STATINS WERE ASSOCIATED WITH A REDUCED GASTRIC CANCER RISK IN PATIENTS WITH ERADICATED *HELICOBACTER PYLORI* INFECTION: A TERRITORY-WIDE PROPENSITY SCORE MATCHED STUDY

RUNNING TITLE: STATINS AND GASTRIC CANCER

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ABSTRACT

Background: Individuals may still develop gastric cancer (GC) even after *H. pylori* (HP) eradication. We aimed to investigate statin effect on GC development in HP-eradicated subjects.

Methods: All adult subjects who were prescribed clarithromycin-based triple therapy between 2003 and 2012 were identified in this retrospective cohort study utilizing a territory-wide electronic healthcare database. Patients were observed from index date of HP therapy, and censored at GC diagnosis, death or December 2015 (study end date). Statin use was defined as ≥ 180-day use after index date. Exclusion criteria included GC diagnosed within the first year after index date, previous GC or gastrectomy, and HP treatment failure. Subdistribution hazard ratio (SHR) of GC with statins was calculated by competing risk regression with propensity score (PS) analysis matching 19 variables (age, sex, comorbidities and other drug usage including proton pump inhibitors, non-steroidal anti-inflammatory drugs, aspirin, cyclooxygenase-2 inhibitors, and metformin).

Results: During a median follow-up of 7.6 years (IQR: 5.1–10.3), 169 (0.27%) of 63,605 patients developed GC at an incidence rate of 3.5 per 10,000 person-years. Among 22,870 PS-matched subjects, statins were associated with a lower GC risk (SHR 0.34; 95% CI:0.19-0.61), in a duration- and dose-response manner (p-trend<0.05).

Conclusion: Statins associated a lower GC risk in a duration- and dose-response manner among HP-eradicated patients.

Impact: This study provides evidence on the additional benefits of statins as chemopreventive agents against GC among HP-eradicated patients.

BACKGROUND

Globally, gastric cancer is the fifth most common cancer and third leading cause of cancer-related death.[1] *Helicobacter pylori (H. pylori)* is the most important etiological agent of gastric cancer (more than 3-fold increase in risk).[2,3] As eradication of *H. pylori* only reduces gastric cancer risk by 47%,[4, 5] there is still an unmet need to identify chemopreventive agents against gastric cancer.

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (an enzyme involved in cholesterol synthesis), and are used for primary and secondary prevention of cardiovascular diseases.[6] In addition to their lipid lowering effect, statins have potential chemopreventive effects on various solid organ tumours, which are believed to be mediated via arresting cell-cycle progression, inducing apoptosis, inhibiting angiogenesis, and immunomodulation.[7] Lovastatin has been shown to suppress genes involved in cell division, upregulate cell cycle inhibitors and suppress anti-apoptotic proteins in human gastric cancer-derived cell lines.[8] In addition, statins inhibit gastric cancer cell growth in mice models.[9]

As yet, there is no randomized clinical trial (RCT) dedicated to investigate the effect of statins on gastric cancer as the primary outcome. Observational studies, on the other hand, yield conflicting results with some studies showing a lower gastric cancer

risk by statins,[10-13] while others failed to show such a benefit.[14-20] Although a recent meta-analysis conclude that statins were associated with lower gastric cancer risk,[21] all included studies enrolled both *H. pylori*-infected and *H. pylori*-negative subjects. In addition, few studies stratified the cancer risk according to cancer location of non-cardia and cardia, as etiological factors are different for these two cancer subtypes, with *H. pylori* infection and gastroesophageal reflux disease being the major risk factors for non-cardia and cardia cancer, respectively.[2, 22] However, in areas where *H. pylori* are prevalent, both non-cardia and cardia gastric cancer could be associated with *H. pylori* infection.[2] To date, there are no studies that specifically investigate the potential chemopreventive role of statins in gastric cancer prevention after *H. pylori* eradication. Therefore, we conducted this territory-wide study to determine the potential effect of statins on gastric cancer risk with stratification to cancer subsites after receiving *H. pylori* eradication therapy.

MATERIAL AND METHODS

Study design and data source

This was a retrospective cohort study based on data retrieved from the territory-wide electronic healthcare database, Clinical Data Analysis and Reporting System (CDARS), of the Hong Kong Hospital Authority. The Hospital Authority is the only public-funded healthcare provider in Hong Kong with a population of around 7.3 million, covering 87-94% of all secondary and tertiary care in the territory during the study period.[23] Essential clinical information such as patient's demographics, death, diagnoses, drug dispensing records, procedures and laboratory results, hospitalization records, attendance of outpatient clinics and emergency departments are all recorded in CDARS. Prescription and dispensing are performed at the same time, and prescription record generally matches the dispensing record. Various studies utilizing CDARS were undertaken,[24-27] demonstrating a high diagnostic coding accuracy (International Classification of Diseases, Ninth Revision [ICD-9]) with positive and negative predictive values of more than 85–90%.

