An Investigation of Proton Pump Inhibitors: Addressing their Utilization and Association with Gastrointestinal Cancers

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Abstract

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are acid suppressant drugs commonly used to manage the symptoms of several gastric conditions. PPIs were first approved for use in the United Kingdom (UK) in 1989, while H2RAs were first approved in 1976. While PPIs are more commonly prescribed than H2RAs, in part due to their superior acid suppression, both drug classes are consistently among the top 25 most prescribed drugs in the hospital setting in the UK. Both drug classes are typically indicated for short-term use, yet there is some evidence that PPIs in particular are increasingly being used for extended periods; this is often without an evidence-based indication or periodic re-evaluation for their ongoing necessity. This has prompted several regulatory agencies to promote PPI deprescribing initiatives, though the effectiveness of these programs remains unclear. Moreover, the safety implications associated with the increased use of PPIs, and particularly with their long-term use, remain uncertain. To date, the use of PPIs has been associated with several adverse health concerns, including enteric infections like *Clostridiodes difficile,* acute interstitial nephritis, and hypomagnesemia. There are also highly inconsistent reports on the potential association between the use of PPIs and gastrointestinal malignancies, including gastric and colorectal cancers. Indeed, this is a biologically plausible association, and one that is particularly contentious, given the severity of these malignancies. However, the existing literature has important methodological shortcomings, which limit the interpretation of the evidence. Given the popularity of acid suppressant drugs and their incomplete safety profile, the overall purpose of my doctoral thesis was to address existing gaps in knowledge regarding the utilization of acid suppressant drugs and the gastrointestinal cancer safety of PPIs.

The objective of the first manuscript was to describe the prescribing patterns of PPIs and H2RAs in the UK over a 29 year period using a cross-sectional population-based study. For this

project, I quantified annual prescription rates in the general population and described the prescribing intensity (i.e., prescribing incidence rate) among acid suppressant drug users using data from the UK Clinical Practice Research Datalink (CPRD). Annual prescription rates were estimated by dividing the number of patients prescribed a PPI or H2RA by the total CPRD population, and changes in prescribing intensity were calculated using negative binomial regression. From January 1, 1990, through December 31, 2018, there were 14,242,329 patients registered in the CPRD, of which 3,027,383 (21.3%) were prescribed at least one PPI or H2RA. PPI prevalence increased from 0.2% in 1990 to 14.2% in 2018, but H2RA prevalence was low throughout follow-up (range 1.2% to 3.4%). Over 20% of patients did not have a recorded indication for acid suppressant use. PPI prescribing intensity increased during the first 15 years of follow-up and plateaued for the remainder, while H2RA prescribing intensity decreased from 1990 to 2009 but has begun to increase over the last five years. This study illustrated that while PPIs remain popular compared to H2RAs, use of PPIs has not completely supplanted use of H2RAs to manage the symptoms of gastric conditions.

The objective of the second manuscript was to determine whether the PPI prescribing guidelines, published by the National Institute for Health and Care Excellence (NICE) in 2014, changed physician prescribing patterns in clinical practice. We used data from the UK CPRD to calculate monthly prescribing rates (number of PPI prescriptions/number of adults in the CPRD). We then used an interrupted time-series analysis to estimate a slope and level change by comparing these monthly rates before (September 2010 to August 2014) and after (September 2014 to August 2018) publication of the guidelines. Before the publication of the guidelines, the monthly prescription rate of PPIs increased by 46.9 (95% confidence interval (CI): 40.8 to 53.0) prescriptions per 100,000 persons. After the guidelines were published, there was no immediate

change in the rate (137.6, 95% CI: -36.7 to 311.9 prescriptions per 100,000 persons), but there was a modest attenuation of the change in monthly rate (-23.9, 95% CI: -14.0 to -33.6 prescriptions per 100,000 persons). However, the predicted rates in the post guideline period mimic the observed rates, suggesting little change in physician prescribing following guideline publication. Thus, despite efforts to minimize the overprescribing of PPIs through these new guidelines, there was little meaningful change in clinical practice.

The objective of the third manuscript was to determine whether new PPI users, compared to new H2RA users, an active comparator representing a clinically meaningful comparison, are at an increased risk of gastric cancer. Using the UK CPRD, we conducted a population-based cohort study from January 1, 1990, to April 30, 2018, with follow-up until April 30, 2019. Cox proportional hazards models were fit to estimate marginal hazard ratios (HRs) and 95% confidence intervals (CIs) of gastric cancer using standardized mortality ratio weights using calendar time-specific propensity scores. The number needed to harm was estimated using the Kaplan-Meier method as a measure of absolute risk. Secondary analyses assessed duration and dose-response relations, and several sensitivity analyses were conducted to assess the robustness of the findings. Throughout follow-up, we identified 973,281 new users of PPIs and 193,306 new users of H2RAs. There were 1,166 incident gastric cancer events in the PPI cohort and 244 incident gastric cancer events in the H2RA cohort. 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: 1.45, 95% CI: 1.06-1.98). The number needed to harm was 2,121 and 1,191 for five and 10 years after treatment initiation, respectively. The HRs increased with increasing duration of PPI use, and the results were consistent across several sensitivity analyses. The findings of this large population-based

cohort study suggest that while the absolute risk of gastric cancer is low, the use of PPIs is associated with an increased risk of gastric cancer compared with the use of H2RAs.

The objective of the fourth manuscript was to determine whether the use of PPIs is associated with an increased risk of colorectal cancer compared with the use of H2RAs. Using the UK CPRD, we identified PPI and H2RA initiators (1,293,749 and 292,387 patients, respectively) from January 1, 1990, to April 30, 2018, with follow-up until April 30, 2019. Cox proportional hazards models were fit to estimate marginal hazard ratios (HRs) and 95% confidence intervals (CIs) of colorectal cancer. The models were weighted using standardized mortality ratio weights using calendar time-specific propensity scores. Secondary analyses assessed duration-response relations, and the number needed to harm at five and 10 years was calculated. Overall, there were 6,759 incident colorectal cancer events among PPI users versus 1,264 events among H2RA users. The use of PPIs was not associated with an overall increased risk of colorectal cancer (HR: 1.02, 95% CI: 0.92 to 1.14). In secondary analyses, HRs increased with cumulative duration of use, cumulative dose, and time since treatment initiation. The number needed to harm was 5,343 and 792 for five and 10 years of follow-up, respectively. This study showed that the use of PPIs, compared with the use of H2RAs, is not associated with an overall risk of colorectal cancer. However, prolonged PPI use may be associated with an increased risk of this malignancy.

Overall, the findings from this thesis provide important knowledge regarding the utilization and cancer safety of acid suppressant drugs. Specifically, the results indicate that both PPIs and H2RAs are continuously overprescribed, often in patients without an underlying indication for use. While treatment guidelines have been updated to curb the overprescribing of PPIs, this has been largely insufficient. While PPIs remain effective, our results suggest that H2RAs are starting to regain favour among general practitioners. This should especially be considered when weighing

the potential harms associated with PPI use, including an increased risk of gastric cancer and a potential increased risk of colorectal cancer. At a minimum, physicians should closely monitor their patients and regularly reassess the need for ongoing PPI treatment, in accordance with guidelines, especially in the long term.

Résumé

Les inhibiteurs de la pompe à protons (IPP) et les antagonistes des récepteurs H2 de l'histamine (anti-H2) sont des médicaments antisécrétoires gastriques qui sont utilisés pour soulager plusieurs symptômes gastriques. Les IPP ont été approuvés pour la première fois au Royaume-Uni en 1989, tandis que les anti-H2 ont été approuvés pour la première fois en 1976. Bien que les IPP soient plus couramment prescrits que les anti-H2, notamment parce qu'ils sont de meilleurs suppresseurs d'acide, les deux classes de médicaments figurent invariablement parmi les 25 médicaments les plus prescrits dans les hôpitaux du Royaume-Uni. Toutes deux sont habituellement indiquées pour une utilisation à court terme, pourtant il y a lieu de croire que les IPP, en particulier, sont de plus en plus utilisés pour de longues périodes; cela se fait sans qu'il existe ni indication fondée sur des données probantes ni réévaluation périodique de la nécessité de leur utilisation. Cet état des choses a poussé plusieurs organismes de réglementation à promouvoir des initiatives de déprescription. Pour l'instant, l'efficacité de ces programmes demeure nébuleuse. Par ailleurs, l'innocuité d'une utilisation accrue, et surtout prolongée, des IPP demeure incertaine. À ce jour, leur utilisation a été associée à plusieurs effets indésirables, y compris des infections entériques comme le *Clostridiodes difficile*, des néphrites interstitielles aiguës et de l'hypomagnésémie. Il existe aussi des rapports contradictoires concernant une association possible entre l'utilisation des IPP et les cancers gastro-intestinaux (gastriques et colorectaux). En fait, une telle association est biologiquement plausible et particulièrement problématique, étant donné la gravité de ces cancers. Cependant, la littérature scientifique existante comporte des lacunes méthodologiques sérieuses qui limitent l'interprétation des données. Compte tenu de la popularité des médicaments antisécrétoires en dépit de leur profil d'innocuité incomplet, l'objectif global de la présente thèse de doctorat était de combler les manques actuels de connaissances sur l'utilisation

des antiacides et la gastro-intestinal cancérogénicité des IPP, en menant à terme des études qui ont conduit à quatre articles.

Le premier article avait pour objet de décrire, au moyen d'une étude transversale basée sur une population, les pratiques de prescription des IPP et des anti-H2 au Royaume-Uni au cours d'une période de 29 ans. Dans le cadre de ce projet, nous avons quantifié les taux annuels d'ordonnances dans la population générale et décrit l'intensité des prescriptions (c.-à-d. taux d'incidence de prescription) chez les utilisateurs de médicaments antisécrétoires à partir de données du Clinical Practice Research Datalink (CPRD) du Royaume-Uni. Les taux annuels d'ordonnances ont été estimés en divisant le nombre de patients qui avaient reçu une ordonnance d'IPP ou d'anti-H2 par la population totale du CPRD; les changements d'intensité des prescriptions, eux, ont été calculés selon un modèle de régression binomiale négative. Du 1er janvier 1990 au 31 décembre 2018, 14 242 329 patients étaient inscrits au CPRD, parmi lesquels 3 027 383 (21,3 %) avaient reçu une ordonnance d'au moins un IPP ou un anti-H2. La prévalence des patients à qui on avait prescrit un IPP a augmenté de 0,2 % en 1990 à 14,2 % en 2018, mais la prévalence de ceux qui avaient reçu une ordonnance d'anti-H2 était faible tout au long de la période de suivi (entre 1,2 % et 3,4 %). Pour plus de 20 % des patients, aucune indication pour la nécessité d'un antisécrétoire n'était consignée. L'intensité des prescriptions d'IPP a augmenté durant les 15 premières années de suivi et a atteint un plateau au cours des années subséquentes, alors que celle des prescriptions d'anti-H2 a diminué entre 1990 et 2009 mais a commencé à s'accroître durant les cinq dernières années. Cette étude a bien illustré que, même si les IPP demeurent plus populaires que les anti-H2, l'utilisation des IPP n'a pas complètement supplanté l'utilisation des anti-H2 pour gérer les symptômes de maladies gastriques.

L'objectif du deuxième article était de déterminer si les lignes directrices en matière de prescription d'IPP, publiées par le National Institute for Health and Care Excellence (NICE) en 2014, avaient entraîné des changements dans les pratiques de prescription en clinique. Nous avons utilisé des données provenant du CPRD pour calculer les taux mensuels d'ordonnances (nombre d'ordonnances d'IPP ÷ nombre d'adultes dans le CPRD). Puis, pour estimer la pente et la variation du niveau de ces taux mensuels avant (de septembre 2010 à août 2014) et après (de septembre 2014 à août 2018) la publication des lignes directrices, nous les avons soumis à une analyse de séries chronologiques interrompues. Avant la publication des lignes directrices, le taux mensuel d'ordonnances des IPP a augmenté de 46,9 (intervalle de confiance [IC] à 95 % : 40,8 à 53,0) ordonnances par 100 000 personnes. Après la publication des lignes directrices, on n'a observé aucune modification immédiate du taux mensuel, qui est passé à 137,6 (IC à 95 % : -36,7 à 311,9) ordonnances par 100 000 personnes, mais il y a eu une diminution modeste de la variation du taux mensuel, soit de -23,9 (IC à 95 % : -14,0 à -33,6) ordonnances par 100 000 personnes. Cependant, dans la période postpublication, les taux observés ont suivi les taux prédits – ce qui suggère que les lignes directrices n'ont pas vraiment influencé les pratiques de prescription et que les efforts déployés pour réduire la prescription abusive d'IPP ont eu peu d'effet.

Le troisième article avait pour objet de déterminer si les nouveaux utilisateurs d'IPP présentent un risque accru de cancer gastrique par rapport aux nouveaux utilisateurs d'anti-H2, un comparateur actif représentant une comparaison cliniquement significative. Au moyen des données du CPRD, nous avons mené une étude de cohorte basée sur une population qui couvrait la période du 1er janvier 1990 au 30 avril 2018, avec suivi jusqu'au 30 avril 2019. Des régressions de Cox (modèles à risque proportionnel) ont été faites pour estimer les rapports de risque (RR) marginaux et les intervalles de confiance (IC) à 95 % du cancer gastrique; une pondération a été

réalisée à l'aide des ratios standardisés de mortalité et des scores de propension spécifiques au temps de calendrier. Le ratio interventions/préjudices a été estimé en utilisant la méthode de Kaplan-Meier comme mesure du risque absolu. Des analyses secondaires ont servi à l'évaluation des relations durée-réponse et dose-réponse, et plusieurs analyses de sensibilité ont été menées pour évaluer la robustesse des résultats. Au cours du suivi, nous avons identifié 973 281 nouveaux utilisateurs d'IPP et 193 306 nouveaux utilisateurs d'anti-H2. Il y a eu 1,166 événements incidents de cancer gastrique dans la cohorte IPP et 244 événements incidents de cancer gastrique dans la cohorte H2RA. Après un suivi médian de 5,0 années, l'utilisation des IPP a été associée à un risque de développer un cancer gastrique 45 % supérieur à celui lié à l'utilisation des anti-H2 (RR : 1,45; IC à 95 % : 1,06 à 1,98). Les ratios interventions/préjudices étaient de 2 121 et 1 191, respectivement, pour cinq ans et dix ans après le début du traitement. Les RR augmentaient avec la durée d'utilisation des IPP, et les résultats étaient cohérents d'une analyse de sensibilité à l'autre. Les résultats de cette vaste étude de cohorte basée sur une population suggèrent que, même si le risque absolu de cancer gastrique est faible, l'utilisation des IPP est associée à un risque de développer ce type de cancer supérieur à celui lié à l'utilisation des anti-H2.

