Proton pump inhibitors and risk of gastric cancer: population-based cohort study

Devin Abrahimi,1,2 Emily Gibson McDonald,3,4 Mireille E Schnitzer,1,5 Alan N Barkun 6,1,6 Samy Suissa 1,2,7 Laurent Azoulay 1,2,8

ABSTRACT

Objective To determine whether new users of proton pump inhibitors (PPIs) are at an increased risk of gastric cancer compared with new users of histamine-2 receptor antagonists (H2RAs).

Design Using the UK Clinical Practice Research Datalink, we conducted a population-based cohort study using a new-user active comparator design. From 1 January 1990 to 30 April 2018, we identified 973 281 new users of PPIs and 193 306 new users of H2RAs. Cox proportional hazards models were fit to estimate HRs and 95% CIs of gastric cancer, and the number needed to harm was estimated using the Kaplan-Meier method. The models were weighted using standardised mortality ratio weights using calendar time-specific propensity scores. Secondary analyses assessed duration and dose–response associations.

Results After a median follow-up of 5.0 years, the use of PPIs was associated with a 45% increased risk of gastric cancer compared with the use of H2RAs (HR 1.01, 95% CI 0.88 to 1.16).9–20 The number needed to harm was 2121 and 1191 for five and 10 years after treatment initiation, respectively. The HRs increased with cumulative duration, cumulative omeprazole equivalents and time since treatment initiation. The results were consistent across several sensitivity analyses.

Conclusion The findings of this large population-based cohort study indicate that the use of PPIs is associated with an increased risk of gastric cancer compared with the use of H2RAs, although the absolute risk remains low.

INTRODUCTION

Acid suppressant drugs, which include proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), are commonly prescribed to manage the symptoms of several gastric conditions.1–4 In recent years, PPIs have become increasingly popular,4 in part due to their superior acid suppression and their perceived safety profile.5–6 However, although controversial, there is some evidence that the use of PPIs may be associated with several adverse gastrointestinal-related health outcomes, including Clostridium difficile infection, enteric colonisation with multidrug-resistant organisms and gastric cancer.7–20

A possible association between PPI use and gastric cancer is biologically plausible, as PPIs are known to cause hypergastrinaemia, which may induce hyperplasia.21 22 To date, several observational studies have examined the association between PPI use and gastric cancer incidence, all of which have reported elevated relative risks ranging from 1.06 to 3.61, aside from one null study (HR 1.01, 95% CI 0.88 to 1.16).9–20 However, these studies had significant methodological shortcomings, which may have exaggerated their findings. The majority of studies compared PPI users to the general population, which likely introduced confounding by indication, while other studies introduced conclusion-altering time-related biases, such as immortal-time bias and time-window bias.23–25

Given that PPIs are one of the most commonly prescribed drug classes worldwide, and uncertainties relating to their association with gastric cancer remain, we conducted a large population-based cohort study to determine whether patients newly treated with PPIs are at an increased risk of gastric cancer compared with patients newly treated with H2RAs.
Methods

Data Source
This study was conducted using the UK Clinical Practice Research Datalink (CPRD). The CPRD is a large primary care database shown to be well representative of the general UK population, which contains the complete records of more than 15 million patients. Recorded data includes patient characteristics, medical diagnoses, prescriptions and lifestyle characteristics. Cancer diagnoses have been previously validated, with positive predictive values for gastro-oesophageal cancers as high as 96%.28–31

Study Population
We used a new-user, active comparator design where patients newly treated with PPIs were compared with patients newly treated with H2RAs. This active comparator was chosen to minimise confounding by indication, given that H2RAs are used for similar indications as PPIs. Cohort entry was defined as the date of the first prescription of either a PPI or an H2RA during the study period (identified using British National Formulary codes, online supplemental tables 1 and 2), from 1 January 1990 (first full year of PPI and H2RA availability) through 30 April 2018. At cohort entry, all patients were required to be at least 40 years old and have at least 1 year of medical information in the CPRD; the latter was necessary to identify new PPI and H2RA users. We excluded patients for whom a PPI and an H2RA were prescribed concomitantly at cohort entry, anyone with a history of gastric cancer (ie, to exclude prevalent cases), rare inherited cancer syndromes (Lynch syndrome, familial adenomatous polyposis, Li-Fraumeni syndrome or Peutz-Jeghers syndrome),32 or Zollinger-Ellison syndrome (online supplemental figure 1). Finally, the cohort was restricted to patients with at least 1 year of follow-up after cohort entry (ie, 1-year lag period) to allow for a latency time-window and minimise detection bias and reverse causality.33

