.2, 571.5, 571.6, 572.2-572.4, 573.5

eTable 2. Incidence rate of gastric cancer of PPIs users for each follow-up year

	2nd year	3rd year	4th year	5th year	6th year	7th year
Number of GC cases	4	3	2	1	3	1
Number of persons at risk	3,084	2,963	2,857	2,567	2,318	2,054
Incidence rate (per 10,000 person-years)	13.0	10.1	7.0	3.9	12.9	4.9
	8th year	**9th year**	**10th year**	**11th year**	**12th year**	
Number of GC cases	1	2	1	0	1	
Number of persons at risk	1,758	1,446	1,126	813	540	
Incidence rate (per 10,000 person-years)	5.7	13.8	8.9	0	18.5	

* There were no gastric cancer cases within the first year of *H. pylori* eradication therapy since these patients were excluded in the current study
PPIs, proton pump inhibitors; GC, gastric cancer

eTable 3. HRs and 95% CIs for the association between PPIs use (frequency and duration) and risk of gastric cancer (multivariable analysis)

	Dose-response relationship (n=63,397, GC=153)		
PPIs frequency	**HR**	**95% CI**	**p-value**
Non-user (<weekly use)	Ref	-	-
Weekly to <daily	2.08	1.29 – 3.61	**0.002**
Daily	3.23	0.98 – 10.60	0.054

	PPIs use ≥ 1 year (n=56,592, GC=128)			PPIs use ≥ 2 years (n=54,958, GC=104)			PPIs use ≥ 3 years (n=53,900, GC=85)		
PPIs frequency	**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	1.28	0.64 – 2.52	0.490	0.71	0.25 – 2.01	0.521	0.27	0.04 – 2.03	0.205
Daily	3.07	0.92 – 10.29	0.068	3.34	0.98 – 11.39	0.054	4.22	1.23 – 14.49	**0.022**

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

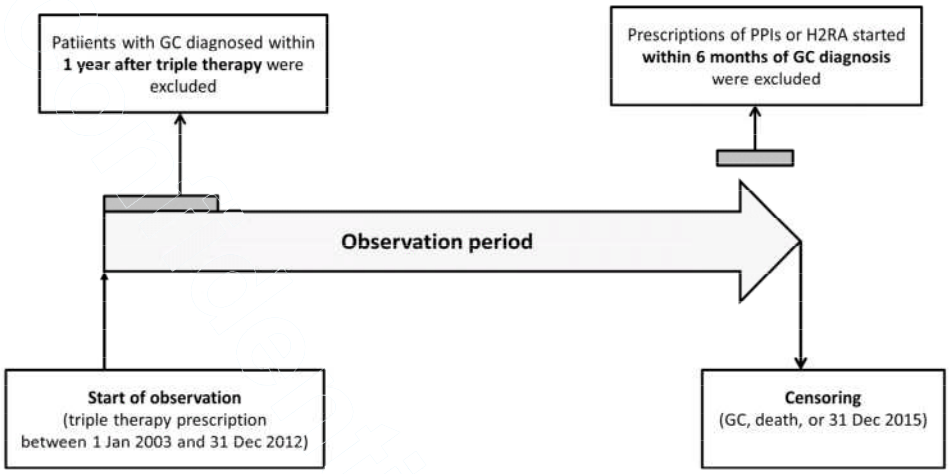
eTable 4. HRs and 95% CIs for the association between PPIs use (frequency and duration) and risk of gastric cancer (propensity score adjustment without trimming)

PPIs frequency	Dose-response relationship (n=63,397, GC=153)		
	HR	**95% CI**	**p-value**
Non-user (<weekly use)	Ref	-	-
Weekly to <daily	2.00	1.15 – 3.48	**0.015**
Daily	3.71	1.13 – 12.20	**0.031**

PPIs frequency	PPIs use ≥ 1 year (n=56,592, GC=128)			PPIs use ≥ 2 years (n=54,958, GC=104)			PPIs use ≥ 3 years (n=53,900, GC=85)		
	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	1.32	0.66 – 2.64	0.432	0.75	0.26 – 2.13	0.582	0.30	0.04 – 2.22	0.236
Daily	3.83	1.14 – 12.83	**0.029**	4.41	1.28 – 15.23	**0.019**	5.46	1.52 – 19.57	**0.009**

Significant p-values were highlighted in bold
* PPIs non-user was defined as <weekly use in subsequent analysis as there was no significant difference between <monthly use and monthly to <weekly use
HR, hazard ratio; 95% CI, 95% confidence interval; PPIs, proton pump inhibitors; GC, gastric cancer

eFigure 1. Study observation period



Abbreviations: GC, gastric cancer; PPIs, proton pump inhibitors; H2RA, histamine 2 receptor antagonist