L'objectif du quatrième article était de déterminer si l'utilisation des IPP est associée à un risque accru de cancer colorectal par comparaison à l'utilisation des anti-H2. Toujours au moyen des données du CPRD, nous avons identifié de nouveaux utilisateurs d'IPP et d'anti-H2 (1 293 749 et 292 387 patients, respectivement) au cours de la période du 1er janvier 1990 au 30 avril 2018, avec suivi jusqu'au 30 avril 2019. Des régressions de Cox (modèles à risque proportionnel) ont été faites pour estimer les rapports de risque (RR) marginaux et les intervalles de confiance (IC) à 95 % du cancer colorectal. Les modèles ont été pondérés à l'aide des ratios standardisés de mortalité et des scores de propension spécifiques au temps de calendrier. Des analyses secondaires

ont évalué les relations durée-réponse, et les ratios interventions/préjudices après 5 ans et 10 ans ont été calculés. Dans l'ensemble, il y a eu 6 759 événements incidents de cancer colorectal chez les utilisateurs d'IPP contre 1 264 événements chez les utilisateurs d'ARH2. L'utilisation des IPP n'était pas associée à une augmentation globale du risque de cancer colorectal (RR : 1,02; IC à 95 % : 0,92 à 1,14). Les analyses secondaires ont révélé que les RR augmentaient avec la durée cumulative d'utilisation, la dose cumulative et le temps écoulé depuis le début du traitement. Les ratios interventions/préjudices étaient de 5 343 et 792, respectivement, après cinq ans et dix ans de suivi. L'étude a démontré que l'utilisation des IPP, lorsque comparée à celle des anti-H2, n'était pas associée à un risque global de cancer colorectal. Cependant, l'utilisation prolongée des IPP peut être associée à un risque accru de ce cancer.

Dans l'ensemble, les résultats décrits dans la présente thèse fournissent des connaissances importantes concernant l'utilisation et la cancérogénicité des médicaments antisécrétoires. Spécifiquement, les résultats indiquent qu'aussi bien les IPP que les anti-H2 font continuellement l'objet de prescription abusive, souvent à des patients pour lesquels il n'existe pas d'indication thérapeutique sous-jacente. Même si les lignes directrices ont été mises à jour pour freiner cette prescription abusive, cela s'est avéré nettement insuffisant pour rectifier la situation. Bien que les IPP demeurent efficaces, nos résultats suggèrent que les anti-H2 connaissent un regain de popularité chez les médecins généralistes. C'est ce qu'il faut prendre en compte quand on pèse les éventuels effets indésirables des IPP, notamment un risque accru de cancer gastrique et, potentiellement, de cancer colorectal. Au minimum, les médecins devraient suivre étroitement leurs patients et réévaluer régulièrement la nécessité de continuer le traitement aux IPP, conformément aux lignes directrices, particulièrement sur le long terme.

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Contribution to Original Knowledge

This thesis provides an original contribution to the literature on the utilization and safety of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs). Despite being available for decades, there are many existing gaps regarding their utilization, especially contemporary data on the prescribing trends of H2RAs. Moreover, recent evidence suggests that PPIs are overprescribed, but it is unclear if this issue extends to H2RAs. Given this, deprescribing initiatives have been proposed, though the effectiveness of these initiatives in the United Kingdom (UK) has not been elucidated. Moreover, while several previous observational studies have attempted to address whether PPIs are associated with gastrointestinal malignancies, each had at least one major methodological flaw, which severely limits the interpretation of the evidence. Thus, this dissertation was designed to address these gaps in knowledge and address the limitations of prior studies. Manuscript 1 addressed trends in prescribing patterns of PPIs and H2RAs over 29 years using the UK Clinical Practice Research Datalink. This study found that while PPIs are considerably more popular than H2RAs, both drugs are overprescribed in patients without a recorded indication for use. This suggests that future deprescribing initiatives may also want to target the burden of H2RA overprescribing. Manuscript 2 was an interrupted time series designed to address the impact of the most recent PPI prescribing guidelines, which had not been previously studied. This manuscript found that physician prescribing patterns were not meaningfully different following the release of the new guidelines. Thus, stronger initiatives in addition to guidelines may be necessary to reduce overprescribing. Manuscripts 3 and 4 were designed to specifically address the limitations of previous studies assessing the gastric and colorectal cancer risk of PPIs. This included using an active comparator, propensity score weights and sophisticated analyses to deal with different sources of bias. These two manuscripts add to the growing safety profile of PPIs, as

the results suggest that the overall use of PPIs is associated with gastric cancer, and prolonged use may be associated with colorectal cancer. Overall, this thesis presents novel information regarding the utilization and gastrointestinal cancer safety of PPIs, which may be considered when prescribing PPIs, particularly in the long term.

I declare that I received guidance and input from my supervisor and thesis committee members on the methodological and substantive areas of my thesis, but the work presented in this dissertation is my own.

Contributions of Authors

Manuscript 1: Trends in acid suppressant drug prescriptions in primary care in the UK: a population-based cross-sectional study. *BMJ open*, *10*(12), e041529.

With the guidance of Dr. Azoulay, I developed the research question and conceptualized this study. I drafted the protocol and obtained ethics approval from the CPRD and Jewish General Hospital. I conducted the data analyses, was responsible for data management, interpreted the findings and drafted the manuscript. All authors contributed to study design, data interpretation and critical revision of the manuscript. Dr. Azoulay acquired the data and is the guarantor for this study.

Manuscript 2: Trends in prescribing patterns of proton pump inhibitors surrounding new guidelines. *Annals of Epidemiology* 55 (2021): 24-26.

With the guidance of Dr. Azoulay, I developed the research question and conceptualized this study. I drafted the protocol and obtained ethics approval from the CPRD and Jewish General Hospital. I conducted the data analyses, was responsible for data management, interpreted the findings and drafted the manuscript. Dr. Schnitzer provided statistical expertise with study design. All authors contributed to study design, data interpretation and critical revision of the manuscript. Dr. Azoulay acquired the data and is the guarantor for this study.

Manuscript 3: Proton Pump Inhibitors and Risk of Gastric Cancer: Population-based Cohort Study. *Gut*, 2021.

With the guidance of Dr. Azoulay, I developed the research question and conceptualized this study. I drafted the protocol and obtained ethics approval from the CPRD and Jewish General Hospital. I conducted the data analyses, was responsible for data management, interpreted the findings and drafted the manuscript. Drs. Suissa and Schnitzer provided statistical and methodological expertise. Drs. McDonald and Barkun provided clinical expertise. All authors contributed to study

design, data interpretation and critical revision of the manuscript. Dr. Azoulay acquired the data and is the guarantor for this study.

Manuscript 4: Proton Pump Inhibitors and Risk of Colorectal Cancer: Population-based Cohort Study. *Gut,* 2021.

With the guidance of Dr. Azoulay, I developed the research question and conceptualized this study. I drafted the protocol and obtained ethics approval from the CPRD and Jewish General Hospital. I conducted the data analyses, was responsible for data management, interpreted the findings and drafted the manuscript. Drs. Suissa and Schnitzer provided statistical and methodological expertise. Drs. McDonald and Barkun provided clinical expertise. All authors contributed to study design, data interpretation and critical revision of the manuscript. Dr. Azoulay acquired the data and is the guarantor for this study.

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List of Abbreviations

BMI	Body mass index
BNF	British National Formulary
CI	Confidence interval
COX-2	Cyclooxygenase-2
CPRD	Clinical Practice Research Datalink
GP	General practitioner
H2RA	Histamine-2 receptor antagonist
HD-PS	High-dimensional propensity score
HR	Hazard ratio
IPCW	Inverse probability of censoring weight
IPSW	Inverse probability of screening weight
NDMA	N-Nitrosodimethylamine
NICE	National Institute for Health and Care Excellence
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
PPI	Proton pump inhibitor
RCT	Randomized controlled trial
SIR	Standardized incidence ratio
SMRW	Standardized mortality ratio weight
SSRI	Selective serotonin reuptake inhibitor
UK	United Kingdom
US	United States

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Chapter 1. Introduction

1.1 Overview

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are commonly prescribed to manage the symptoms of gastric conditions, including peptic ulcer disease, gastroesophageal reflux disease, and dyspepsia.[1-3] PPIs have been available for over three decades, with omeprazole being the first PPI approved in Canada in 1989.[4] Since then, several other drugs have been added to this class, including lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole.[5] All PPIs have similar efficacies in managing gastric conditions,[1] but vary in costs, which is their main difference.[6] While H2RAs (including cimetidine, famotidine, ranitidine, and nizatidine) are also used across similar indications, they are less effective at lowering the amount of stomach acid compared to PPIs and are thus less favourably prescribed.[1] Typically, the use of these drugs requires a prescription, though some PPIs and H2RAs are now available over the counter in many countries (i.e. Canada, United States [US] and United Kingdom [UK]). Indeed, omeprazole (a PPI) has been available over-the-counter in the UK (study setting) since 2004,[7] while ranitidine (an H2RA) has been available over-the-counter since 1995.[8]

In recent years, there have been concerns about the increasing inappropriate use of PPIs, whereby patients are prescribed long-term PPIs with failure to reevaluate for ongoing necessity, or prescribed PPIs with an off-label or no evidence-based indication for use.[9 10] In 2015, PPIs were among the top 10 most prescribed drugs in Canada,[11] with over 33 million prescriptions dispensed in 2016.[12] While short-term use is recommended for most indications,[13-15] there is evidence that the majority of individuals taking PPIs are using them chronically, often without a proper indication.[16-18] Indeed, between 40% and 55% of primary care patients in the US and the UK do not have an evidence-based indication for long-term PPI use.[19 20] As a result of this dramatic

increase in PPI use, there have been efforts to implement deprescribing programs which aim to reduce unnecessary PPI usage in Canada and the UK.[17 21] Indeed, the National Institute for Clinical Evidence (NICE) in the UK has recommended deprescribing PPIs in primary care starting in 2014.[21] Deprescribing is the medically supervised tapering or stopping of a medication that is no longer indicated, in some cases is associated with harm, or that is of little added benefit.[22 23] PPI deprescribing can be described as dose de-escalation or yearly treatment reassessment. However, there is little evidence on the effectiveness of these recommendations. This overuse is particularly relevant considering several safety concerns associated with the use of PPIs, including incident and recurrent *Clostridiodes difficile* (and other enteric infections), enteric colonization with multi-drug resistant organisms, acute interstitial nephritis, hypomagnesemia, and gastrointestinal malignancies.[24-34]

On a population level, the potential association with gastric or colorectal cancer could have significant implications on the utilization and prescribing patterns of PPIs. Indeed, gastric cancer is associated with a poor five-year survival rate of less than 30%,[35 36] and colorectal cancer is the second and third leading cause of death from cancer among Canadian men and women, respectively, with an increasing incidence among younger adults.[37 38] While several observational studies have been conducted to determine whether PPIs are associated with gastric or colorectal cancer, the results have been inconsistent.[39-59] Moreover, each study had at least one major conclusion altering bias, limiting the conclusion that may be drawn. Given the widespread overuse of acid suppressant drugs and their incomplete safety profile, carefully designed observational studies are required to address the existing knowledge gaps.

1.2 Research Objectives

The primary goal of this doctoral thesis was to address the gaps in knowledge regarding the utilization and gastrointestinal cancer safety of PPIs. The specific objectives were:

1. To examine the prescribing patterns of PPIs and H2RAs over a 29-year period among general practitioners in the UK.

2. To determine whether the 2014 NICE PPI guidelines changed physician prescribing patterns in clinical practice.

3. To determine whether the use of PPIs, when compared with the use of H2RAs, is associated with an increased risk of incident gastric cancer.

