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

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12

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1 **LIST OF ABBREVIATIONS**

2

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
<i>H. pylori</i>	<i>Helicobacter pylori</i>
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

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1 **ABSTRACT**

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

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

14 **Result:** Among the 63,397 eligible subjects, 153 (0.24%) developed GC during a  
15 median follow-up of 7.6 years. PPIs use was associated with an increased GC risk  
16 (HR 2.44; 95% CI 1.42–4.20), while H2RA was not (HR 0.72; 95% CI:0.48–1.07).  
17 The risk increased with duration of PPIs use (HR 5.04 [95% CI:1.23–20.61], 6.65  
18 [95% CI:1.62–27.26] and 8.34 [95% CI:2.02–34.41] for  $\geq 1$  year,  $\geq 2$  years and  $\geq 3$

1 years, respectively). The adjusted absolute risk difference for PPIs versus non-PPIs

2 use was 4.29 excess GC (95%:CI 1.25 to 9.54) per 10,000 person-years.

3 **Conclusion:** Long-term use of PPIs was still associated with an increased GC risk in

4 subjects after HP eradication therapy.

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1 **SIGNIFICANCE OF THIS STUDY**

2 **What is already known on this subject?**

- 3 • Although *Helicobacter pylori* (*H. pylori*) eradication has been shown to reduce  
4 the risk of gastric cancer development, a considerable proportion of these  
5 individuals continues to progress to gastric cancer even after successful  
6 eradication of *H. pylori*.
- 7 • Previous studies have shown that the risk of gastric cancer was increased by  
8 43% among PPI users but the major confounding factor, *H. pylori*, was not  
9 adjusted in these analyses and the causal relationship may be biased.

10

11 **What are the new findings?**

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

15

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

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

19

## 1 INTRODUCTION

2 Gastric cancer is the third leading cause of cancer related mortality in the world.<sup>1</sup>

3 Although *Helicobacter pylori* (*H. pylori*) eradication has been shown to reduce the

4 risk of gastric cancer development by 33-47%<sup>2, 3</sup>, a considerable proportion of these

5 individuals continues to progress to gastric cancer even after eradication of *H. pylori*.

6 Apart from baseline gastric histology at the time of eradication<sup>4</sup>, data are sparse on

7 other modifiable risks of gastric cancer development, particularly on the role of

8 concurrent medications.

9

10 Proton pump inhibitors (PPIs) are among the most commonly prescribed medications

11 in the world since the first PPI has become available in the 1980s.<sup>5</sup> Although PPIs are

12 generally considered safe, recent data have demonstrated various adverse effects

13 associated with long-term use of PPIs including bone fracture,<sup>6</sup> *Clostridium difficile*

14 infection,<sup>7</sup> pneumonia,<sup>8</sup> myocardial infarction and even stroke.<sup>9</sup> Apart from the

15 systemic adverse effects, there are also concerns on the long-term safety profile of

16 PPIs in the stomach. The use of PPIs is associated with profound acid suppression,

17 which could worsen atrophic gastritis.<sup>10</sup> The risk is considerably higher in individuals

18 infected with *H. pylori* who are susceptible to the development of corpus atrophy.<sup>11</sup>

19 Moreover, PPIs stimulate the production of gastrin, which is a potent growth factor,



1 and hypergastrinemia has been shown to induce hyperplasia of enterochromaffin-like  
2 cells.<sup>11</sup> A recent meta-analysis showed that the risk of gastric cancer is increased by  
3 43% among PPI users.<sup>12</sup> However, these studies included both *H. pylori*-infected and  
4 *H. pylori*-negative subjects. Although previous short-term studies had suggested the  
5 resolution of corpus atrophy with *H. pylori* eradication therapy in patients with  
6 gastroesophageal reflux disease<sup>13, 14</sup>, it remains uncertain whether the potential risk of  
7 PPIs on gastric cancer development could be eliminated by clearance of *H. pylori*.

8  
9 This population-based study aimed to determine the risk of gastric cancer  
10 development among individuals who had received treatment for *H. pylori* with focus  
11 on the role of long-term PPIs.

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14

1 **METHODS**

2 **Data source**

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

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

4

## 5 **Study Subjects**

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

1 of these agents started within six months prior to the gastric cancer diagnosis were  
2 excluded from analyses.<sup>25, 26</sup>

3

4 Since gastric cancer can masquerade as non-healing ulcer, all patients with gastric  
5 ulcer diagnosed at the time of or any time after receiving triple therapy were excluded.