This study was conducted in accordance with Declaration of Helsinki. Each patient was assigned an anonymous identifier (reference key) in CDARS to protect confidentiality. Therefore, written informed consent was not required with ethics

approval obtained from the Institutional Review Board of the University of Hong Kong and the Hong Kong West Cluster of the Hospital Authority.

Study Subjects

All *H. pylori*-infected adults aged ≥18 years who had received a course of clarithromycin-based triple therapy for *H. pylori* between 1 January 2003 and 31 December 2012 (i.e. index date) were identified from CDARS. The use of triple therapy was identified by co-prescription of one of the proton pump inhibitors (PPIs) with clarithromycin and either amoxicillin or metronidazole with the correct doses, same prescription start date and a treatment duration of 7-14 days as previously described.[25, 26] Clarithromycin-based triple therapy was the first-line treatment for *H. pylori* due to the low clarithromycin resistance rate (8%)[28] and high eradication rate (> 90%) in Hong Kong during the study period.[29] Endoscopy-based tests (including histology and rapid urease test) as well as urea breath test are the only diagnostic tests for *H. pylori* infection available in local public hospitals.

Exclusion criteria were: (1) gastric cancer development within the first year of index date (to exclude prevalent cases due to possibly missed/delayed diagnosis); (2) history of gastric cancer or gastrectomy before index date; (3) triple therapy failure. Due to

unavailability of direct ICD-9 code, triple therapy failure was inferred by repeated clarithromycin-based triple therapy, or requirement of a second-line therapy (either PPI-levofloxacin-amoxycillin or bismuth-based quadruple therapy), or a third-line therapy (rifabutin-based therapy). Subject recruitment process is depicted in **Figure 1.**

Study Outcome and data validation

The outcome of interest was gastric adenocarcinoma. We observed the patients from index date, and they were censored at cancer diagnosis, death or study end date (31 December 2015). **Supplementary Table 1** shows the ICD-9 codes for gastric adenocarcinoma. The date of cancer diagnosis was the earliest date of hospitalization for treatment and/or workup.

As individuals are anonymized in CDARS, we could only validate the outcome of subjects in our institution (Queen Mary Hospital) which is an acute hospital and a tertiary referral center. The clinical details of 14 (8.3%) patients with gastric cancer were reviewed, with all fulfilling the selection criteria. Histology reports revealed all cases being adenocarcinoma without *H. pylori* infection.

Exposure of interest and covariates

The exposure of interest was statin usage after index date. Simvastatin, atorvastatin and rosuvastatin were the only statins available in the public hospitals. Covariates used for propensity score (PS) matching (described in details in later section) included the age of receiving triple therapy, sex, alcohol use, smoking, prior peptic ulcer disease, diabetes mellitus,[30] and other comorbidities (hypertension, dyslipidemia, ischemic heart disease, atrial fibrillation, congestive heart failure, stroke, cirrhosis, and chronic renal failure) as well as usage of other drugs (non-steroidal anti-inflammatory drugs [NSAIDs], aspirin,[25] cyclooxygenase-2 [COX-2] inhibitors, metformin[26] and PPIs[31]) (**Table 1**). As the true prevalence of smoking and alcoholism may be underestimated by diagnosis coding only, a large set of comorbidities were included to serve as surrogate markers of these two imperfectly measured confounders. The diagnosis codes of these variables are shown in **Supplementary Table 1**.

We defined statin exposure (as well as other medications) as ≥180-day use after index date during the observation period according to Lee et al[11]. The date of prescription, daily dose, and duration of each prescription were collected. To investigate dose-response relationship, we quantified statin use based on the defined daily doses (DDDs) to unify the dose for different statins (one DDD is equivalent to simvastatin

30mg, atrovastatin 20mg and rosuvastatin 10mg).[32] With this approach, the cDDD would take both the potency and quantity of statins into consideration, which is a common proxy for both duration and dose effect of different statins. Cumulative DDD (cDDD) was then derived by summing the DDDs of any statins during observation period. To investigate the duration-response relationship, statin use was categorized into three groups: (i) non-statin use, (ii) < 5 years, and (iii) ≥ 5 years.