4. To determine whether new users of PPIs are at an increased risk of colorectal cancer compared to new users of H2RAs.

1.3 Structure

This manuscript-based thesis contains eight chapters. Chapter 1 describes the overall rationale and objectives of this thesis. Chapter 2 is a detailed background on acid suppressant drugs, including their utilization, deprescribing initiatives, and the existing evidence on their association with gastrointestinal malignancies. Chapter 3 presents details on UK Clinical Practice Research Datalink (CPRD), the data source used for all four manuscripts, and additional details on the methodologies used in subsequent chapters. Chapters 4 through 7 are manuscripts that address each thesis objective listed in *section 1.2*. Chapter 4 is a utilization study using the CPRD examining the prescribing patterns of PPIs and H2RAs from 1990 through 2018 in the UK. Chapter 5 is an interrupted time-series analysis that examines physician prescribing patterns following the publication of the 2014 NICE PPI guidelines. Chapter 6 is an observational cohort study addressing whether PPI use is associated with the incidence of gastric cancer compared to H2RA use. Chapter

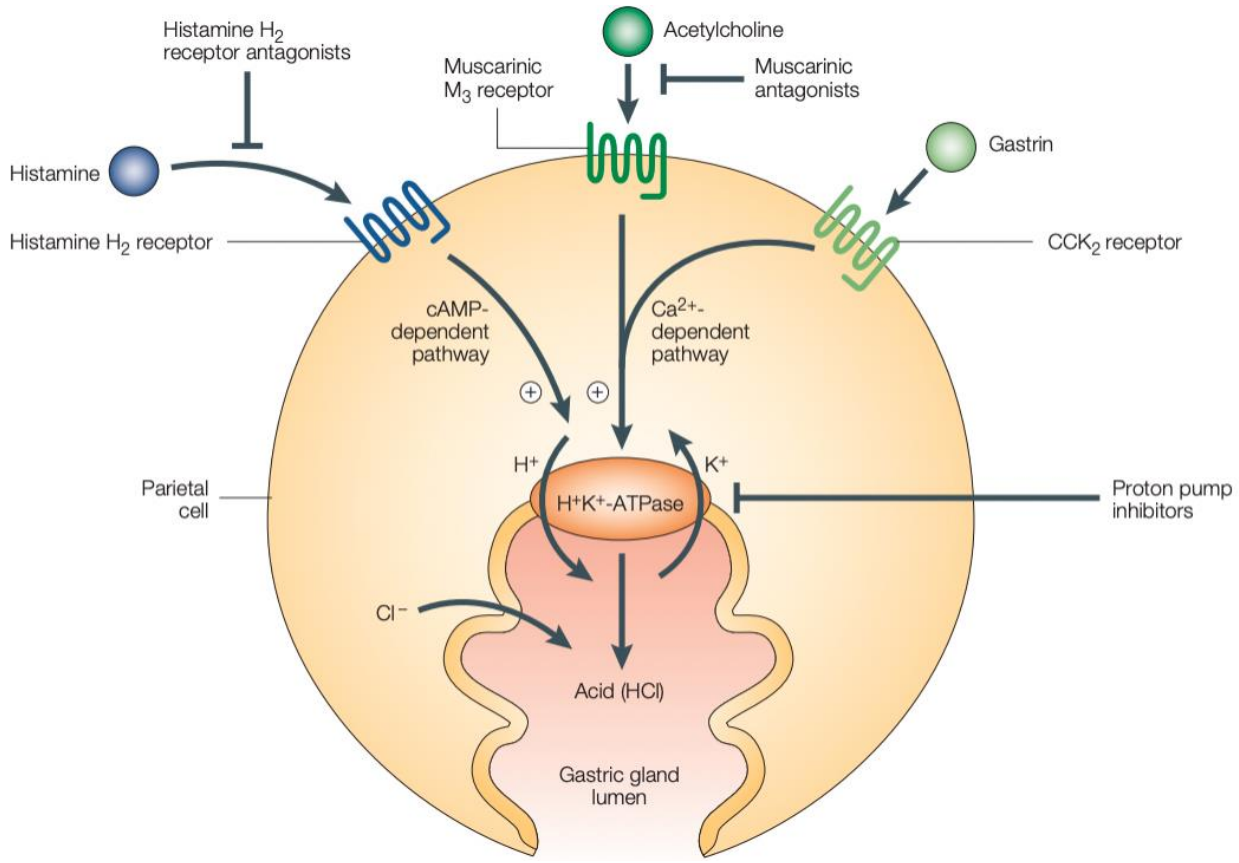
7 is an observational cohort study on the colorectal cancer safety of PPIs compared to H2RAs. Finally, Chapter 8 summarizes the findings of the four manuscripts and provides a general discussion on the clinical implications and future directions. The references for the four manuscripts are listed in their corresponding chapter, while the remainder of the thesis has a general reference list at the end of this thesis.

Chapter 2. Literature Review

2.1 Acid Suppressant Drugs Mechanism of Action

PPIs and H2RAs act to decrease the amount of acid produced by the stomach through different mechanisms (**Figure 2.1**).[3] Given this, PPIs induce superior acid suppression compared to H2RAs, which might partially explain their increased use over time.[1 3] This may also explain why PPIs are more commonly associated with more serious adverse events than H2RAs.[24-34 60 61]

Figure 2.1 PPI and H2RA mechanism of action



Reprinted with permission from Nature Reviews Drug Discovery.[3]

2.1.1 Proton Pump Inhibitors

PPIs inhibit the hydrogen-potassium-ATPase, enzymes on the surface of parietal cells responsible for gastric acid secretion.[3 62] PPIs are ingested as prodrugs, and can only bind with hydrogen-potassium-ATPase when they are converted to their activated form by acid; once covalently bound, the acid secretion is inhibited.[3 62 63] While their plasma half-life is one hour, their inhibitory effects last longer due to the strong disulfide bonds formed with hydrogen-potassium ATPases.[62 63] Individual PPIs differ in their pharmacokinetic properties, including different bioavailabilities and peak plasma levels, but all have similar efficacies in managing symptoms of acid-related disorders.[1 62 63]

2.1.2 Histamine-2 Receptor Antagonists

H2RAs exert their acid-lowering effects by reversibly binding to histamine H2 receptors on gastric parietal cells.[63] This binding inhibits endogenous histamine from activating the receptor and releasing gastric acid.[63] Given their mechanism, H2RAs begin to work quickly after ingestion with a duration of 4 to 10 hours,[63] all with similar efficacy.[64] However, the use of H2RAs does not impact the ability of gastrin or acetylcholine from stimulating parietal cells; as such, H2RAs do not entirely block acid secretion.[1] Moreover, the effects of H2RAs are shorter lasting than PPIs,[65] and long-term use may lead to tachyphylaxis, a decreased response over time.[63]

2.2 Patterns of Acid Suppressant Drugs Over Time

Acid suppressant drugs are commonly prescribed medications,[25 66 67] with PPIs consistently among the top 10 most prescribed drugs in Canada.[11] In 2016, over 33 million PPI prescriptions were dispensed in Canada,[12] and there were over 50 million dispensations in England in 2015.[24] Contemporary data on the use of H2RAs is lacking, given that they are an older drug class. Indeed, the first H2RA, cimetidine, was approved for use in the UK in 1976, while the first PPI,

omeprazole, was first approved in the UK in 1989.[4 68] Despite being available for over four decades, H2RAs remain among the top 25 most prescribed medications in the hospital setting in the UK.[69]

A recent utilization study described the trends in PPI use in the UK from 1990 to 2014.[70] Using CPRD data, the authors illustrate an increase in the PPI period and point prevalence over the study period from 0.2% to 15.0%, and 0.03% to 7.7%, respectively.[70] While PPI prevalence has been increasing, the authors estimated that 14.0% to 21.3% of these patients do not have a recorded indication for PPI use, and 47.0% of long-term users, defined as continuous use for over one year, do not have an indication for long-term treatment.[70] Moreover, among these long-term uses, 60% did not attempt to discontinue or step down their treatment,[70] as recommended by the 2014 NICE guidelines (described in detail in *section 2.2.2*).[21] However, given that the study period ended in 2014, which was only a few months after the publication of the NICE guidelines (September 2014), this study was not designed to assess the effectiveness of the new guidelines adequately. This study also did not address the utilization patterns of other acid suppressant drugs, like H2RAs, so it is unclear how these drugs have been used in recent years and whether they are overprescribed in a similar fashion to PPIs.

2.2.1 Indications for Use

PPIs are widely prescribed given that they are indicated in a variety of different gastric conditions (**Table 2.1**).[2] While H2RA treatment can also be used across these indications, given the superior acid suppression capabilities of PPIs, PPIs are considered more favourable.[1] As illustrated in **Table 2.1**, short-term treatment courses (<8 weeks) are recommended for the majority of indications.[2 13 14] However, as described above, there is mounting evidence to suggest that many patients are using PPIs chronically, many without an evidence-based indication which would

require chronic use.[19 20 70] In addition, there is increasing evidence to suggest that many patients using PPIs have no underlying indication for treatment whatsoever.[16-18 70] As a result of this dramatic increase, especially among patients for whom use is not indicated, there has been a recent emphasis on deprescribing programs,[17 21] which are designed to curb unnecessary prescribing.[23]

Table 2.1 Evidence-based recommendations for PPI therapy

Indication	Evidence-based recommendation
Gastroesophageal reflux disease	• 8-week PPI course for moderate to severe cases • Lifestyle changes and/or H2RA course, followed by PPI course for mild cases • Attempt to deprescribe at least once per year
Dyspepsia	• 8-week course for symptom improvement
Peptic ulcer disease	• 8-week course to reduce re-bleeding in high-risk lesions • Discontinue after 8 weeks if no other indication
Helicobacter pylori infection	• High dose PPI + antibiotic for 14 days
Ulcer prophylaxis	• NSAID + prior upper gastrointestinal bleed + age over 60 or antithrombotic therapy or corticosteroid or prior gastrointestinal event including peptic ulcer history or upper gastrointestinal bleeding = PPI or H2RA recommended while on NSAID therapy • Dual antiplatelet therapy + prior upper gastrointestinal bleed + age over 60 or antithrombotic therapy or corticosteroid or prior gastrointestinal event including peptic ulcer history or upper gastrointestinal bleeding = PPI recommended while on dual antiplatelet therapy • After endoscopic variceal ligations = 10-day PPI course
Zollinger-Ellison syndrome	• Life-long use appropriate until gastrinoma is resected

Abbreviations: PPI: proton pump inhibitor; H2RA: histamine-2 receptor antagonist; NSAID: nonsteroidal anti-inflammatory drug

Adapted from Benmassaoud A., et al. Potential harms of proton pump inhibitor therapy: rare adverse effects of commonly used drugs. CMAJ 2015.[2]

2.2.2 Deprescribing Programs

Deprescribing is the organized process of dose reduction or medication stopping of treatments that are no longer beneficial or causing undue harm.[22 23] Deprescribing initiatives are designed to encourage optimal prescribing of medications, typically in situations where a certain

drug is over-prescribed, either in individuals without an evidence-based indication for use or inappropriate treatment durations. Given the pervasiveness of PPI use, especially in recent years,[11] [12] it is unsurprising that PPIs have been a target of several deprescribing programs, including in Canada and the UK.[17] [21] In Canada, evidence-based clinical practice guidelines aimed to encourage PPI deprescribing were developed in 2017.[17] These guidelines recommend deprescribing PPIs in most adults after four weeks of treatment and provide a deprescribing algorithm for physicians to make safe decisions regarding stopping PPI use.[17] Other initiatives, including Choosing Wiseley Canada's '*Bye-Bye, PPI*' campaign, target physicians through electronic messaging on medical records of patients whose PPI treatment exceeds eight weeks.[71] At the minimum, Choosing Wisely Canada recommends reevaluating ongoing indication yearly for all patients, and attempting to stop or reduce PPI use annually for most patients.[72]

In 2014, the UK's National Institute for Clinical Evidence (NICE) published an updated PPI treatment guideline as a response to the growing popularity of PPIs and their potential adverse effects.[21] The guidelines recommend an annual review of ongoing necessity to treatment at a minimum and encourage low-dose treatments over high dose alternative.[21] The guidelines also encourage treatment with H2RA as an alternative.[21] While one would expect PPI prescribing to decrease in recent years following these initiatives, there is little evidence on whether these programs are effective. Evaluating the effectiveness of these programs is a necessary step to inform future guidelines and stronger initiatives if necessary.

2.3 General Safety of Acid Suppressant Drugs

While PPIs were once considered to be generally well-tolerated, recent evidence suggests possible associations with several adverse health outcomes.[24-34] These include enteric infections such as *Clostridiodes difficile*, acute interstitial nephritis, hypomagnesaemia, increased intestinal

colonization with multidrug-resistant organisms, and gastrointestinal malignancies.[24-34] In contrast, use of H2RAs are more commonly associated with mild adverse events, like headache and constipation,[22] though they have also been associated with more serious health outcomes like delirium and acute interstitial nephritis.[60 61] Most recently, certain H2RAs, including ranitidine and nizatidine, have been found to be contaminated with N-nitrosodimethylamine (NDMA),[73] a probable carcinogen as classified by the International Agency for Research on Cancer Classification.[74] While this has prompted some regulatory agencies to remove these products from the market,[75 76] real-world studies of other medications contaminated with NDMA revealed no association with cancer incidence.[77]

2.4 PPIs and Gastric Cancer

A potential association between PPIs and gastric cancer is particularly serious, as gastric cancer is associated with poor survival rates.[35] While several observational studies have reported an increased risk between use of PPIs and gastric cancer, these studies had important methodological shortcomings and generated highly heterogeneous findings.[39-50] Given the poor quality of the existing evidence, it remains unclear whether PPIs are associated with an increased risk of gastric cancer. Additional information is required to better assess the safety profile of this popular drug class.