Exposure Definition
All patients were followed starting 1 year after cohort entry until an incident diagnosis of gastric cancer (identified using Read codes [online supplemental table 3], 1 year after switching between the study drug classes [ie, switch from PPI to H2RA or vice versa to account for the 1-year lag period, with person-time during the lag period attributed to initial exposure], death from any cause, end of registration with the general practice, or end of the study period [30 April 2019], whichever occurred first. Patients were considered continuously exposed from cohort entry, regardless of treatment termination, as this exposure definition aligns with the hypothesised biological mechanism (ie, an irreversible effect of PPIs on gastric cancer development that persists even after treatment discontinuation).

Potential Confounders
We considered a wide range of potential confounders, all measured on or before cohort entry. These included demographic

Figure 1  Study flow chart describing the construction of the proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) cohorts.
Table 1  Baseline characteristics of PPI and H2RA users before and after weighting

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before weighting</th>
<th>PPI</th>
<th>H2RA</th>
<th>ASD</th>
<th>After weighting*</th>
<th>PPI</th>
<th>H2RA</th>
<th>ASD</th>
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<tbody>
<tr>
<td>Total</td>
<td>973 281</td>
<td>198 306</td>
<td>973 281</td>
<td>972 083</td>
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<td>Age (mean, SD)</td>
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<td>60.4 (13.1)</td>
<td>60.4 (13.0)</td>
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<td>436 521 (44.9)</td>
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<td>7912 (4.0)</td>
<td>55 957 (5.8)</td>
<td>56 352 (5.8)</td>
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<tr>
<td>Smoking status</td>
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<tr>
<td>Current</td>
<td>260 166 (26.7)</td>
<td>50 856 (25.7)</td>
<td>260 166 (26.7)</td>
<td>259 094 (26.7)</td>
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<td></td>
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<tr>
<td>Former</td>
<td>141 467 (14.5)</td>
<td>20 490 (10.3)</td>
<td>141 467 (14.5)</td>
<td>142 286 (14.6)</td>
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<td>Never</td>
<td>538 106 (55.3)</td>
<td>100 006 (50.4)</td>
<td>538 106 (55.3)</td>
<td>537 236 (55.3)</td>
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<td>26 954 (13.6)</td>
<td>33 542 (3.5)</td>
<td>33 467 (3.4)</td>
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<tr>
<td>&lt;25 kg/m²</td>
<td>361 873 (37.2)</td>
<td>67 314 (33.9)</td>
<td>361 873 (37.2)</td>
<td>362 379 (37.3)</td>
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<td>25–29.9 kg/m²</td>
<td>326 240 (33.5)</td>
<td>58 226 (29.4)</td>
<td>326 240 (33.5)</td>
<td>325 379 (33.5)</td>
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<tr>
<td>≥30 kg/m²</td>
<td>177 306 (18.2)</td>
<td>27 732 (14.0)</td>
<td>177 306 (18.2)</td>
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<td>Atrial fibrillation</td>
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<td>35 757 (3.7)</td>
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<td>14 860 (7.5)</td>
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<td>90 836 (9.3)</td>
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<td>Cancer</td>
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<td>81 000 (8.3)</td>
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<tr>
<td>Chronic kidney disease</td>
<td>21 232 (2.2)</td>
<td>6 372 (3.2)</td>
<td>21 232 (2.2)</td>
<td>21 920 (2.3)</td>
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<td>Congestive heart failure</td>
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<td>55 (0.0)</td>
<td>293 (0.0)</td>
<td>371 (0.0)</td>
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<td>Hypercholesterolaemia</td>
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<td>33 809 (17.1)</td>
<td>293 279 (30.1)</td>
<td>292 404 (30.1)</td>
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<td>Hypertension</td>
<td>311 466 (32.0)</td>
<td>51 441 (25.9)</td>