Statistical analyses

We used R version 3.2.3 (R Foundation for Statistical Computing) statistical software to perform the statistical analyses. We expressed continuous variables as median and interquartile range (IQR). PS analysis was used to control for confounding due to unbalance in treatment allocation. PS was derived by multivariable logistic regression taking various covariates (age, sex, comorbidities and concurrent medications) into consideration. As such, any difference in cancer risk would be theoretically ascribed to statin effect solely. Furthermore, we excluded individuals in the extreme ends of PS distribution to reduce the effect of unmeasured confounding.[33] Twenty categories of 5% each for the PS distribution were created, followed by trimming of the first and 20^{th} PS categories (i.e. PS trimming).

We used PS matching as the primary analysis to calculate gastric cancer risk with statin usage with reference to non-statin usage. Statin users were matched to non-statin users in a 1:1 ratio with replacement using a greedy distance-based matching algorithm with the logit of the PS within 0.1 standard deviation. Due to the strict matching criteria, the final patient number was 11,678 and 11,192 in statin and non-statin groups. The balance of covariates between the two groups was assessed by absolute standardized difference (ASD), which was derived from the absolute difference in means or proportions divided by the pooled standard deviation. An ASD of < 0.20 indicates good balance for a particular covariate. Imbalance covariates with ASD > 0.20 after matching were adjusted for in the competing regression risk model.[34]

Competing risk regression model was used to estimate the subdistribution hazard ratio (SHR),[35] as death was a competing risk for gastric cancer with statin users having higher cardiovascular risk (**Table 1**) and thus mortality. Stratified analysis was performed according to the location of gastric cancer (cardia and non-cardia regions), as the underlying carcinogenic mechanisms differ.[22] The PS adjusted absolute difference in cancer risk between the two groups was derived by (adjusted HR – 1) x (crude incidence rate of gastric cancer in non-statin users). The duration- and dose-

response relationship between statins and gastric cancer was derived by the competing risk regression model using PS adjustment after trimming. The trend for duration-response of statins was assessed by Cochran-Armitage test. The survival difference between the statin and non-statin users was illustrated in terms of Kaplan-Meier curve and log-rank p-value.

Sensitivity analyses were conducted by (1) changing the days of exposure to define statin use (≥ 30 and ≥ 90 days), (2) not including other comorbidities except for peptic ulcer disease and diabetes mellitus, (3) PS regression adjustment with trimming (with all covariates included into the competing risk regression model), (4) multivariable analysis as well as (5) Cox proportional hazards model (effect estimate expressed as adjusted HR). 'Complementary log-log'-scaled Kaplan-Meier plot and schoenfeld residuals for statin use (p-value > 0.05) confirmed non-violation of the Cox proportional-hazard assumption. Prior statin users (defined as individuals with any statin prescription within two years before the index date) were excluded in further sensitivity analysis.

To address potential immortal time bias that may spuriously augment the beneficial effect of a drug,[36] further sensitivity analysis was performed by treating all

medications including statins as time-varying covariates in the multivariable Cox model,[37] in which the observation period was disintegrated into yearly intervals and medication usage was defined as ≥90-day use in each interval. Statistical significance was defined by a two-sided p-value of <0.05.

RESULTS

Cohort characteristics

We identified 63,605 eligible subjects. **Table 1** shows the baseline characteristics of the cohort. Out of 54,594 subjects with available ethnicity data, 54,219 (99.3%) were Asian. The mean age of receiving clarithromycin-based triple therapy was 55.6 (±14.6) years, and 46.6% were male. There were 15,990 (25.1%) statin users in the cohort (simvastatin:12,578 [78.7%]; atorvastatin:532 [3.3%]; rosuvastatin:275 [1.7%]; use of two or more statins at different times: 2605 [16.3%]). Before PS matching, most of the baseline characteristics were imbalance between statin and non-statin users. However, there was no statistically significant difference in the median number of upper endoscopies (statin users: 2, IQR:1.5–3 vs non-statin users: 2, IQR: 1–3;p=0.892). After PS matching, a balance of covariates were achieved between the two groups except for chronic renal failure (ASD > 0.2), which was adjusted for in the subsequent competing risk regression model.

Risk of gastric cancer development

During a median follow up of 7.6 years (IQR:5.1–10.3) with 484,680 person-years, 169 (0.27%) patients were diagnosed with gastric cancer at an incidence rate of 3.5 per 10,000 person-years. Gastric cancer patients were diagnosed at a median of 71.1 years (IQR:61.6–81.8), and they received eradication therapy at a median of 66.7

years (IQR:56.6–76.5). The location of these cancers were as follows: 34 (20.1%) in cardia, 98 (58.0%) in non-cardia region, and site was unspecified in 37 (21.9%) cases.