2.4.1 Gastric Cancer Epidemiology

Gastric cancer is the fourth most commonly diagnosed cancer[36] and is the second leading cause of cancer death worldwide.[35 36 78] In 2018, there were over one million individuals diagnosed with gastric cancer, with almost 800,000 deaths globally.[79] The most common risk factors for this disease include smoking, alcohol abuse, and *Helicobacter pylori* infection.[36] Given the steady decline of *Helicobacter pylori* infections and the adoption of healthier lifestyles, gastric cancer

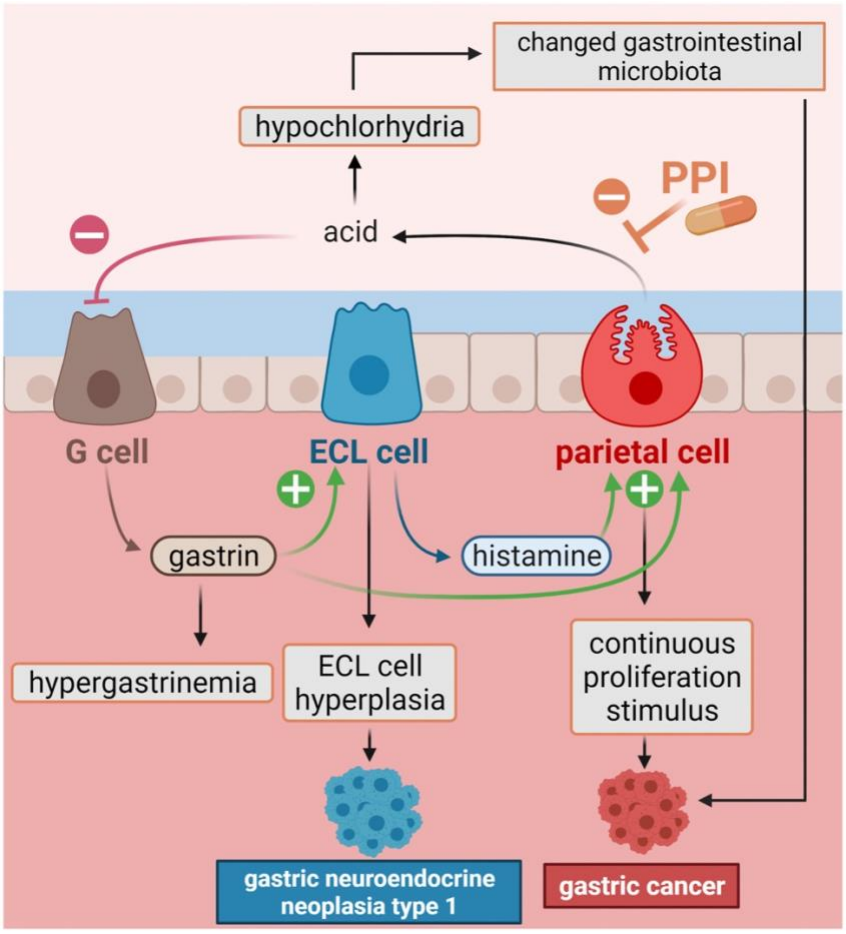
incidence has decreased over the past 20 years by about 5%.[36 80] Nonetheless, it remains a significant burden on the Canadian health care system, with annual treatment costs estimated at over half a billion dollars.[81] Notwithstanding this economic cost, gastric cancer remains a disease that is difficult to treat, and as such, is associated with a poor five-year survival rate of less than 30%.[35 36] Positive patient outcomes depend on early detection,[78] which is rare as gastric cancer is often an asymptomatic disease in its early stages.[35] Moreover, many initial symptoms of gastric cancer are non-specific, including weight loss, abdominal pain, and vomiting.[82] Given their non-specific nature, a patient presenting with these symptoms may have a variety of different gastrointestinal diagnoses before an eventual diagnosis of gastric cancer. This may lead to initiation of an acid suppressant drug for an incorrect diagnosis that is a symptom of early gastric cancer (i.e., protopathic bias). Given this, ultimately, most gastric cancers are diagnosed at advanced stages once the cancer cells have metastasized to other tissues.[35 78]

2.4.2 PPIs and Gastric Cancer Biologic Plausibility

Notwithstanding the popularity and effectiveness of PPIs, there are concerns that their use may negatively affect the stomach cytology and may contribute to the development of serious gastric conditions, including gastric cancer.[29-31] While this mechanism is not entirely known, it may be mediated by several factors (**Figure 2.2**).[83] First, prolonged PPI use may cause hypergastrinemia, defined as the elevated secretion of gastrin from G-cells, as gastrin secretion is inhibited by acidity.[84] Gastrin is considered a potent growth factor, which may induce hyperplasia.[83 85] Second, long-term PPI use has been associated with changes to the gut microbiome, including reduced microbial diversity.[83 86 87] These changes have been shown to contribute to an increased risk of gastric cancer.[88] Finally, some studies have suggested that chronic suppression of acid secretion by PPIs may be associated with atrophic gastritis, chronic

inflammation of the stomach mucous membrane. [83 89 90] While atrophic gastritis is one of the main precursors to gastric cancer,[91] not all studies have reported this association.[92] Thus, any combination of these factors may contribute to an increased gastric cancer risk among PPI users.

Figure 2.2 Potential mechanism for PPIs and gastric cancer development



Reprinted with permission from Best Practice & Research Clinical Gastroenterology.[83]

2.4.3 Randomized Controlled Trials of PPIs and Gastric Cancer

To my knowledge, there have been no randomized controlled trials (RCTs) specifically designed to investigate the effect of PPIs on gastric cancer incidence, although several RCTs have been conducted to investigate the effect of PPIs on gastric pre-cancerous lesions.[93-99] To date, the results of these RCTs have been synthesized in two meta-analyses.[100 101] In the first, safety data from six RCTs were combined to assess the association between PPI use and premalignant or

malignant gastric lesions.[100] While this study found no significant differences between the randomized groups, most of these RCTs (4 out of 6) had a moderate risk of bias according to the Cochrane risk-of-bias tool.[100] In the second meta-analysis, data from seven RCTs were used to identify associations between PPI use and gastric lesions (corporal atrophy development, corporal intestinal metaplasia, and enterochromaffin-like cell hyperplasia).[101] While non-significant increases were identified for corporal atrophy development and corporal intestinal metaplasia, significant but imprecise increased risks were found for simple and focal hyperplasia (odds ratio (OR): 5.01, 95% confidence interval (CI): 1.54-16.26; OR: 3.98, 95% CI: 1.31-12.16, respectively).[101] However, this study also included low-quality trials (risk of bias: high=4, unclear=3).[101] It is important to note that these RCTs had relatively small sample sizes (159 to 554 patients) and relatively short durations of follow-up (6 to 60 months).[93-101] Moreover, the clinical significance of these associations is not entirely known, as the characterization of these lesions is not well understood.[102] Most recently, an RCT investigating the effects of pantoprazole and several safety outcomes did not find an association with gastric cancer (hazard ratio (HR): 1.04, 95% CI: 0.77-1.40).[92] However, this trial was of short duration (mean follow-up of 3 years) and was not powered to assess gastric cancer as a safety outcome.

2.4.4 Observational Studies of PPIs and Gastric Cancer

To date, 12 observational studies have examined the association between PPI use and gastric cancer incidence (summarized in **Table 2.2**).[39-50] The majority of these studies have reported elevated relative risks (ranging from 1.01 to 3.61). However, each study had at least one major methodological shortcoming, severely limiting the interpretation of the findings. Indeed, except for one study that compared PPI use to an active comparator consisting of H2RAs[50] (and a second that used this comparison in a secondary analysis),[45] all other studies compared PPI use

with non-use (primarily composed of individuals from the general population). These latter studies may suffer from significant confounding by indication, which is introduced when the reason for prescribing a drug is also associated with the outcome.[103] Confounding by indication is an important bias in this context as individuals with gastric conditions are already at an increased risk of gastric cancer compared with the general population.[104 105] Based on these studies, it is impossible to determine whether the observed associations are due to the exposure or the underlying disease. Other major limitations include the inclusion of prevalent users, which may introduce survival bias and confounding,[106] important time-related biases such as immortal-time and time-window bias,[107-109] and failure to account for cancer latency.[110] In this context, these conclusion-altering biases can lead to spurious and exaggerated associations.

Table 2.2 Summary of observational studies assessing the association between PPIs and gastric cancer[39-50]

First Author (Year)	Study Design	Study Size	Effect estimate (95% CI)	Main Limitation
Rodriguez (2006)	Nested case-control	10,522	Cardia: OR: 1.06 (0.57-1.99) Non-cardia: OR: 1.75 (1.10-2.79)	Time-window bias Confounding by indication
Tamim (2008)	Nested case-control	8,229	OR:1.46 (1.22-1.74)	Time-window bias Confounding by indication
Poulsen (2009)	Cohort	18,790	OR: 1.3 (0.7-2.3)	Confounding by indication Immortal time bias
Brusselaers (2017)	Cohort	843,003	SIR: 3.38, (3.23-3.53)	Confounding by indication Latency bias
Niikura (2017)	Cohort	533	HR: 3.61 (1.49-8.77)	Confounding by indication
Cheung (2018)	Cohort	63,397	HR: 2.44 (1.42-4.20)	Immortal time bias Latency bias
Lai (2018)	Nested case-control	1,298	OR: 2.00 (1.36-2.95)	Time-window bias Prevalent users
Peng (2019)	Nested case-control	2,122	OR: 2.48 (1.92-3.20)	Time-window bias Prevalent users
Liu (2020)*	Cohort	471,779	HR: 1.28 (0.86-1.90)	Confounding by indication Prevalent users
Liu (2020)*	Case-control	6,523	OR: 1.49 (1.24-1.80)	Confounding by indication Prevalent users
Lee (2020)	Nested case-control	11,776	OR: 1.07 (0.81-1.42)	Confounding by indication
Seo (2021)	Cohort	11,741	HR: 2.37 (1.56-3.68)	Confounding by indication On treatment exposure definition
Shin (2021)	Cohort	78,766	HR: 1.01 (0.88-1.16)	Immortal time bias

Abbreviations: OR: odds ratio; HR: hazard ratio, SIR: standardized incidence ratio
*Presented in the table twice as the paper conducted two separate studies

To my knowledge, there have been three meta-analyses that have pooled the results of some of the studies described in **Table 2.2**.[29-31] These studies demonstrated that use of PPIs was significantly associated with an increased risk of gastric cancer, with effect estimates ranging from 1.39 to 2.01.[29-31] However, these meta-analyses combined results from studies of different designs, which is not recommended, given the heterogeneity between cohort and case-control studies.[111] More importantly, as outlined above, the quality of the studies included in these meta-analyses is questionable, making it difficult to draw definitive conclusions based on their results.

2.5 PPIs and Colorectal Cancer

There are also concerns that the use of PPIs may increase the risk of colorectal cancer.[47 51-59] This may be mediated through the elevation of serum gastrin levels associated with the prolonged use of PPIs,[84] as gastrin is a potent growth factor involved in the pathogenesis of colorectal cancer.[112-117] To date, observational studies investigating this association have been limited by small sample sizes, short durations of follow-up, and significant methodological shortcomings.[47 51-59] Given the increasing use of PPIs and the lethality of colorectal cancer, which is the second and third leading cause of cancer death among Canadian men and women, respectively,[37] additional studies are needed to better inform the safety profile of these drugs.

2.5.1 Epidemiology of Colorectal Cancer

Colorectal cancer is typically diagnosed via screening with a combination of fecal occult blood testing (or fecal immunochemical testing), sigmoidoscopy and colonoscopy, with an eventual diagnosis confirmed on biopsy. Diagnosis may be as a result of screening programs, or following signs and symptoms of disease, including rectal bleeding, abdominal pain, and changes in bowel habits.[118 119] These symptoms are often a result of tumour growth, so can be variable depending on the location of the tumour, and stage of disease.[119] While screening programs have

led to a secular decline in colorectal cancer incidence overall,[120 121] its incidence is increasing in younger adults,[38] and is expected to be the third most commonly diagnosed cancer in Canada in 2020, with 27,000 new cases projected by the end of this year.[37] In addition to its decreasing incidence, improvements in cancer care have contributed to decreasing global trends in colorectal cancer mortality.[122] Nonetheless, colorectal cancer remains the second and third leading cause of death from cancer among Canadian men and women, respectively.[37] Indeed, the 5-year survival for colorectal cancer varies from 13% to 90% based on the stage at diagnosis.[110] As such, colorectal cancer is associated with a high economic burden; the management of a colorectal cancer patient costs an average of $20,000 to $40,000.[123] While there are several modifiable risk factors for colorectal cancer, including physical inactivity, obesity, heavy alcohol use, and tobacco consumption, there are also non-modifiable risk factors, including age, family history, and genetic predisposition.[110]

2.5.2 PPIs and Colorectal Cancer Biologic Plausibility

Chronic suppression of acid through continuous PPI use causes hypergastrinemia, the elevated secretion of gastrin from G-cells.[84] High gastrin levels lead to increased secretion of gastric acid, which has been shown to promote the proliferation of both normal and malignant colonic and rectal cancer cells in vitro.[112-117] Animal models also suggest that hypergastrinemia leads to adenoma progression, an important precursor to colorectal cancer.[124] While the evidence in humans is limited, one longitudinal study among colorectal cancer cases and controls showed that gastrin levels above normal (i.e., >90 pg/mL) were associated with an almost five-fold increased risk of colorectal cancer.[125] Given that PPIs can increase serum gastrin levels up to 4,000 pg/mL in some patients, with high levels persisting even after PPI withdrawal, prolonged use of PPIs may, in turn, increase the risk of colorectal cancer.[126] While one study among PPI users found

that PPI use was not associated with an increased frequency, growth, or histology of adenomatous polyps, it was limited by its small sample size (n=310) and use of an on-treatment exposure definition, which is inappropriate for cancer incidence.[127]

2.5.3 Randomized Controlled Trials of PPIs and Colorectal Cancer

To my knowledge, there have been no randomized controlled trials (RCTs) specifically designed to investigate the effect of PPIs on colorectal cancer incidence. Indeed, two meta-analyses intended to investigate the colorectal cancer risk among PPI users failed to identify any RCTs in their systematic searches.[33 128] While existing RCTs reported data on other rare cancers, such as gastric cancer (described in detail in *section 2.4.3*), none reported on colorectal cancer incidence. [92 129 130] The lack of cancer specific RCT data is not surprising, given that RCTs are not designed or powered to address cancer as a safety endpoint.