<td>311 466 (32.0)</td>
<td>310 451 (31.9)</td>
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<td>Venous thromboembolism</td>
<td>44 121 (4.5)</td>
<td>7 944 (4.0)</td>
<td>44 121 (4.5)</td>
<td>44 645 (4.6)</td>
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<tr>
<td>Chronic kidney disease</td>
<td>54 247 (5.6)</td>
<td>4 044 (2.0)</td>
<td>54 247 (5.6)</td>
<td>55 217 (5.7)</td>
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<tr>
<td>Gastric metaplasia</td>
<td>49 495 (5.1)</td>
<td>10 105 (5.1)</td>
<td>49 495 (5.1)</td>
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<tr>
<td>Gastric surgery</td>
<td>32 113 (3.3)</td>
<td>7 568 (3.8)</td>
<td>32 113 (3.3)</td>
<td>33 737 (3.5)</td>
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<tr>
<td>Gastric ulcer disease</td>
<td>85 760 (8.8)</td>
<td>13 108 (6.6)</td>
<td>85 760 (8.8)</td>
<td>85 927 (8.8)</td>
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<td>Dialysis</td>
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<td>304 (0.2)</td>
<td>794 (0.1)</td>
<td>807 (0.1)</td>
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<td>Gastric surgery</td>
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<td>645 (0.3)</td>
<td>6 678 (0.3)</td>
<td>2 654 (0.3)</td>
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<tr>
<td>Barrett's oesophagus</td>
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<td>79 (0.0)</td>
<td>29 288 (3.0)</td>
<td>36 27 (0.4)</td>
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<td>Helicobacter pylori infection</td>
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<tr>
<td>Gastric-oesophageal reflux disease</td>
<td>86 985 (8.9)</td>
<td>17 461 (8.1)</td>
<td>86 985 (8.9)</td>
<td>90 581 (9.3)</td>
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<tr>
<td>Peptic ulcer disease</td>
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<td>8 623 (4.4)</td>
<td>29 338 (3.0)</td>
<td>29 795 (3.1)</td>
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<tr>
<td>Dyspepsia</td>
<td>169 147 (17.4)</td>
<td>60 869 (30.7)</td>
<td>169 147 (17.4)</td>
<td>172 000 (17.8)</td>
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</tr>
<tr>
<td>Gastritis</td>
<td>41 343 (4.3)</td>
<td>11 094 (5.6)</td>
<td>41 343 (4.3)</td>
<td>42 142 (4.3)</td>
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<tr>
<td>Stomach pain</td>
<td>273 864 (28.1)</td>
<td>58 350 (29.4)</td>
<td>273 864 (28.1)</td>
<td>277 333 (28.6)</td>
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<tr>
<td>Metformin</td>
<td>56 972 (5.9)</td>
<td>6 286 (3.2)</td>
<td>56 972 (5.9)</td>
<td>57 053 (5.9)</td>
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<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>692 208 (71.1)</td>
<td>123 534 (62.3)</td>
<td>692 208 (71.1)</td>
<td>689 062 (70.9)</td>
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<tr>
<td>Antiplaetlets</td>
<td>231 359 (23.8)</td>
<td>37 483 (18.9)</td>
<td>231 359 (23.8)</td>
<td>232 216 (23.9)</td>
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<tr>
<td>Dual antiplatelets</td>
<td>67 206 (6.9)</td>
<td>9 164 (4.6)</td>
<td>67 206 (6.9)</td>
<td>68 440 (7.0)</td>
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<tr>
<td>Cyclooxygenase-2 inhibitors</td>
<td>82 509 (8.5)</td>
<td>8622 (4.4)</td>
<td>82 509 (8.5)</td>
<td>82 734 (8.5)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Continued on June 22, 2023 by guest. Protected by copyright.
The models were weighted using standardised mortality ratio weights estimated using calendar time-specific propensity scores. The propensity scores were estimated using logistic regression as the predicted probability of receiving a PPI versus an H2RA conditional on the covariates listed above and within 5-year calendar year bands of cohort entry (1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2018). Calendar year bands were used to account for temporal changes in acid suppressant drug prescribing, changes in gastric cancer incidence, heterogeneity in covariate definitions during the study period. Calendar-time specific propensity scores may result in better confounding control compared with a single propensity score model. Patients in non-overlapping regions of the propensity score distributions were trimmed.