6 As there may be a delay in the diagnosis of gastric cancer, patients who developed  
7 gastric cancer within the first year of *H. pylori* eradication therapy were excluded.

8 Patients with history of gastric cancer, previous gastrectomy or those who failed triple  
9 therapy were also excluded to ensure homogeneity of our study cohort. We defined  
10 failure of *H. pylori* eradication therapy as the requirement of subsequent prescriptions  
11 of (a) repeated course of clarithromycin-based triple therapy; (b) a second-line  
12 therapy (bismuth-based quadruple therapy or PPI-levofloxacin-amoxicillin); or (c) a  
13 third-line therapy (rifabutin-based therapy). **Figure 1** illustrates the inclusion and  
14 exclusion process of patients in this study. The time frame of the study is shown in  
15 **eFigure 1**.

16

## 17 **Outcomes**

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

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

10

### 11 **Study variables**

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

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

3

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

10

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

1 We used similar approaches as adopted by Poulsen et al<sup>28</sup> to ascertain smoking status  
2 and alcohol consumption as these data was not available in the CDRAS. Smoking was  
3 identified by the ICD-9 code of V15.82 while chronic obstructive pulmonary disease  
4 (COPD) (ICD-9 codes: 491, 492, 496) was also used as proxy of heavy smoking.  
5 Heavy alcohol consumption was identified by alcohol-related diseases, including  
6 hepatic and gastrointestinal diseases, neurological and psychiatric diseases (ICD-9:  
7 291, 303, 305.0, 571, 980). The diagnostic codes of other variables are listed in  
8 **eTable 1.**

9  
10 In the primary analysis, the exposure categories of various medications were  
11 categorized similarly into non-regular use (<weekly use; reference group) and regular  
12 use (at least weekly use) as described by Thrift et al.<sup>30</sup> The treatment duration of each  
13 prescription of a particular medication was defined as the difference between the  
14 prescription start date and end date within the observation period. The total treatment  
15 duration of that particular medication was then calculated by summing up the  
16 treatment duration of each prescription.

17

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

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

5

## 6 **Data validation**

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

12

## 13 **Statistical analyses**

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



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

8

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

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

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## 1 RESULTS

### 2 Patient Characteristics

3 A total of 74,612 subjects had received clarithromycin-based triple therapy during the  
4 10-year period. After excluding patients who did not fulfil our inclusion criteria  
5 (**Figure 1**), 63,397 subjects were included in the final analysis. The median age of this  
6 cohort at the time of *H. pylori* eradication therapy was 54.7 years (IQR: 46.0 – 65.4  
7 years) and 46.5% were men. The median follow-up was 7.6 years (IQR: 5.1 – 10.3  
8 yeas) and the total follow-up duration was 483,259 person-years. The baseline  
9 characteristics of the whole cohort and the subgroups according to PPIs and H2RA  
10 use are shown in **Tables 1 and 2** .

11

### 12 Risk of Gastric Cancer Development

13 One hundred and fifty-three (0.24%) subjects developed gastric cancer after *H. pylori*  
14 eradication therapy. Among them, 31 (20.3 %) cancer were in the cardia and 95 (62.1  
15 %) in the non-cardia regions. The sites were not specified in the remaining 27 (17.6%)  
16 cases (ICD-9: 151.9). Similar ratio were observed for all the stomach cancer cases  
17 (n=12,898) diagnosed in Hong Kong during the study period (13.4% in cardia, 67.5%  
18 in non-cardia and 19.1% cases with sites unspecified).

19

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

5

6 The median age at cancer diagnosis was 71.4 years (IQR 61.1 – 81.5 years). Patients  
7 who developed gastric cancer received *H. pylori* eradication therapy at a median age  
8 of 65.4 years (IQR 56.4 – 76.2 years), and the median time from *H. pylori* treatment  
9 to cancer development was 4.9 years (IQR: 2.7 – 7.2 years). The overall incidence  
10 rate of gastric cancer in this cohort was 3.2 per 10,000 person-years. The incidence  
11 rate of gastric cancer for each year is shown in eTable 2, which ranged from 2.5 to  
12 5.8 per 10,000 person-years. Notably, there were no gastric cancer cases within the  
13 first year of follow-up, as these cases were excluded.

14

### 15 Association of PPIs use and risk of gastric cancer

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

1 use with gastric cancer development by either multivariable analysis (HR 2.19, 95%  
2 CI 1.31 – 3.66) or propensity score adjustment without trimming (HR 2.14, 95% CI  
3 1.27 – 3.58).