2.5.4 Observational Studies of PPIs and Colorectal Cancer

To date, 10 observational studies have examined the association between PPI use and colorectal cancer incidence (Chapter 7, **Supplementary Table 7.19**).[47 51-59] Overall, the effect estimates of these studies have been inconsistent, with relative risks ranging from 0.85 to 2.54.[47 51-59] While three of these studies assessed the association between colorectal cancer and H2RA use (relative risks ranging from 0.80 to 2.10),[53 54 58] no studies used H2RAs as an active comparator. Instead, all studies compared PPI use with non-use, the latter primarily composed of individuals from the general population. This comparator group is problematic as it can introduce significant confounding by indication.[103] In the context of this study question, individuals with gastric conditions, such as GERD, are already at an increased risk of colorectal cancer compared to the general population.[131] Thus, these studies cannot differentiate between meaningful changes in risk due to exposure to PPIs or underlying disease. Moreover, no prior study has reported on the

absolute risk of colorectal cancer associated with the use of PPIs, a measure that would better inform the risk-benefit profile of this drug class. Beyond this, each study had at least one major methodological shortcoming, severely limiting the interpretation of their results. This includes the inclusion of prevalent users,[106] time-window bias, which results from differential exposure opportunities between cases and controls,[108] and latency bias.[110] These conclusion-altering biases can lead to spurious and exaggerated associations in both directions, limiting the conclusions drawn from the existing evidence.

There have been three meta-analyses that have pooled the results of most of the aforementioned PPI studies,[32-34] but none pooled data for the H2RA studies. While all three PPI meta-analyses did not demonstrate an overall association with colorectal cancer,[32-34] one study showed a dose-response relationship, with cumulative durations of at least five years of PPI use associated with a 19% increased risk of colorectal cancer (OR 1.19, 95% CI: 1.09 – 1.31).[34] However, it is important to note that the quality of the studies included in the meta-analyses was questionable, making it difficult to draw firm conclusions from their findings. Importantly, the risk of bias tool used to assess quality in these studies does not consider the conclusion-altering biases described above that arise in pharmacoepidemiologic studies.[132] Given the conflicting results of previous studies and their important methodological limitations, additional well-conducted studies that avoid these biases are needed to assess whether the use of PPIs is associated with the incidence of colorectal cancer.

2.6 Summary

Millions of patients use PPIs and H2RAs yearly to manage symptoms of gastric-related disorders,[11 12] with PPIs considered a more favourable treatment option given their superior acid suppression ability.[1] Given their popularity, PPIs have become increasingly overprescribed in

practice,[2 13 14 19 20 70] and physicians are recommended to deprescribe PPIs in patients who no longer require treatment.[17 21] However, there is no evidence regarding the effectiveness of these recommendations. Further, there is little contemporary data on the utilization patterns of H2RAs, and it is thus unclear if H2RAs are overprescribed to a similar extent as PPIs. While effective, uncertainties remain regarding the overall safety of PPIs, especially in the long-term. Indeed, a potential association with gastrointestinal malignancies[29-32] could have important public health implications, given the economic burden of these cancers on the health care system.[81 123] Moreover, gastric cancer is associated with poor survival,[35] and there are few known modifiable risk factors for colorectal cancer.[110] Thus, addressing whether PPIs are associated with the incidence of gastrointestinal malignancies will provide patients, physicians, and regulatory agencies with necessary information regarding the overall safety of this popular drug class. Overall, this thesis will address the gaps in knowledge on the utilization and gastrointestinal cancer safety of PPIs through several observational studies using real-world data.

Chapter 3. Methodology

The methodology for this thesis is described in detail in each corresponding manuscript (Chapters 4 through 7). This section describes additional information on some of the methods, including the data source, cohort formation, and weighting methods.

3.1 Data Source

3.1.1 History of CPRD

All four manuscripts in this thesis use data from the UK CPRD, a large computerized database of longitudinal primary care records.[133 134] First established in 1987 as the Value Added Medical Product Dataset, it later expanded to become the General Practice Research Database in 1993, and finally, the CPRD in 2012, which now contains the records of over 15 million patients.[135] The CPRD is a constantly growing database of primary care records, which are updated monthly by general practitioners (GPs) from practices across England, Scotland, Wales, and Northern Ireland. The geographic distribution of the practices participating in the CPRD has been shown to be representative of the UK population, and age, sex, and body mass index (BMI) distributions of patients in the CPRD are similar to those reported by the National Population Census.[56] GPs are trained to systematically record data, which is then subject to various quality control checks by the CPRD. Only once the data is considered 'up to standard' can it be used for research purposes.[133 135] Up to standard practices are those that consistently provide high-quality data, and patients coming from these practices are considered 'acceptable' when they have continuous follow-up (i.e., no date inconsistencies), a valid gender, and a recorded year of birth.[133 135] Today, GPs are financially incentivized to provide complete data under the Quality Outcomes Framework.[136]

3.1.2 The Role of General Practitioners

In the UK, GPs are considered the gatekeepers to health and are the primary point of contract for non-emergencies. To receive secondary care, a referral is first needed from one's GP (referrals are recorded in the CPRD). Following a referral, the referring physician will report back to the GP so that patient records can be updated, and the GP can resume long-term care. Thus, while an initial diagnosis is typically made by a specialist, this diagnostic date would be recorded in the CPRD. More importantly, in the UK, GPs are responsible for the long-term care of most chronic conditions, including gastric disorders, and would thus be responsible for prescribing drugs to manage these conditions (i.e., PPIs and H2RAs).[137] The CPRD can be linked to other databases, including the Hospital Episodes Statistics, which contains records of inpatient and outpatient encounters in National Health Services hospitals,[138] and the Office for National Statistics, a database of electronic death certificates.[139]

3.1.3 Data Validity

Data recorded in the CPRD has been previously validated in several different studies, generating high positive predictive values and high sensitivities for a variety of diagnoses.[135 140-144] Importantly, cancer diagnoses have been previously validated, with positive predictive values for gastroesophageal cancers as high as 96%.[143-146] Medical diagnoses and procedures, patient symptoms, and administrative actions are recorded using the Read code classification.[135 142-144 147] The Read code classification is a clinical terminology system that has been used in the UK since the early 1980s to organize clinical outcomes.[148] Outcomes are organized by chapter, and terms are organized from general to specific. Prescription details, such as dose and quantity, are automatically transcribed using a coded drug dictionary based on the *British National Formulary* (BNF). Laboratory data are automatically added to records using electronic linkage, and additional

sources of data such as specialist referrals can be manually entered by general practitioners.[135] Unlike administrative databases, the CPRD collects information on lifestyle variables that are important cancer risk factors, including BMI, and quantitative and qualitative data on smoking and alcohol use.[135] Given the high quality and richness of this data, the CPRD is commonly used in pharmacoepidemiology research, with over 2,700 peer-reviewed publications published to date.[149]

3.2 Cohort formation

For all four objectives, we used the CPRD to identify a base cohort of patients registered with a general practitioner from January 1, 1990, to December 31, 2018. The follow-up period within the base cohort started at the latest of the following dates:

1. The calendar date a patient registered with their current general practice, or
2. The date a practice was last considered 'up to standard' as defined in *section 3.1*, or
3. January 1, 1990.

The end of the follow-up period within the base cohort was defined as the earliest of the following dates:

1. The date a patient ends their registration within their current general practice, or
2. The last collection date within a practice, which is the date a practice no longer contributes data to the CPRD, or
3. December 31, 2018.

This base cohort was used for Objective 1 (Chapter 4), but for the remaining objectives, study-specific inclusion and exclusion criteria were applied. For Objective 2 (Chapter 5), the base cohort was restricted to adults (≥18 years old), with follow-up from September 1, 2010 to August 31, 2018, reflecting the age and time period of the most recent NICE guidelines.[21] For Objectives 3 and 4 (Chapters 6 and 7), we used the base cohort to identify patients newly treated with PPIs or

H2RAs. We then applied study-specific inclusion and exclusion criteria (described in detail in Chapters 6 and 7). To allow for up to one year of potential follow-up, patients could only enter the cohort until April 30, 2018 (end of data availability April 30, 2019). For these two studies, patients were followed until the earliest of exit from the base cohort, one year after a switch between the study drugs, date of death, date of gastric cancer diagnosis (Objective 3), or date of colorectal cancer diagnosis (Objective 4). A schematic of the cohort formation for Objective 3 is illustrated in **Supplementary Figure 6.1** (Chapter 6), though the same principles were applied for Objective 4 (Chapter 7).

3.3 Interrupted Time-series Analysis

For objective 2 (Chapter 5), we used an interrupted time-series analysis[150 151] to examine the impact of the 2014 NICE guidelines on physician PPI prescribing.[21] This quasi-experimental design allows one to investigate the impact of an intervention by comparing incidence rates before and after an intervention (intervention = guideline publication). In this setting, this involved quantifying the monthly prescribing rate before the publication of the guidelines (September 2010 to August 2014) and comparing them to the monthly prescribing rates after the publication of the guidelines (September 2014 to August 2018). PPI prescribing rates were calculated by dividing the number of PPI prescriptions by the number of patients in the Clinical Practice Research Datalink in each calendar month. This 96-month timeframe was selected to minimize the impact of confounding from other interventions, as there were no PPI safety warnings issued in the UK during this time, nor were there updates to prescribing guidelines. To maximize power, we identified an equal number of data points before and after the intervention.[151] An increase or decrease in the prescribing incidence rate in the post-intervention period was considered an impact of the 2014 NICE guidelines.

For this model, a dummy variable was created to represent the intervention status which was coded as '0' in the pre-intervention time period and '1' in the post-intervention time period. The unit of analysis was calendar months, which equated to 48 pre- and post-intervention periods. Using segmented autoregression and data from the pre-intervention period, we projected PPI prescribing rates after September 2014;[150 151] this approximates what would have been observed had the NICE guidelines not been published. Using two separate parameters, we estimated the short-term difference of the prescribing rate (i.e., level change) and change in rate (i.e., slope change) in the post-intervention period.[150 151]

3.4 Exposure Definition

For all objectives, we identified PPI and H2RA prescriptions in the CPRD using British National Formulary Codes, which are listed in Chapters 6 and 7 (Supplementary Tables 1 and 2). We considered all PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) and H2RAs (nizatidine, famotidine, cimetidine, and ranitidine) that were available in the UK during the study period. For Objectives 3 and 4, the first recorded PPI or H2RA prescription in the CPRD was used to define cohort entry and exposure status. To account for cancer latency, a one-year lag period was applied to all exposures. Thus, person-time at risk started one year after cohort entry, and in the event of a switch between study drugs, patients were censored one year following a switch.

Under this exposure definition, patients were considered continuously exposed to their cohort entry drug for the entirety of their follow-up. While this does not consider treatment terminations, it aligns with the potential irreversible biological mechanism behind this possible association described in *sections 2.4.2* and *2.5.2*. This definition also avoids biases related to reverse causation, where use of PPIs or H2RAs may be terminated at early symptoms and signs of

cancer,[152] and minimizes potential detection bias around the time of treatment initiation (i.e., screening for cancer may be differential between PPI and H2RA users).[153] Indeed, the threats to internal validity caused by reverse causation or detection bias are far greater than those of considering patients continuously exposed (which has the effect of diluting the point estimates towards the null).

3.5 Weighting Methods

For Objectives 3 and 4 (Chapters 6 and 7), weighting methods were used to balance the study groups. The primary models used calendar time-specific propensity scores to reweigh the exposure groups using standardized mortality ratio weights (SMRWs).[154 155] Using SMRWs, PPI patients were given a weight of 1, and H2RA patients were weighted using the odds of the treatment probability.[154 156] Application of these weights allows the comparator patients to be representative of the treated population, which allows for estimation of the *average treatment effect in the treated*.[154 156] A benefit of this approach is that no treated individuals (i.e., PPI users) are lost from the analysis, unlike in propensity score matching.[156] In sensitivity analyses for both projects, inverse probability of censoring weights (IPCWs) were added to assess the potential impact of informative censoring from drug switching and death.[157-159] Finally, in Chapter 7, we conducted an additional sensitivity analysis to investigate the impact of differential screening uptake between study arms using inverse probability of screening weights (IPSWs).[160]

3.5.1 Calendar Time-specific Propensity Scores

Valid causal inference from propensity score methods requires the assumption of 'no unmeasured confounders'.[161] This requires that any variable affecting treatment assignment or outcome status be included in the propensity score model and specified correctly.[161] In cases where calendar time is a confounder, the relationship between calendar time and other confounders must

be carefully considered.[155] For Objectives 3 and 4, calendar time meets the criteria for confounding, as use of PPIs has been increasing over time,[70] and there have been strong temporal trends with the incidence of gastric and colorectal cancer.[122] [162] Moreover, given that the study period spans almost 30 years, heterogeneity in covariate distributions over the study period must also be considered. In these circumstances, calendar time-specific propensity scores can be used to correctly model calendar time.[155]