Relationship between statins and gastric cancer

The median duration of statin use was 3.6 years (IQR:1.6–5.9), with a median cDDD of 432 (IQR:181.6–323.2). Thirty-one (0.19%) of 15,990 statin users developed gastric cancer (crude incidence rate: 2.4 per 10,000 person-years). In contrast, 138 (0.29%) non-statin users developed gastric cancer (crude incidence rate: 3.8 per 10,000 person-years). After PS matching, statins were associated with a lower gastric cancer risk (adjusted SHR:0.34, 95% CI:0.19–0.61) (**Table 2**). The PS adjusted absolute risk difference was 2.6 fewer gastric cancers (95% CI:1.56–3.12) per 10,000 person-years when comparing statin with non-statin use. **Figure 2** shows the Kaplan Meier plot of gastric cancer incidence among statin and non-statin users (log-rank $p<0.001$). Stratified analysis shows statins remained protective for non-cardia cancer (SHR:0.48, 95% CI:0.24–0.98), but borderline significance was noted for cardia cancer (SHR:0.31, 95% CI:0.09–1.03).

Sensitivity analyses by changing days of exposure to define statin use to ≥ 30 and ≥ 90 days show similar results (≥ 30-day use: SHR 0.34, 95% CI:0.20–0.59; p<0.001; ≥ 90-day use: SHR 0.32, 95% CI:0.18–0.56; p<0.001;). By not including other comorbidities except for peptic ulcer disease and diabetes mellitus, the SHR was 0.45 (95% CI:0.27–0.77; p=0.003). A total of 3,621 patients had prior statin use and were excluded for sensitivity analysis. The adjusted SHR was 0.26 (95% CI:0.12–0.55; p<0.001). Sensitivity analysis by competing risk regression model using PS regression adjustment with trimming and multivariable analysis yield similar results (**Table 2**). PS matching with Cox model also showed that adjusted HR of gastric cancer with statins was 0.29 (95% CI:0.16–0.52). When analyzing medications as time-varying covariates in the multivariable Cox model, the adjusted HR was 0.54 (95% CI:0.35–0.87).

Duration- and dose-response association between statins and gastric cancer

Table 3 shows that a lower gastric cancer risk was observed among patients who used statins longer (SHR 0.46 [95% CI:0.25–0.86] for < 5 years of use and SHR 0.43 [95% CI:0.29–0.66] for ≥5 years of use; p-trend<0.001). In addition, the SHR of gastric cancer with every 100 increase in cDDD of statins was 0.90 (95% CI:0.81–0.99).

DISCUSSION

Individuals can develop gastric cancer despite successful *H. pylori* eradication. In this cohort study of more than 63,000 patients with prior *H. pylori* treatment, we demonstrate that statins were associated with a 66% decrease in gastric cancer risk in a duration- and dose-dependent manner.

To date, association between statins and gastric cancer remains elusive. Although a previous meta-analysis of 11 studies[21] conclude that statins were associated with a lower risk of gastric cancer, one of the major limitations of the included studies was the failure to acknowledge the *H. pylori* status.[21] The study by Chiu et al[10] was the only one that adjusted for *H. pylori* eradication, but 85% of the patients had unknown *H. pylori* status in that study. Failure to account for this causative factor likely poses a significant impact on determining the causal relationship and magnitude of beneficial effect of statins on gastric cancer. In addition, gastric cancer was the primary outcome of interest in two studies only.[10, 11] Also, inadequate adjustment for major risk factors (history of peptic ulcer diseases[38], diabetes mellitus[39] and medication usage [aspirin/NSAIDs,[40, 41] metformin[42] and PPIs[43]]) may either under- or over-estimate the effects of statins.[44] Of note, post-hoc analyses of randomised controlled trials of cardiovascular studies included a relatively short follow-up duration, with potential ascertainment bias and bias from competing risks.[44]