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

7  
8 After stratification by the site of tumour, PPIs use was only found to be significantly  
9 associated with an increased risk of non-cardia gastric cancer (HR 2.59, 95% CI 1.42  
10 – 4.72) but not cardia cancer (HR 1.97, 95% CI 0.57 – 6.82). Sensitivity analysis  
11 yielded similar results.

12

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

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

1 progressive increase in the risk of gastric cancer with more frequent use of PPIs (HR  
2 2.43 [95% CI 1.37 – 4.31] for “weekly to < daily use”, and HR 4.55 [95% CI 1.12 –  
3 18.52] for “daily use”). Sensitivity analysis yielded similar results (**eTables 2 and 3**).  
4 Furthermore, the effect of long-term PPIs on gastric cancer development was studied  
5 with regard to the duration of PPIs therapy ( $\geq 1$  year,  $\geq 2$  years and  $\geq 3$  years). As  
6 shown in **Table 4**, the risk increased with longer duration of PPIs use (HR 5.04 [95%  
7 CI 1.23 – 20.61] for at least 1 year of use; HR 6.65 [95% CI 1.62 – 27.26] for at least  
8 2 years of use and HR 8.34 [95% CI 2.02 – 34.41] for at least 3 years of use).

9

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

11 To test for potential confounding, H2RA was used as a negative control exposure.  
12 The HR of gastric cancer with H2RA use on univariate analysis was 0.95 (95% CI  
13 0.67 – 1.33), while the HR from propensity score adjustment with trimming was 0.72  
14 (95% CI 0.48 – 1.07).

15

#### 16 **Comparison of the incidence rates of gastric cancer with a matched cohort of**

#### 17 **PPIs users who had not received *H. pylori* eradication therapy**

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

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

8

1 **DISCUSSION**

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

14

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



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

13

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

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

12

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

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

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

5

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

1 63,000 *H. pylori*-infected subjects, the small number of gastric cancer cases did not  
2 allow for any meaningful evaluation of the dosage effect and role of different PPIs.  
3 However, it was recently shown that there was no difference in the gastric cancer risk  
4 between longer and shorter-acting PPIs.<sup>35</sup> Fourth, PPIs users may have a higher  
5 chance to undergo endoscopy than non-PPI users, and therefore surveillance bias may  
6 lead to a higher risk of gastric cancer as observed in current study. However, as  
7 shown in eTable

8  
9 Lastly, the detailed histological findings of gastric biopsies at baseline and at the time  
10 of gastric cancer development were not available in the CDARS, precluding more in-  
11 depth analysis between the association of PPIs and baseline histology on gastric  
12 cancer development.

## 14 CONCLUSION

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

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1 **FIGURE LEGEND**

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

4 Abbreviations: GC, gastric cancer; GU, gastric ulcer

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

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	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

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

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	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;

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**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		
	(n=63,397, GC=153)			(n=63,397, GC=153)			(n=63,397, GC=153)			(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	<b>0.003</b>	2.19	1.31 – 3.66	<b>0.003</b>	2.14	1.27 – 3.58	<b>0.004</b>	2.44	1.42 – 4.20	<b>0.002</b>

  

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	<b>0.001</b>	2.56	1.46 – 4.49	<b>0.001</b>	2.43	1.38 – 4.28	<b>0.002</b>	2.59	1.42 – 4.72	<b>0.002</b>

  

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

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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

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

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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			<b>0.002</b>		
Daily	4.55			1.12 – 18.52			<b>0.034</b>		
PPI frequency	PPI use ≥ 1 year			PPI use ≥ 2 years			PPI use ≥ 3 years		
	(n=50,932, GC=112)			(n=49,462, GC=88)			(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	<b>0.024</b>	6.65	1.62 – 27.26	<b>0.009</b>	8.34	2.02 – 34.41	<b>0.004</b>

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

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

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<b>Before matching</b>	<b>Number of patients</b>	<b>Number of person-years</b>	<b>Number of GC cases</b>	<b>Incidence rate (per 10,000 person-years)</b>	<b>Incidence rate ratio with 95% CI</b>
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)
<b>After matching</b>	<b>Number of patients</b>	<b>Number of person-years</b>	<b>Number of GC cases</b>	<b>Incidence rate (per 10,000 person-years)</b>	<b>Incidence rate ratio with 95% CI</b>
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

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