Using the propensity scores, patients exposed to PPIs were given a weight of 1, while patients exposed to H2RAs were given a weight of the odds of the treatment probability (propensity score / (1-propensity score)). This upweights the comparator patients (ie, H2RA users) to represent the treated population (ie, PPI users). Covariate balance was assessed before and after weighting using standardised differences, with differences of less than 0.10 indicative of good balance.

We calculated crude incidence rates of gastric cancer with 95% CIs, based on the Poisson distribution, and constructed weighted Kaplan-Meier curves to compare the cumulative incidence of gastric cancer for PPI and H2RA users. The pseudo population created by weighting should balance the study covariates outlined above so that cumulative incidence of gastric cancer can be compared between PPI and H2RA users. Cox proportional hazards models were fit to estimate weighted HRs of gastric cancer with 95% CIs using robust variance estimators. We also

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before weighting</th>
<th>After weighting*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin analogues</td>
<td>1564 (0.2)</td>
<td>1692 (0.2)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>216,197 (22.2)</td>
<td>1692 (0.2)</td>
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<td>Anticoagulants</td>
<td>37,461 (3.9)</td>
<td>1692 (0.2)</td>
</tr>
<tr>
<td>Steroids</td>
<td>155,048 (15.9)</td>
<td>1692 (0.2)</td>
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<tr>
<td>1990–1994</td>
<td>7839 (0.8)</td>
<td>7857 (0.8)</td>
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<tr>
<td>1995–1999</td>
<td>36,611 (3.8)</td>
<td>36,711 (3.8)</td>
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<tr>
<td>2000–2004</td>
<td>148,408 (15.3)</td>
<td>148,453 (15.3)</td>
</tr>
<tr>
<td>2005–2009</td>
<td>327,938 (33.7)</td>
<td>328,102 (33.8)</td>
</tr>
<tr>
<td>2010–2018</td>
<td>452,485 (46.5)</td>
<td>452,485 (46.5)</td>
</tr>
</tbody>
</table>

Before weighting: counts (percentages), unless otherwise stated; after weighting: count, rounded to the nearest whole number, (percentages), unless otherwise stated.

*Pseudopopulation created by applying standardised mortality ratio weights from calendar time-specific propensity scores. AQL: absolute standardised difference; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.; ASD, absolute standardised difference; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

Statistical analysis

The models were weighted using standardised mortality ratio weights estimated using calendar time-specific propensity scores. The propensity scores were estimated using logistic regression as the predicted probability of receiving a PPI versus an H2RA conditional on the covariates listed above and within 5-year calendar year bands of cohort entry (1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2018). Calendar year bands were used to account for temporal changes in acid suppressant drug prescribing, changes in gastric cancer incidence, heterogeneity in covariate definitions during the study period. Calendar-time specific propensity scores may result in better confounding control compared with a single propensity score model. Patients in non-overlapping regions of the propensity score distributions were trimmed.

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We calculated crude incidence rates of gastric cancer with 95% CIs, based on the Poisson distribution, and constructed weighted Kaplan-Meier curves to compare the cumulative incidence of gastric cancer for PPI and H2RA users. The pseudo-population created by weighting should balance the study covariates outlined above so that cumulative incidence of gastric cancer can be compared between PPI and H2RA users. Cox proportional hazards models were fit to estimate weighted HRs of gastric cancer with 95% CIs using robust variance estimators. We also
calculated the number needed to harm at five and 10 years of follow-up using the Kaplan-Meier method.\textsuperscript{44}