Although being an observational study, our study had a large sample size (>63,000) with long follow-up duration (median 7.6 years), eliminated the confounding effect of *H. pylori* infection, and used PS matching to minimise bias. Importantly, few studies systematically evaluated the duration- and dose-response of statins use.[44] The chemopreventive effects of statins shown in this study (SHR 0.34) was greater than that reported by previous studies (odds ratios ranging from 0.68 to 0.84)[10, 12, 13], except for the study by Lee et al[11] which recruited patients with diabetes mellitus only (odds ratio: 0.21). The greater risk reduction observed in this study could be due to the inclusion of subjects with prior *H. pylori* infection, therefore having a higher gastric cancer risk. We also performed stratified analysis according to cancer site, which had not been performed in any of the previous studies. We found that statins was protective against non-cardia cancer, while the beneficial effect was of borderline significance for cardia cancer (SHR of 0.31 with p=0.055). This result should be interpreted with caution due to underpower (number of cardia cancer cases=34). Lastly, our study used the territory-wide healthcare database with complete capture of diagnosis, drug prescription and dispensing records, which could address potential selection, information and recall biases of previous observational studies.[45] Surveillance or ascertainment bias was unlikely as there existed no difference in the

number of upper endoscopies between the statin and non-statin users. The robustness of the result was further supported by various sensitivity analyses, in particular by using time-varying covariates in treating all medications to address potential immortal time bias. Furthermore, as statin users generally had more comorbidities like cardiovascular diseases and diabetes mellitus (**Table 1**), this negates the concern of healthy user bias.[46] As such, any beneficial effect of statin would only be underestimated (i.e. biased towards null).

There are several limitations of this study. First, residual and unmeasured confounding may still exist for an observational study despite PS matching. Second, information on some risk factors were unavailable in our database, for instance, diet, body mass index, and family history. Third, the accuracy of diagnosis code could only be confirmed by validation of a small subset of gastric cancer patients who had follow-up in our institution. There is also likely an underestimation of prevalence of smoking and alcohol use with ICD-9 codes of COPD and alcohol-related diseases only, although the inclusion of a large set of comorbidities helps to act as surrogate markers for these two imperfectly measured confounders. Fourth, identification of patients with failure of clarithromycin-based triple therapy was indirect rather than based on the actual post-treatment *H. pylori* status since this information was

unavailable in the database. Nevertheless, the re-treatment rate of 13% in our study was consistent with that reported in our locality during the study period.[28] *H. pylori* recurrence could not be ascertained in this database. However, a past local study showed an annual recurrence rate of 3.3% only.[47] Fifth, compliance to medications could not be confirmed, although non-compliance will usually underestimate the beneficial effect of statins. Although data on over-the-counter (OTC) medication usage is unavailable, this is unlikely is a major concern as medications are dispensed at a very low cost from hospital pharmacy in Hong Kong. Unlike western countries, OTC purchase of aspirin is uncommon in Hong Kong. The leading anti-pyretic agent is paracetamol whereas NSAIDs are more often used in pain relief. Sixth, as data on baseline gastric histology was not available, we could not determine on what stages along the Correa cascade that statins exert the strongest effect. Lastly, generalizability of the study result to other statins is a concern, as the majority of patients (79%) were prescribed simvastatin. In addition, this study only focuses on the specific group of *H. pylori*-eradicated patients. Further research on the chemopreventive effects of statins in both *H. pylori*-positive and negative subjects is mandated.

CONCLUSIONS

Long-term statin use associated a lower gastric cancer risk in a dose- and duration-response manner among *H. pylori*-eradicated patients. Our findings may help in decision making for initiating statins in patients at high gastric cancer risk.

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Table 1. Baseline characteristics of study cohort before and after propensity score matching