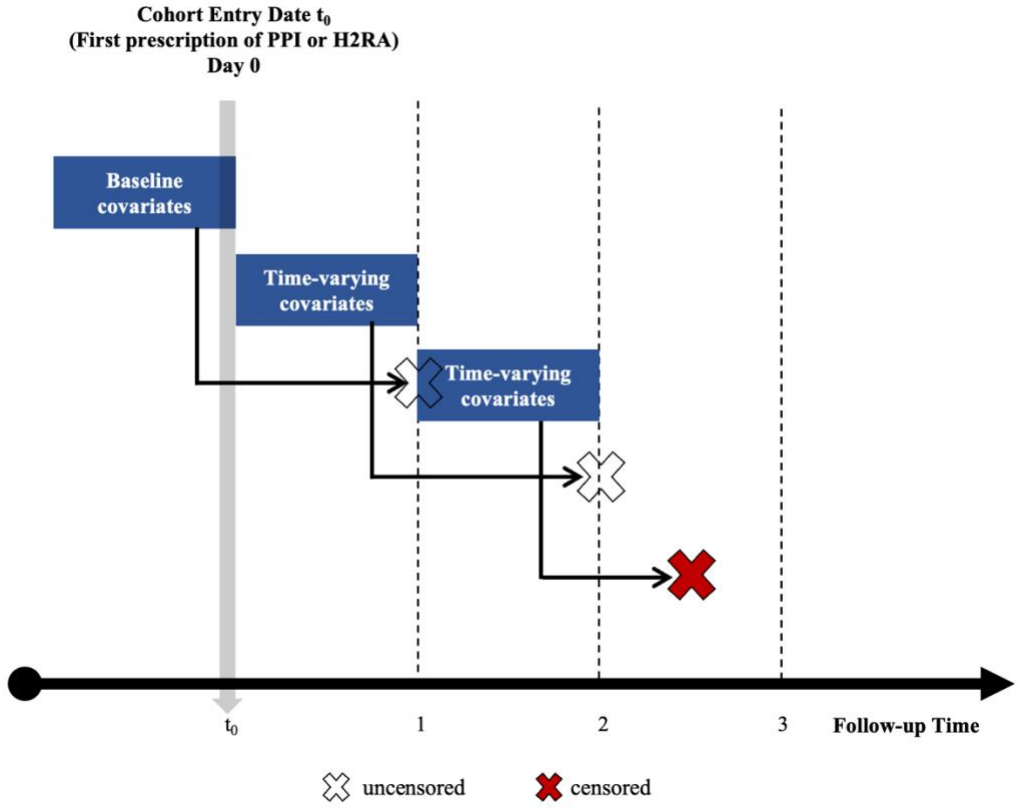
Calendar time-specific propensity scores involve estimating propensity scores within strata of calendar year. This strata-specific estimate may result in better control for confounding compared to including calendar year as a confounder in a single propensity score model.[155] In Objectives 3 and 4, we stratified the cohort into the following 5-year bands according to year of cohort entry: 1990-1994, 1995-1999, 2000-2004, 2005-2009, 2010-2018. Within each stratum, separate propensity score models were fit using multivariable logistic regression to estimate the predicted probability of receiving a PPI versus an H2RA conditional on baseline covariates. These calendar time-specific propensity scores were then used to reweigh the cohort using SMRWs as described above.

3.5.2 Inverse Probability of Censoring Weights

For Objectives 3 and 4, we used IPCWs as a sensitivity analysis to assess the impact of differential switching from drug crossovers and to investigate death as a competing risk. To calculate these weights, the follow-up period was divided into one-year intervals, separately for the PPI and H2RA cohorts (**Figure 3.1**). Using two separate logistic regression models, we calculated the predicted probability of remaining uncensored and not dying in each interval, conditional on variables measured in the previous interval. Using the product of the weights, we calculated conditional probabilities of remaining uncensored across all intervals for each patient.

Weights were stabilized using intercept only models, and unstable wights were truncated at the 0.5th and 99.5th percentiles. These IPCWs were combined with the SMRWs from the primary model to calculate an overall weight for the Cox proportional hazards model.

Figure 3.1 1-year binning for the calculation of IPCWs



3.5.3 Inverse Probability of Screening Weights

In the UK, there is an extensive bowel cancer screening program targeted to all adults aged 60 to 74 (age 50 to 74 in Scotland) who are registered with a general practitioner.[163] Every two years, all adults meeting the age criterion are mailed a fecal occult blood testing kit, regardless of prior participation in the program.[163] Adults over the age of 75 may receive a kit by calling a free helpline.[163] If patients return their kit and abnormalities are found, they are invited for a colonoscopy; otherwise, patients are not contacted until the next screening.[163] Over the past five years, faecal immunochemical tests have started to replace fecal occult blood testing across the

UK,[163] as they do not require any preparation (i.e., avoidance of food or medication) before use and have higher specificity.[164] As of April 2021, the screening program is expanding to include adults aged 50 and above.[163]

To assess the potential impact of different participation in the screening program described above among PPI and H2RA users, we conducted a sensitivity analysis that combined the SMRWs from the primary analysis with IPSWs. IPSWs were calculated in two-year intervals, given that screening is conducted biennially in the UK.[163] Covariates for these weights were taken from the preceding interval. This analysis distinguished between screening and diagnostic events, where only the former was considered. For this analysis, IPSWs were stabilized using the overall proportion of colorectal screening within the study population (20%).[160] Thus, patients with a screening event in a particular interval were given a weight of $0.2/P_{screen}$, while patients who were not screened in a given interval were weighted by $0.8/(1- P_{screen})$.[160] The combined SMRW and IPSW was used to reweigh the cohort to estimate marginal hazard ratios for colorectal cancer using Cox proportional hazards models.

3.6 Power Calculations

3.6.1 Gastric Cancer

The incidence of gastric cancer in individuals over the age of 40 in the UK is approximately 10 per 100,000 person-years.[165] Individuals with gastric conditions are at an increased risk of gastric cancer compared to the general population, with an estimated incidence rate of 20 per 100,000 person years. [104] [105] Thus, in a cohort of 1.5 million patients, with an average follow-up of 9 years (as reported in a recent CPRD study of patients initiating antihypertensive drugs)[166] we expect to identify 2,700 incident gastric cancer events. With an expected PPI prevalence of 70%, H2RA prevalence of 30%, and a two-tailed alpha of 5%, this study will have virtually 100% power

to detect a clinically relevant HR above 1.20, which can be considered a conservative estimate based on previous studies (relative risks ranging from 1.06 to 3.61).

3.6.2 Colorectal Cancer

The incidence of colorectal cancer in adults is approximately 105 per 100,000 person-years.[167] Thus, in a cohort of 1.5 million patients, with an average follow-up of 5 years (as reported in a recent CPRD study of the same population), we expect to identify 7,875 incident colorectal cancer events. With an expected PPI prevalence of 70%, H2RA prevalence of 30%, and a two-tailed alpha of 5%, this study will have 99% power to detect a clinically significant increased risk above 1.25.

3.7 Ethics

All study protocols were approved by the Independent Scientific Advisory Committee of the CPRD (protocol numbers 19_119RA, 20_076, 21_000341) and by the Research Ethics Board of the Jewish General Hospital.

Chapter 4. Trends in Acid Suppressant Drug Prescriptions in Primary Care in the UK: A Population-based Cross-sectional Study

4.1 Preface

Acid suppressant drugs have been used to manage the symptoms of several gastric-related disorders for decades.[1-3] While effective, there have been recent concerns regarding their overuse, particularly in primary care.[19 20] Indeed, a recent utilizations study found that between 14.0% and 21.3% of patients do not have a recorded indication for PPI use, while 47.0% of long-term users do not have an indication that supports such extensive use.[70] Nonetheless, the same study found that PPI period prevalence remains high, increasing from 0.2% in 1990 to 15.0% in 2014.[70] However, this study did not assess the prescribing patterns of H2RAs, which can be used as an alternative to PPIs.[1] Indeed, there is limited literature on the contemporary patterns of H2RAs, given that they are an older drug class first introduced in the 1970s.[62] There is emerging evidence regarding safety signals associated with the use of PPIs, including enteric infections such as *Clostridium difficile*, acute interstitial nephritis, hypomagnesemia, increased intestinal colonization with multidrug-resistant organisms, and gastrointestinal malignancies.[24-34] Given this, understanding treatment alternatives is a key component in managing the care of gastric related disorders. Moreover, understanding the burden of the overprescribing phenomenon and whether this extends to H2RAs, is an important public health consideration that may inform future guidelines and deprescribing initiatives. Thus, the first objective of this thesis was to examine the prescribing patterns of PPIs and H2RAs over a 29-year period among general practitioners in the UK. This paper was published in *BMJ Open* 2020;10:e041529.[168]

4.2 Title Page

Trends in acid suppressant drug prescriptions in primary care in the UK: a population-based cross-sectional study

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June 10, 2020

4.3 Abstract

Objective: To examine proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) prescribing patterns over a 29-year period by quantifying annual prevalence and prescribing intensity over time.

Design: Population-based cross-sectional study.

Setting: More than 700 general practices contributing data to the UK Clinical Practice Research Datalink (CPRD).

Participants: Within a cohort of 14 242 329 patients registered in the CPRD, 3 027 383 patients were prescribed at least one PPI or H2RA from 1 January 1990 to 31 December 2018.

Primary and secondary outcome measures: Annual prescription rates were estimated by dividing the number of patients prescribed a PPI or H2RA by the total CPRD population. Change in prescribing intensity (number of prescriptions per year divided by person-years of follow-up) was calculated using negative binomial regression.

Results: From 1990 to 2018, 21.3% of the CPRD population was exposed to at least one acid suppressant drug. During that period, PPI prevalence increased from 0.2% to 14.2%, while H2RA prevalence remained low (range: 1.2%–3.4%). Yearly prescribing intensity to PPIs increased during the first 15 years of the study period but remained relatively constant for the remainder of the study period. In contrast, yearly prescribing intensity of H2RAs decreased from 1990 to 2009 but has begun to slightly increase over the past 5 years.

Conclusions: While PPI prevalence has been increasing over time, its prescribing intensity has recently plateaued. Notwithstanding their efficacy, PPIs are associated with a number of adverse effects not attributed to H2RAs, whose prescribing intensity has begun to increase. Thus, H2RAs remain a valuable treatment option for individuals with gastric conditions.

4.4 Strengths and Limitations of This Study

- Largest and most comprehensive study to date describing trends of acid suppressant drug prescribing over a 29-year period.
- Large sample size allows detailed description of trends by age group, sex and indication.
- Prescriptions in the Clinical Practice Research Datalink are issued by general practitioners, so it was not possible to assess patient adherence.
- We did not have data on prescriptions recorded in hospital, by specialists, or from over the counter.

4.5 Introduction

Proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) are acid suppressant drugs used in the management of gastric conditions, including peptic ulcer disease and gastro-oesophageal reflux disease.[1 2] The first H2RA, cimetidine, was approved for use in the UK in 1976, while omeprazole, a PPI, was later approved in 1989.[3 4] While both drug classes have been used for over three decades, PPIs have been shown to have superior efficacy in reducing stomach acid compared with H2RAs[1] and are thus more favourably used. Nonetheless, both drug classes are among the top 25 most prescribed medications in the hospital setting in the UK.[5]

In recent years, there have been concerns about the increasing uptake of PPIs, with emerging evidence that they are being prescribed to individuals without an evidence-based indication or for longer durations than necessary.[6–10] Indeed, the number of individuals using PPIs has been increasing significantly since their introduction in 1989.[11] In England alone, more than 50 million PPI prescriptions were dispensed in 2015.[3] In contrast, there is limited information on the older drug class, H2RAs, with regard to their prescribing patterns in recent years. It is also less well known whether H2RAs are also being overprescribed in a similar fashion to PPIs.

While PPIs are generally well tolerated and perceived to have an excellent safety profile,[1 9] recent evidence suggests that long-term use, beyond the recommended 4–8 weeks duration for most conditions, may be associated with certain adverse health outcomes. These include enteric infections such as Clostridium difficile, acute interstitial nephritis, hypomagnesaemia and increased intestinal colonisation with multidrug-resistant organisms.[3 12–15]

Given their widespread use and these potential adverse effects, the National Institute for Health and Care Excellence (NICE) recommended new treatment guidelines for PPI use in primary care in 2014.[16] These new guidelines emphasise an annual review to determine ongoing need, and

to use the lowest dose of PPI on an as-needed basis for symptom relief.[16] Treatment with H2RAs is recommended when patients are unresponsive to PPIs.[16] Prescribing patterns of PPIs have not been evaluated since the publication of these guidelines, and it remains unknown if the guidelines had an impact on the uptake of H2RAs. Thus, the objective of this utilisation study was to determine the prescribing patterns of PPIs and H2RAs in UK primary care over a 29-year period.

4.6 Methods

4.6.1 Data Source

This study was conducted using the Clinical Practice Research Datalink (CPRD), a large primary care database with records of over 15 million patients, shown to be well representative of the general UK population.[17 18] The CPRD contains information on demographics, diagnoses and procedures,[19] and prescriptions issued by general practitioners are recorded using the British National Formulary. The data are audited regularly, and diagnoses recorded in the CPRD have been extensively validated.[20 21]

4.6.2 Study Population

Using the CPRD, we identified a cohort of patients who were registered with a general practitioner from 1 January 1990 to 31 December 2018. We did not impose any age restrictions to allow the evaluation of PPI and H2RA prescribing trends in both paediatric and adult populations. Patients were followed from the latest date at which their practice started contributing data to the CPRD, their personal date of registration with their general practice, or the start of the study period (1 January 1990). Follow-up ended at the earliest date at which their practice stopped contributing data to the CPRD, their personal end of registration with their general practice, or the end of the study period (31 December 2018).

4.6.3 Exposure Definition

We identified all PPIs and H2RAs prescriptions within the study period using the British National Formulary (online supplemental tables 1 and 2). This included five PPI types (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole) and four H2RA types (ranitidine, cimetidine, famotidine and nizatidine). Prescription duration was calculated using the number of days' supply recorded in the CPRD. If this value was not recorded, we divided the

prescription quantity by the numeric daily dose to ascertain duration. If none of these variables were recorded, we used the mode of the prescription duration for PPIs and H2RAs, separately.

4.6.4 Statistical Analysis

4.6.4.1 Prevalence

For each calendar year, we calculated the prevalence of PPIs and H2RAs, separately. The numerator for these prescription rates was the number of individuals receiving at least one acid suppressant drug in a given year (PPI and H2RA prescriptions were considered separately). The denominator was the total number of patients registered in the CPRD in a given year. Thus, prevalence was calculated per year by dividing the number of prescriptions over the number of patients in the CPRD for each calendar year between 1990 and 2018. Secondary analyses were conducted to determine prevalence among certain subgroups. Specifically, the rates were stratified by age (<18, 18–39, 40–59 and ≥60), sex and individual drug type.