**Secondary analyses**

We performed four prespecified secondary analyses. The first set of analyses modelled PPI use as a time-varying variable, updated at each person-day of follow-up, to determine whether the association varies by cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation. The cumulative duration was defined by summing the durations of each PPI prescription from cohort entry until the time of the risk set. To account for the different potencies of PPI types, we converted all PPI prescriptions to omeprazole equivalents using the WHO defined daily dose (online supplemental table 4).\textsuperscript{45} Cumulative omeprazole equivalents were then calculated by summing the dose of each prescription from cohort entry until the time of each event-defining risk set. Finally, time since treatment initiation was defined as the time between the cohort entry until the time of the risk set. HRs for these secondary exposures were estimated according to predefined categories, and cumulative duration and dose were also modelled flexibly using restricted cubic spline models.\textsuperscript{44} Second, we assessed the possibility of a drug-specific effect by stratifying the analyses by individual PPI molecules (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole or combinations). Third, we investigated potential effect measure modification by age and sex by including an interaction term in the model between exposure status and these variables. Finally, we calculated stratified HRs according to approved indications at baseline and within strata of the year of cohort entry.

**Sensitivity analyses**

We conducted six sensitivity analyses to assess the robustness of our findings. First, given uncertainties related to the optimal length of the latency time window, we repeated the primary analysis by increasing the exposure lag period to three, five and 10 years. Second, to assess the impact of informative censoring, we did not censor patients who switched from PPIs to H2RAs and vice versa (ie, analogous to an intention-to-treat exposure definition whereby patients are considered continuously exposed to their cohort entry drug until the end of follow-up). Third, as an alternative method to investigate the impact of informative censoring, we combined the standardised mortality ratio weights with stabilised inverse probability of censoring weights to account for censoring from drug switching during follow-up.\textsuperscript{46,47} and to account for the competing risk of death (online supplemental method 1).\textsuperscript{48} Fourth, as certain H2RAs (such as ranitidine), have recently been found to be contaminated with N-nitrosodimethylamine (NDMA), a probable carcinogen,\textsuperscript{49} we repeated the analysis with follow-up truncated on 31 December 2017, which is before the time NDMA contaminants were found.\textsuperscript{49} Fifth, to investigate the impact of residual confounding, we repeated the primary analysis using the high-dimensional propensity score (HD-PS) approach to reweigh our study population (online supplemental method 2).\textsuperscript{50} We considered all predefined covariates listed above, along with 200 empirically selected covariates from the HD-PS algorithm for this analysis. Finally, we conducted a post hoc sensitivity analysis to address the potential impact of residual confounding using the approach proposed by Ding and VanderWeele (online supplemental method 3).\textsuperscript{51} All analyses were conducted with SAS V.9.4 (SAS Institute) and R (R Foundation for Statistical Computing, Vienna, Austria).

**Patient and public involvement**

We did not include patients as study participants as our study involved the use of secondary data. Patients were not involved in the design or implementation of the study. We do not plan to involve patients in the dissemination of results, nor will we disseminate results directly to patients.

**RESULTS**

The cohort included 973 281 new PPI users and 198 306 new H2RAs users (figure 1). These exposure groups were followed for a median (Q1, Q3) duration of 5.1 (2.7, 8.4) and 4.2 (1.9, 8.3) years, respectively, including the 1-year lag period. There were 1166 incident gastric cancer events in the PPI cohort, which generated a crude incidence rate of 23.9 (95% CI 22.3 to 25.3) per 100 000 person-years. In the H2RA cohort, there were 244 incident gastric cancer events, which generated a crude incidence rate of 25.8 (95% CI 22.6 to 29.2) per 100 000 person-years.

Table 1 shows the baseline characteristics of the PPI and H2RA exposure groups. Before weighting, PPI users were more likely to be obese, have a prior diagnosis of hypercholesterolaemia, chronic kidney disease, and H. pylori infection, but were less likely to have dyspepsia compared with H2RA users. PPI users were also more likely to have been prescribed NSAIDs, COX-2 inhibitors and SSRIs. Overall, most H2RA users entered the cohort earlier in the study period, while most PPI users entered later in the study period. After weighting, PPI users and H2RA users were well balanced on all study covariates (standardised differences below 0.10). During the follow-up period, H2RA users were more likely to have been censored due to a switch to a PPI than PPI users to a switch to H2RAs (56.2% vs 7.9%, respectively).