		Before PS Matching			After PS Matching *		
	All (n=63,605)	**Statin (n=15,990)**	**Non-statin (n=47,615)**	**ASD#**	**Statin (n=11,678)**	**Non-statin (n=11,192)**	**ASD#**
Age at triple therapy (years)	55.6 (+/-14.6)	62.6 (+/-11.1)	53.5 (+/-14.9)	0.66	61.7 (+/-11.0)	63.6 (+/-13.8)	0.18
Male sex (n, %)	29629 (46.6%)	8041 (50.3%)	21588 (45.3%)	0.09	5714 (48.9%)	5313 (47.5%)	0.01
Duration of follow-up (years)	7.6 (5.1 – 10.3)	8.0 (5.5 – 10.5)	7.4 (4.9 – 10.2)	-	7.9 (5.5 – 10.3)	7.1 (4.7 – 9.8)	-
Smoking (n, %)	1647 (2.6%)	561 (3.5%)	1086 (2.3%)	0.08	394 (3.4%)	327 (2.9%)	0.02
Alcohol (n, %)	556 (0.9%)	78 (0.5%)	478 (1.0%)	0.01	51 (0.4%)	45 (0.4%)	0.01
History of GU (n, %)	1463 (2.3%)	448 (2.8%)	1015 (2.1%)	0.05	322 (2.8%)	286 (2.6%)	0.03
History of DU (n, %)	1913 (3.0%)	444 (2.8%)	1469 (3.1%)	0.02	318 (2.7%)	270 (2.4%)	0.01
DM (n, %)	7436 (11.7%)	4652 (29.0%)	2784 (5.8%)	0.44	2827 (24.2%)	1821 (16.3%)	0.07
Dyslipidemia (n, %)	5082 (8.0%)	3974 (24.9%)	1108 (2.3%)	0.39	1897 (16.2%)	851 (7.6%)	0.08
Hypertension (n, %)	13173 (20.7%)	6776 (42.4%)	6397 (13.4%)	0.47	4271 (36.6%)	3221 (28.8%)	0.06
IHD (n, %)	5756 (9.0%)	4189 (26.2%)	1567 (3.3%)	0.37	2054 (17.6%)	1092 (9.8%)	0.05
AF (n, %)	2439 (3.8%)	1107 (6.9%)	1332 (2.8%)	0.16	770 (6.6%)	653 (5.8%)	0.04
CHF (n, %)	2554 (4.0%)	1300 (8.1%)	1254 (2.6%)	0.18	831 (7.2%)	612 (5.5%)	0.02
Stroke (n, %)	4005 (6.3%)	2422 (15.1%)	1583 (3.3%)	0.28	1485 (12.7%)	929 (8.3%)	0.01
CRF (n, %)	1416 (2.2%)	764 (4.8%)	652 (1.4%)	0.14	487 (12.7%)	362 (8.3%)	0.40
Cirrhosis (n, %)	1049 (1.6%)	115 (0.7%)	934 (2.0%)	0.02	75 (0.6%)	86 (0.8%)	0.03
Aspirin (n, %)	11116 (17.5%)	7684 (48.1%)	3432 (7.2%)	0.63	4215 (36.1%)	2287 (20.4%)	0.01
Metformin (n, %)	8993 (14.1%)	6200 (38.8%)	2793 (5.9%)	0.57	3772 (32.3%)	2253 (20.1%)	0.06
NSAIDs/ COX-2 inhibitors (n, %)	14692 (23.1%)	4435 (27.7%)	10257 (21.5%)	0.10	1418 (12.1%)	1383 (12.4%)	0.01

PPIs (n, %)	7715 (12.1%)	2955 (18.5%)	4760 (10.0%)	0.18	1224 (10.5%)	1020 (9.1%)	0.02

Age of receiving triple therapy was expressed as mean (years) +/- 1 standard deviation
Duration of follow-up was expressed as median (years) with interquartile range
Categorical variables were expressed as number (%)
Drug use was defined as use for more than 180 days, and expressed as number (%)
Abbreviations: PS, propensity score; ASD, absolute standardized difference; 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
* PS matching was performed after trimming of the extreme PS strata (5^{th} and 95^{th} percentiles). Non-statin users were matched to statin users on PS within a caliper width of 0.1. All variables were included in the model for PS estimation
[#] Variables with an ASD > 0.20 is considered to be imbalance

Table 2. Association between statin use and gastric cancer risk (whole cohort and stratified analysis according to non-cardia and cardia regions)

Statin use	Univariate analysis (n=63,605, GC=169)			PS matching* (n=22,870, GC=62)			PS adjustment* (n=57,243, GC=150)			Multivariable analysis (n=63,605, GC=169)		
All GC	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**
Non-statin use	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
Statin use	0.61	0.41–0.92	0.020	0.34	0.19–0.61	<0.001	0.33	0.18–0.59	<0.001	0.44	0.28–0.68	<0.001
Non-cardia GC	**(n=63,571, GC=135)**			**(n=22,865) GC=36)**			**(n=57,123, GC=120)**			**(n=63,571, GC=135)**		
	SHR	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**
Non-statin use	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
Statin use	0.56	0.35–0.90	0.017	0.48	0.24–0.98	0.044	0.33	0.17–0.65	0.001	0.46	0.27–0.74	0.002
Cardia GC	**(n=63,470, GC=34)**			**(n=22,865) GC=15)**			**(n=57,123, GC=30)**			**(n=63,470, GC=34)**		
	SHR	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**
Non-statin use	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
Statin use	0.83	0.39–1.90	0.660	n.a.[#]	n.a.[#]	n.a.[#]	0.31	0.09–1.03	0.055	n.a.[#]	n.a.[#]	n.a.[#]

Statin use was defined as use for more than 180 days
Abbreviations: PS, propensity score; SHR, subdistribution hazard ratio; 95% CI, 95% confidence interval; PS, propensity score; GC, gastric cancer
* PS analysis was performed after trimming of the extreme PS strata (5^{th} and 95^{th} percentiles)
[#] SHR could not be calculated as the estimation procedure for fitting the subdistribution hazard model failed to converge