Prevalence was also calculated among new users only by restricting the population to individuals receiving their first acid suppressant prescription (ie, PPI or H2RA) within the study period. To determine new use, individuals prescribed acid suppressants were required to have at least 1 year of medical history in the CPRD prior to their first prescription. Similarly, patients in the CPRD were required to have at least 1 year of follow-up to contribute to the denominator. Individuals coprescribed a PPI and H2RA as their first prescription were excluded from this analysis. Thus, prevalence was calculated for each year between 1991 and 2018 in new users and stratified according to the same variables described above.

4.6.4.2 Indications for Use

Indications for use among new users (ie, first of either a PPI or H2RA prescription within the study period) was inferred using Read codes recorded at any time prior to the first prescription.

Indications were classified as evidence based (dyspepsia, gastroprotection, gastro-oesophageal reflux disease, peptic ulcer disease, *Helicobacter pylori* infection, Barrett's oesophagus and Zollinger-Ellison syndrome), non-evidence-based gastroprotection, off-label (stomach pain and gastritis or duodenitis), and no recorded indication.[2] To define individuals using acid suppressant drugs for gastroprotection, we considered individuals prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) or dual antiplatelet therapy within 90 days prior to their first PPI or H2RA prescription. To be classified as evidence-based gastroprotection, these patients additionally required at least one of the following risk factors (age ≥60, history of bleed or ulcer, or concomitant use of anticoagulants, antiplatelets, corticosteroids).[2] All individuals with a coprescription for NSAIDs or dual antiplatelet therapy, but without a risk factor, were assumed to be using acid suppressants for non-evidence based gastroprotection. In secondary analyses, we stratified indications by sex and illustrated the incidence of indications over time by dividing the number of patients with each indication per year by the population in the CPRD with at least 1 year of follow-up.

4.6.4.3 Prescribing Intensity

For each calendar year, we calculated the prescribing intensity of PPI and H2RA use, separately. The numerator for these rates was the number of prescriptions received for either acid suppressant drug in a given year (prescriptions longer than 30 days were converted into 30-day equivalents (eg, one 90-day prescription was equivalent to three 30-day prescriptions), for a maximum of 12 prescriptions per year). The denominator for these rates was the total person-years of follow-up that were contributed by drug users in a given year. Thus, yearly prescribing incidence rates were calculated by dividing the number of prescriptions over the person-years of follow-up for each year between 1990 and 2018. To determine whether prescribing intensity changed during

the study period, we stratified the study period by 5-year intervals and estimated incidence rate ratios with 95% CIs using negative binomial regression, with log of follow-up time included as an offset variable.

4.6.4.4 Persistence

As there is some evidence that PPIs are being used for inappropriate durations,[6–10] but there is limited evidence on H2RA use, we examined persistence to both drugs by calculating the cumulative incidence of discontinuation in new users of PPIs and H2RAs. Time to discontinuation was defined as the time from the first prescription of an acid suppressant drug to the end of the first treatment episode. Exposure was considered continuous if the duration of one prescription overlapped with the start of the subsequent prescription, allowing for a 30-day grace period. The end of a treatment episode was defined as the first of: (1) a treatment gap exceeding 30 days, (2) a switch from PPI to H2RA or vice versa, or (3) administrative censoring (ie, if a practice stopped contributing data to the CPRD, a patient was no longer registered with their general practice, or if the study period ended). The length of the grace period was changed to 7 and 60 days in a sensitivity analysis. We used Kaplan-Meier curves to illustrate the cumulative incidence of discontinuation of PPIs and H2RAs, separately, as a function of duration of use to show the cumulative probability of persisting to the first treatment episode. In a secondary analysis, we described the cumulative incidence of discontinuation according to indications for use (evidence-based, non-evidence-based gastroprotection, off-label and no recorded indication). All analyses described above were conducted with SAS V.9.4 (SAS institute) and R (R Foundation for Statistical Computing, Vienna, Austria).

4.6.5 Patient 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.

4.7 Results

Within a cohort of 14 242 329 patients (51.4% female) registered in the CPRD, 3 027 383 (21.3%) patients were prescribed at least one PPI or H2RA during the study period, corresponding to 58 926 373 and 9 386 908 prescriptions, respectively. Among patients prescribed an acid suppressant drug, there were 1 654 323 (54.7%) females and 2 920 176 (96.5%) adults (at least 18 years old). Throughout follow-up, there were 2 714 785 (19.1%) individuals prescribed at least one PPI, 855 248 (6.0%) individuals prescribed at least one H2RA, and 542 650 (3.8%) individuals prescribed both drug classes.

Among patients newly prescribed an acid suppressant drug (n=2 085 825), 81.5% (n=1 699 837) were initially prescribed a PPI, while 18.5% (n=385 988) were initially prescribed a H2RA. Table 1 presents the characteristics of these users at the time of their first prescription. PPI users were slightly older than H2RA users at the time of initial prescription, but there were no sex differences between the two groups. Only 43.5% and 45.3% of PPI and H2RA users, respectively, had an evidence-based indication for use, with dyspepsia being the most common recorded indication. Non-evidence-based gastroprotection was more common in PPI users (21.4%) than the H2RA users (13.3%). About one in five PPI and H2RA users did not have a recorded indication for use. When stratifying indications by sex, females were more commonly prescribed PPIs for off-label indications compared with males (online supplemental table 3). The incidence of indications for acid suppressant use was relatively consistent over time, with gastro-oesophageal reflux disease the only evidence-based indication that slightly increased over follow-up (online supplemental figure 1).

Figures 1–3 illustrate the overall, sex and age-stratified prevalence of PPI and H2RA, respectively. Throughout follow-up, PPI prevalence sharply increased from 0.2% in 1990 to 14.2%

in 2018. In contrast, the prevalence of H2RAs remained consistently low throughout the study period (range: 1.2%–3.4%). PPIs were more commonly prescribed in females and both drug classes were more commonly prescribed in adults at least 60 years old. Overall and sex-stratified prevalence of use were similar among new users (online supplemental figures 2 and 3), though the prevalence of H2RA use among new users was consistent across all age categories over the past decade (online supplemental figure 4). Omeprazole was the most commonly prescribed PPI during the study period, followed by lansoprazole (online supplemental figure 5). At the beginning of the study period, ranitidine and cimetidine were both frequently prescribed, though after 2004 ranitidine was almost exclusively the only H2RA prescribed (online supplemental figure 5).

Throughout the study period, the prescribing intensity of PPIs ranged from 0.07% in 1990, increasing to a peak intensity of 0.98% in 2012. In contrast, the prescribing intensity of H2RA use decreased over the study period from the highest intensity of 1.95% in 1990, to the lowest intensity of 0.08% in 2013 (online supplemental figure 6). PPI yearly prescribing intensity sharply increased during the first 5 years of the study period, moderately increased until 2004, after which prescribing intensity plateaued (online supplemental table 4). In contrast, H2RA yearly prescribing intensity decreased from 1990 to 2009, and has begun to increase slightly over the past 5 years.

Within new users of PPIs (n=1,699,837) the median duration of the first treatment course was 144 (IQR (IQR): 59–870) days. Reasons for discontinuation are presented in table 1, which illustrates that the majority of PPI users (52.5%) discontinued their first treatment course due to a gap of at least 30 days between prescriptions. Overall, a small percentage (2.6%) of PPI users discontinued their original treatment due to a switch to H2RAs. In contrast, the median duration of the first H2RA treatment course among new H2RA users (n=3 85 988) was 279 (IQR: 61–1645) days. Approximately one-third of H2RA users discontinued use due to each of the following: a

treatment gap exceeding 30 days, administrative censoring, or because of a switch to a PPI. Online supplemental table 5 presents duration of treatment and reasons for discontinuation under alternate grace periods. When a grace period of 7 days was applied, the median (IQR) duration of PPI and H2RA use was 66 (36–560) and 149 (38–1479) days, respectively. When a grace period of 60 days was used, the median (IQR) duration of PPI use was 231 (89–1097) days, and H2RA use was 381 (91–1785) days. The reasons for discontinuation remained consistent when considering these alternate grace periods.

Figure 4 illustrates the time to discontinuation of both drug classes. While persistence to PPIs and H2RAs declined within the first year of use, 37.5% of PPI users and 46.9% of H2RA users persisted to their original treatment course beyond the 1 year recommended duration,[16] and 12.6% of PPI users and 23.1% of H2RA users persisted to their original treatment course after 5 years. When examining persistence by indication, persistence to both PPIs and H2RAs was highest among patients with an off-label or no recorded indication for use (online supplemental figures 7 to 10).

4.8 Discussion

To our knowledge, this is the largest and most comprehensive study conducted to date to examine prescribing patterns of both PPIs and H2RAs in the UK. Throughout the study period, 21.3% of the CPRD population received at least one prescription for an acid suppressant drug (PPI only: 19.1%, H2RA only: 6.0%, PPI and H2RA: 3.8%). The overall prevalence of PPI prescribing has increased from 1990 to 2018, while the prevalence of H2RA remained low. Yearly prescribing intensity to PPIs increased during the first 15 years of the study period but remained relatively consistent for the remainder of the study period. In contrast, yearly prescribing intensity of H2RAs decreased from 1990 to 2009 but has begun to increase over the past 5 years.

The overall high prevalence of PPI use in the UK is consistent with a utilisation study of PPIs using CPRD data, but whose follow-up period ended at the end of 2014.[11] Importantly, our study further contextualises the landscape of prescribing acid suppressant drugs by also describing trends of H2RA use. While H2RAs are considerably less popular than PPIs, we observed almost 10 million prescriptions within our study period, suggesting that their use has not been completely supplanted by PPIs. While use of H2RAs may be associated with delirium and acute interstitial nephritis,[22 23] they are generally well tolerated. Indeed, H2RAs are more commonly associated with mild adverse effects like headache and constipation,[22] not the serious adverse effects associated with use of PPIs.[3 12–15] Thus, H2RAs continue to represent an important treatment option for individuals with gastric conditions. Finally, while the prevalence of acid suppressant drugs is consistent with the market availability of both drug classes, it cannot be explained by an increase in the incidence of indications for PPIs and H2RAs, which have been relatively consistent over time.

To our knowledge, this is the first study to describe contemporary prescribing practices following the most recent NICE recommendations in 2014.[16] Given that H2RA prescribing intensity has begun to increase following publication of the guidelines, this may suggest a gradual shift in prescribing to favour H2RAs. Indeed, the guidelines recommend treatment with PPIs at the lowest dose for the shortest amount of time, and thus may favour longer-term H2RA prescriptions. Future studies should investigate the impact of the NICE recommendations more thoroughly.

Our study demonstrated a sex difference among PPI prescribing patterns and an age difference among prescribing patterns of both PPIs and H2RAs; women were more frequently prescribed PPIs and adults at least 60 years old were more frequently prescribed both drug classes. As women are more likely to report symptoms of gastric reflux than men,[24] this would lead to more frequent prescribing of acid suppressant drugs to manage these symptoms. Moreover, dyspepsia, the most common evidence-based indication, was more commonly diagnosed in women. The age difference may be explained by the increasing incidence of dyspepsia with age,[25] or through an increased need for gastroprotection in the elderly, whereby patients over the age of 60 who are prescribed NSAIDs or dual antiplatelet therapy are indicated to receive an acid suppressant drug for gastroprotection.[2]

In recent years, there have been concerns about the increasing inappropriate use of PPIs.[6] [7] Indeed, between 40% and 55% of primary care patients in the USA and the UK do not have an evidence-based indication for long-term PPI use.[26] [27] This is particularly relevant as PPIs are associated with a number of serious adverse events including enteric infections and hypomagneasemia.[3] [12–15] While there is some evidence that use of PPIs may also be associated with dementia, pneumonia and gastric cancer,[3] [28] not all studies have confirmed these

associations.[29 30] Our study adds to the growing literature surrounding inappropriate use, as we illustrated that these issues extend to H2RA users as well. Indeed, a little over 20% of PPI and H2RA users have no recorded indication for use, while 37.5% and 46.9%, respectively, remain on their original treatment course at 1 year of follow-up, despite recommendations to limit use to 4–8 weeks at a time for symptomatic treatment of gastro-oesophageal disease and peptic ulcer disease.[16] As illustrated by the stratified persistence patterns, a significant portion of this high persistence is among patients with an off-label, or no recorded indication for use. This provides further evidence on the inappropriate use of acid suppressant drugs.

This study has several strengths. To our knowledge, this is the largest and most comprehensive study to date describing the trends of acid suppressant drugs over time. Our study describes the use of PPIs and H2RAs over a 29-year period, which is almost the entirety of PPI market availability. Importantly, we provide new data on the recent use of H2RAs, which indicates that this drug class is gaining favour among general practitioners. Second, the data we used in this study has been well validated,[20 21] and shown to be representative of the UK general population.[17 18] Finally, the large sample size allowed us to provide detailed information of trends by age group and sex, and investigate use among rare indications, including Barrett's oesophagus and Zollinger-Ellison syndrome.