Table 2 shows the results of the primary and secondary analyses. While the crude HR was below the null value (HR: 0.92), the use of PPIs was associated with an increased risk of gastric cancer after adjusting for calendar year strata (HR: 1.34, 95% CI 1.14 to 1.57). In the fully adjusted model, the use of PPIs was associated with a 45% increased risk of gastric cancer, compared with the use of H2RAs (HR: 1.45, 95% CI 1.06 to 1.98). Similarly, PPI users had a higher cumulative incidence of gastric cancer than H2RA users. The weighted cumulative incidence curves diverged after two years of follow-up (or years after treatment initiation) (figure 2). The number needed to harm was 2121 and 1191 after five and 10 years after treatment initiation, respectively.

In secondary analyses, the HRs increased with cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation (table 2). These patterns were consistent in the restricted cubic spline models (online supplemental figures 2 and 3). The median (Q1, Q3) cumulative duration of PPI use was 139 days but was variable by indication, ranging from 130 (36, 715) days for H. pylori infection, but were less likely to have dyspepsia compared with H2RA users. PPI users were also more likely to have been prescribed NSAIDs, COX-2 inhibitors and SSRIs. Overall, most H2RA users entered the cohort earlier in the study period, while most PPI users entered later in the study period. After weighting, PPI users and H2RA users were well balanced on all study covariates (standardised differences below 0.10). During the follow-up period, H2RA users were more likely to have been censored due to a switch to a PPI than PPI users to a switch to H2RAs (56.2% vs 7.9%, respectively).

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All PPI molecules were associated with elevated HRs for gastric cancer (ranging from 1.19 to 1.48; online supplemental table 5). While the point estimates increased with age (online supplemental table 6), and females had a slightly higher HR than males (online supplemental table 7) the CIs for these analyses were overlapping, which suggests no effect measure modification by age or sex. HRs were elevated among patients with gastro-oesophageal disease (HR 1.38, 95% CI 0.59 to 3.22) and peptic ulcer disease (HR 1.53, 95% CI 0.49 to 4.92) (online supplemental table 8). When stratifying by calendar year strata, there was some heterogeneity in the HRs (ranging from 0.87 to 2.55), though the CIs...
Stomach for all strata were largely overlapping (online supplemental table 9).

Figure 3 summarises the results of the primary and sensitivity analyses (shown in detail in online supplemental tables 10–14). Overall, the findings were highly consistent with those of the primary analysis, with HRs ranging between 1.26 for the intention-to-treat analysis and 2.21 for the 10-year lagged analysis. Based on a post hoc analysis, an unmeasured confounder would need to be strongly related to both the exposure and outcome to nullify the observed association (online supplemental table 15).

DISCUSSION

Principal findings
In this large population-based cohort study, we observed that new users of PPIs are at a 45% increased risk of gastric cancer (HR 1.45, 95% CI 1.06 to 1.98) compared with new users of H2RAs, with a number needed to harm of 2121 and 1191 for five and 10 years after treatment initiation, respectively (figure 4). In secondary analyses, the risk increased with cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation. The results remained highly consistent across several sensitivity analyses that addressed different sources of bias.

Comparison with previous studies
The findings of this study are in line with those of several previous observational studies, with previous estimates ranging from 1.01 to 3.61,9–20 including one study conducted using the same database.16 However, our study used an active comparator and was explicitly designed to assess the comparative safety of PPIs versus H2RAs. This is a clinically relevant question that was not addressed by previous studies. Indeed, other studies may have overestimated the risk of PPIs on gastric cancer incidence by comparing PPI users to the general population,9–19 given that patients with gastric conditions are already at an increased risk of

![Figure 2](https://example.com/figure2.png)

**Figure 2** Weighted Kaplan-Meier curve illustrating the cumulative incidence of gastric cancer in patients newly prescribed proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RA). Follow-up starts 1 year after cohort entry. Curves are weighted using standardised mortality ratio weights: PPI patients are given a weight of 1, while H2RA patients are upweighted by the odds of the treatment probability.