Table 3. Association between duration and dose of statin use and gastric cancer risk (propensity score adjustment)

Statin use	SHR*	95% CI	p-value	p-trend
Duration				
Non-statin use	Ref	-	-	
< 5 years	0.46	0.25 – 0.86	0.015	<0.001
≥ 5 years	0.43	0.29 – 0.66	<0.001	
Dose				
Non-statin use	Ref	-	-	
Statin use (for every 100 increase in cDDD)	0.90	0.81 – 0.99	0.037	

Abbreviations: SHR, subdistribution hazard ratio; 95% CI, 95% confidence interval

* SHR was derived by PS adjustment after trimming of the extreme PS strata (5^{th} and 95^{th} percentiles)

FIGURE LEGENDS

Figure 1: Patient selection flow diagram

Abbreviations: GC, gastric cancer

Figure 2: Kaplan Meier plot of gastric cancer incidence among propensity score matched statin and non-statin users

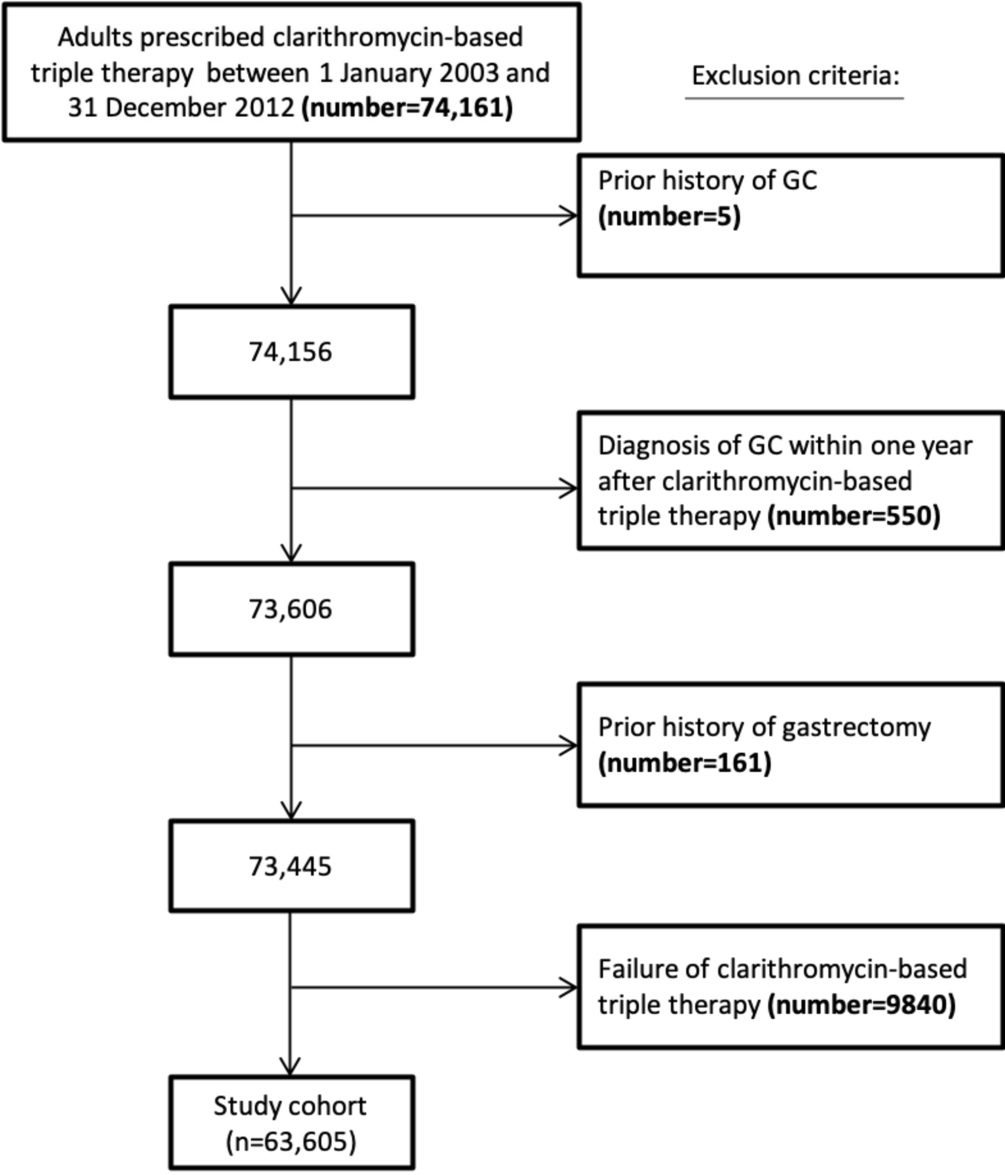

Figure 1

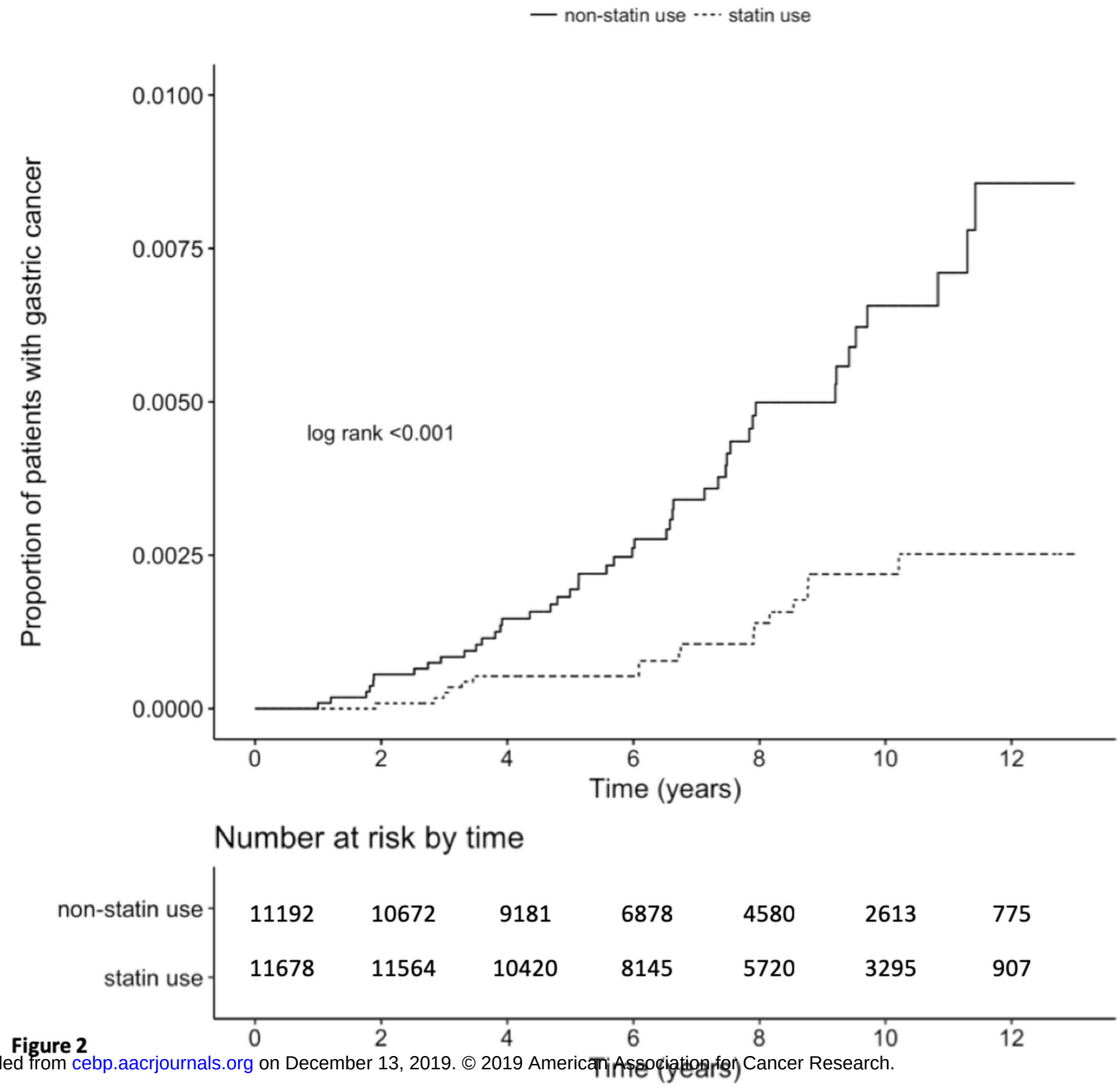

Figure 2

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Statins were associated with a reduced gastric cancer risk in patients with eradicated Helicobacter pylori infection: a territory-wide propensity score matched study

Ka Shing Cheung, Esther W Chan, Angel YS Wong, et al.

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