![Table 2](https://example.com/table2.png)

**Table 2** Crude and adjusted HRs for the association between the use of PPIs and gastric cancer compared with the use of H2RAs

- **H2RAs**
  - 244 events, 947 person-years
  - Incidence rate: 25.8 (22.6 to 29.2)
  - Crude HR: 1.00
  - Calendar-year weighted HR: 1.00 (reference)
  - Marginal HR: 1.00 (reference)

- **PPIs**
  - 1166 events, 4887 person-years
  - Incidence rate: 23.9 (22.5 to 25.3)
  - Crude HR: 0.92
  - Calendar-year weighted HR: 1.34 (1.14 to 1.57)
  - Marginal HR: 1.45 (1.06 to 1.98)

**Cumulative duration of proton pump inhibitors**

- <2 years: 861 events, 3380 person-years
  - Incidence rate: 22.5 (21.0 to 24.0)
  - Crude HR: 0.82
  - Calendar-year weighted HR: 1.21 (1.03 to 1.42)
  - Marginal HR: 1.33 (0.96 to 1.83)

- ≥4 years: 165 events, 538 person-years
  - Incidence rate: 30.7 (26.2 to 35.7)
  - Crude HR: 1.47
  - Calendar-year weighted HR: 2.09 (1.67 to 2.62)
  - Marginal HR: 2.40 (1.68 to 3.45)

**Cumulative omeprazole dose equivalents**

- <14600 mg: 886 events, 3933 person-years
  - Incidence rate: 22.5 (21.1 to 24.1)
  - Crude HR: 0.83
  - Calendar-year weighted HR: 1.22 (1.04 to 1.43)
  - Marginal HR: 1.33 (0.97 to 1.83)

- 14600–28199 mg: 147 events, 502 person-years
  - Incidence rate: 29.2 (24.7 to 34.4)
  - Crude HR: 1.27
  - Calendar-year weighted HR: 1.81 (1.45 to 2.26)
  - Marginal HR: 2.05 (1.46 to 2.89)

- ≥29200 mg: 143 events, 451 person-years
  - Incidence rate: 29.5 (24.7 to 34.9)
  - Crude HR: 1.39
  - Calendar-year weighted HR: 2.03 (1.60 to 2.58)
  - Marginal HR: 2.34 (1.62 to 3.37)

**Time since proton pump inhibitor initiation**

- <2 years: 293 events, 892 person-years
  - Incidence rate: 32.8 (29.2 to 36.8)
  - Crude HR: 0.94
  - Calendar-year weighted HR: 1.63 (1.17 to 2.29)
  - Marginal HR: 1.25 (0.69 to 2.28)

- ≥4 years: 539 events, 2590 person-years
  - Incidence rate: 20.8 (19.1 to 22.6)
  - Crude HR: 0.98
  - Calendar-year weighted HR: 1.26 (1.01 to 1.56)
  - Marginal HR: 1.82 (1.09 to 3.02)

*Crude incidence rate per 100 000 person-years.
†Weighted using standardised mortality ratio weights.
H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.
gastric cancer. Thus, our study represents an important addition by minimising potential confounding by indication through the use of an active comparator. Beyond this, there were other significant limitations in previous studies, such as the inclusion of prevalent users, which may have introduced survival bias and confounding, important time-related biases such as immortal-time bias and time-window bias, and failure to account for cancer latency. In this context, these conclusion-altering biases can lead to spurious and exaggerated associations, limiting the conclusions drawn from previous studies. We attempted to address these limitations through careful study design and numerous sensitivity analyses.

An association between PPI use and gastric cancer is biologically plausible and may be mediated by several different factors. PPIs are known to cause hypergastrinaemia (elevated secretion of gastrin from G-cells), as gastrin secretion is inhibited by acidity. Gastrin is considered a potent growth factor, which may induce hyperplasia. Second, long-term PPI use may lead to changes in the gut microbiome, including reduced microbial diversity. Changes to the gut microbiota have been shown to contribute to an increased risk of gastric cancer. Third, although disputed, chronic suppression of acid secretion by PPIs may be associated with atrophic gastritis (chronic inflammation of the stomach mucous membrane), which is one of the main precursors to gastric cancer; although not all studies have reported this association. Taken together, these factors may contribute to gastric cancer development among PPI users. Finally, given that H2RAs decrease acid suppression by blocking the effects of histamine only, they are less effective than PPIs, and are associated with lower gastrin levels (ie, less likely to induce hypergastrinaemia). Thus, from a theoretical biological perspective, H2RAs are less likely to be associated with an increased risk of gastric cancer than PPIs.

Strengths and limitations of this study
This study has several strengths. First, to our knowledge, this is the largest study with the longest follow-up period conducted to date. Given the number of gastric events observed in our cohort, this study was sufficiently powered to address the long-term safety of PPIs and assess the risk among important subgroups, including by duration of use. Second, we restricted the cohort to new drug users, eliminating biases associated with the inclusion of prevalent users. Third, the comparator group consisted of patients prescribed H2RAs, an active comparator that likely minimised confounding by indication. Moreover, the use of propensity score-weighted methods ensured an excellent balance of all baseline confounders. Finally, our results remained highly consistent across several sensitivity analyses.

**Figure 3** Forest plot summarising the results of primary and sensitivity analyses, with weighted HRs and 95% CIs for the association between use of proton pump inhibitors and gastric cancer, compared with the use of histamine-2 receptor antagonists. NDMA: N-Nitrosodimethylamine.

**Figure 4** Graphical summary highlighting the main findings of the association between the use of proton pump inhibitors (PPIs) and gastric cancer, compared with the use of histamine-2 receptor antagonists (H2RA). IR, incidence rate; NNH, number needed to harm.
This study also has some limitations. First, prescriptions in the CPRD are written by general practitioners and not specialists, which may lead to some exposure misclassification. However, in the UK, general practitioners are responsible for the long-term care of most chronic conditions, including gastric disorders; thus, we expect this misclassification to have been minimal. Similarly, it was not possible to directly assess treatment adherence, although this possible source of exposure misclassification is unlikely to be differential between the exposure groups. Second, PPIs and H2RAs are available over the counter in the UK, potentially leading to some missing prescription information. However, there is a financial incentive for patients requiring long-term PPI or H2RA use to receive prescriptions from their general practitioner rather than purchasing drugs over the counter. Third, it was not possible to stratify on the gastric cancer type (cardia vs non-cardia) as this information is not consistently recorded in the CPRD. Fourth, some secondary outcomes, like infection, which is not routinely tested for PS. The potential impact of confounding from unmeasured or unknown confounders, including race and ethnicity. Moreover, there may be some residual confounding from imperfectly captured covariates, like H. pylori infection, which is not routinely tested for by general practitioners. Reassuringly, results from the HD-PS model, which considered an additional 200 empirically selected covariates, which may be proxies for unknown or unmeasured confounders, were highly consistent with the primary analysis. Moreover, given the strength of the observed association, a post-hoc analysis showed that any unmeasured confounder would need to be strongly associated with both the exposure and outcome to nullify the observed results.

In summary, the results of this large real-world study suggest that patients newly treated with PPIs may be at an increased risk of gastric cancer compared with patients newly treated with H2RAs, although the absolute risk remains low. While PPIs have established clinical benefits when used according to evidence-based guidelines, this study highlights the need for physicians to regularly reassess the necessity of ongoing treatment. This is especially important in patients who are prescribed PPIs in the long term and for patients without an evidence-based indication for use.

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Contributors All authors conceived and designed the study. LA acquired the data. DA and LA did the statistical analyses. MES and SS provided statistical expertise. All authors analysed and interpreted the data. EGM and ANB provided clinical expertise. DA wrote the manuscript, and all authors critically revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for the accuracy of the work. LA supervised the study and is the guarantor.

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Competing interests SS participated in advisory meetings or as a guest speaker for Astara Biotherapeutics, Boehringer-Ingelheim, Bristol-Myers-Squibb, Merck and Pfizer, all unrelated to this study. LA served as a consultant for Janssen and Pfizer for work unrelated to this study. The other authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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