This study also has some limitations. Prescriptions recorded in the CPRD are those issued by general practitioners, and thus, it is not possible to assess patient adherence or determine if a patient filled a prescription. While this may slightly affect the estimate of cumulative incidence of discontinuation, the rest of our analyses focus on physician prescribing trends. These would not be influenced by patient adherence and are a better indicator of whether physicians are following guidelines. Second, it is possible that the trends reported in this study are underestimated, as we

do not have information on prescriptions recorded in hospital or by specialists. However, this is unlikely to lead to substantial underestimation, as general practitioners in the UK are responsible for long-term patient care.[31] However, it remains possible that the lack of hospitalisation data led to the underestimation of patients requiring short-term treatment with acid suppressant drugs. Third, this study uses data from the UK only, and as such, it is possible that prescribing trends will differ in alternate settings. Finally, this study did not include data on over the counter use of medications. Thus, the relatively high prevalence of patients exposed to acid suppressant drugs (21.3%) would be even higher if over the counter PPI and H2RA usage was considered. Lack of over the counter data may have led to the underestimation of patients using acid suppressant drugs for gastroprotection, as it is possible that some patients receive an NSAID prescription over the counter. This study demonstrates that while prevalence of PPI use has increased with time, its prescribing intensity has plateaued over the past 15 years. In contrast, while prevalence of H2RAs was consistently low throughout the study period, its prescribing intensity has begun to slightly increase over the past 5 years. Given that PPIs are associated certain adverse effects not attributed to H2RAs, H2RAs remain a valuable treatment option for individuals with gastric conditions.

4.9 Acknowledgements

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Contributors: DA, EGM, MS and LA conceived and designed the study. LA acquired the data. DA and LA did the statistical analyses. DA, EGM, MS and LA analysed and interpreted the data. DA wrote the manuscript and EGM, MS and LA critically revised the manuscript. LA supervised the study and is the guarantor. DA, EGM, MS and LA approved the final version of the manuscript and agree to be accountable for the accuracy of the work.

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4.11 Figure Legends

Figure 4.1 Overall prevalence of proton pump inhibitor and histamine-2 receptor antagonist use.

Figure 4.2 Sex-stratified prevalence of proton pump inhibitor and histamine-2 receptor antagonist use.

Figure 4.3 Age-stratified prevalence of (A) proton pump inhibitor use and (B) histamine-2 receptor antagonist use.

Figure 4.4 Persistence to original treatment course for proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) initiators.

4.12 Tables and Figures

Table 4.1 Characteristics of Individuals Newly Prescribed Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Characteristic	PPI†	H2RA†
Total	1,699,837	385,988
Male, n (%)	768,781 (45.2)	167,683 (43.4)
Age, years (mean, SD)	53.4 (18.9)	48.6 (21.1)
Age group, n (%)		
< 18 years	34,590 (2.0)	30,057 (7.8)
18-39 years	393,052 (23.1)	109,205 (28.3)
40-59 years	596,469 (35.1)	116,174 (30.1)
≥60 years	675,726 (39.8)	130,552 (33.8)
Evidence-based indication, n (%)*	740,177 (43.5)	174,836 (45.3)
Dyspepsia	316,831	112,737
Gastroprotection	288,360	41,350
Gastro-oesophageal reflux disease	158,405	33,480
Peptic ulcer disease	50,239	14,453
Helicobacter pylori infection	41,430	2,526
Barrett's oesophagus	4,180	137
Zollinger-Ellison syndrome	24	5
Non-evidence based gastroprotection, n (%)	363,992 (21.4)	51,476 (13.3)
Off-label indication, n (%)*	253,591 (14.9)	72,431 (18.8)
Stomach pain	231,715	64,188
Gastritis or duodenitis	35,908	13,096
No recorded indication, n (%)	342,077 (20.1)	87,245 (22.6)
Reason for discontinuation†		
Switch to other class	43,988 (2.6)	124,648 (32.3)
Treatment gap > 30 days	893,230 (52.5)	122,928 (31.8)
Administrative Censoring	762,619 (44.9)	138,412 (35.9)

*Indication categories are not mutually exclusive.
†Median (IQR) duration of first treatment course for PPI users and H2RA users was 144 (59–870) days and 279 (61–1645) days, respectively.

Figure 4.1 Overall prevalence of proton pump inhibitor and histamine-2 receptor antagonist use

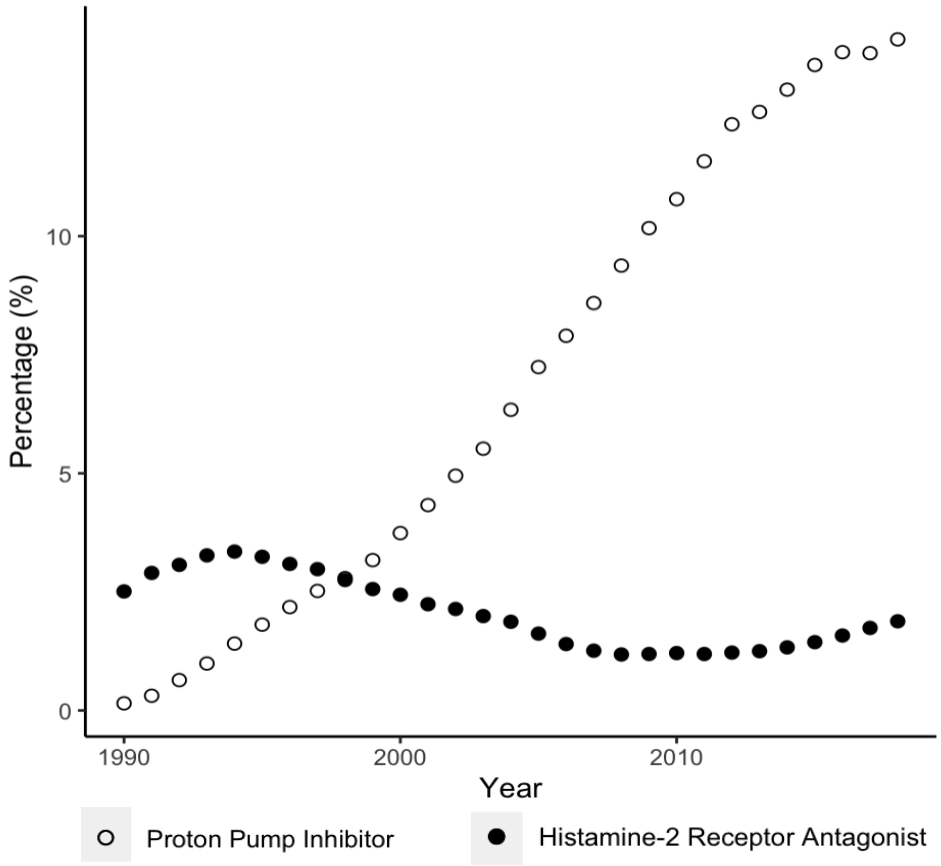


Figure 4.2 Sex-stratified prevalence of proton pump inhibitor and histamine-2 receptor antagonist use

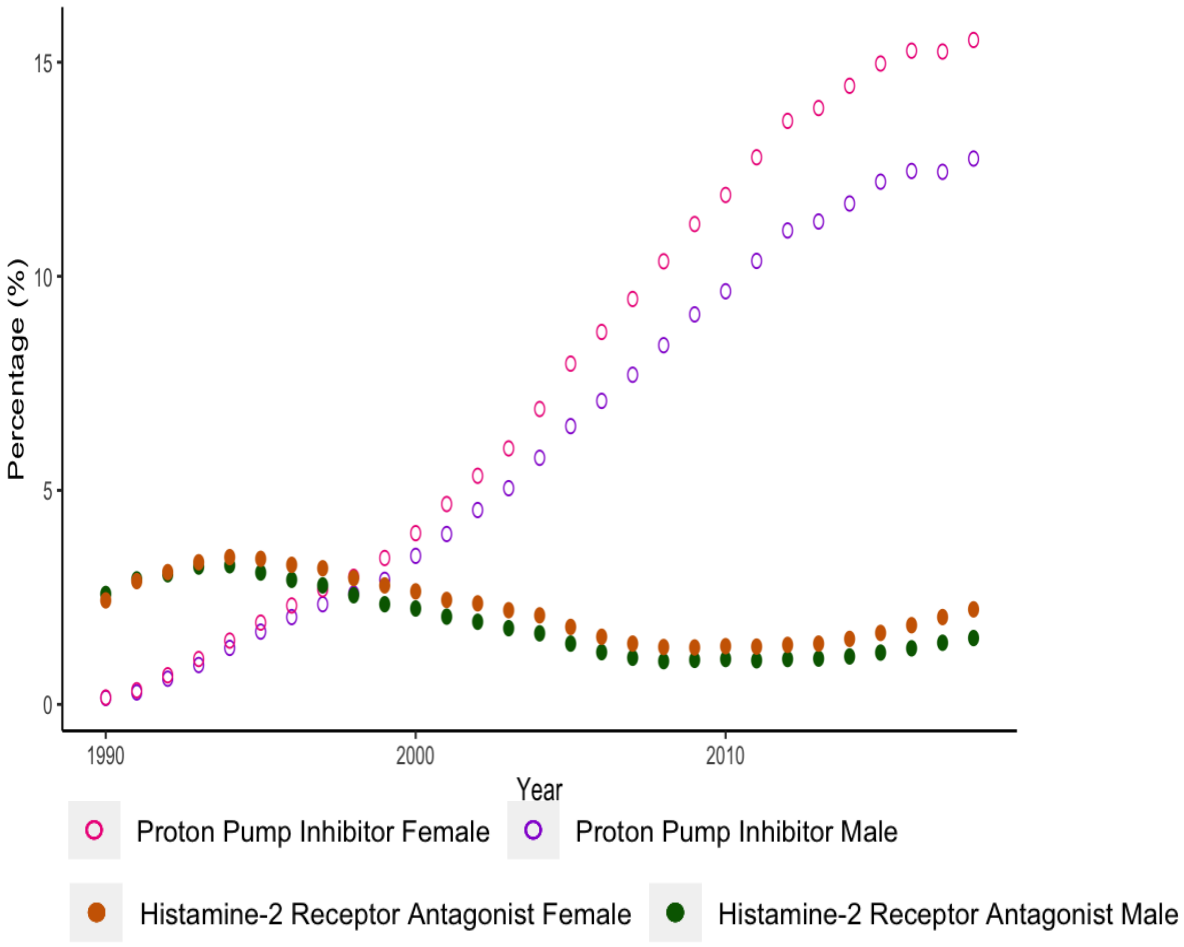


Figure 4.3 Age-stratified prevalence of (A) proton pump inhibitor use and (B) histamine-2 receptor antagonist use

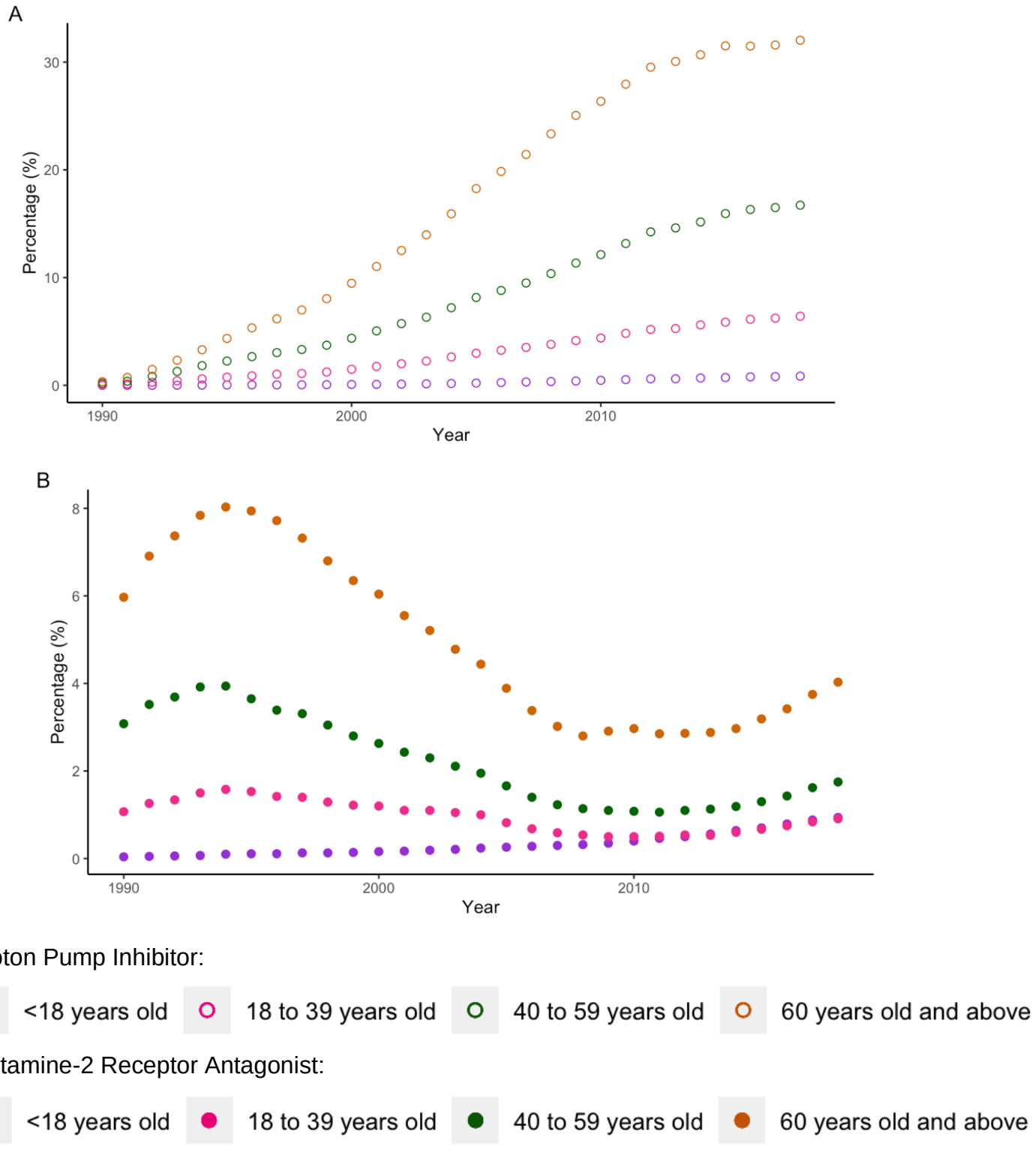
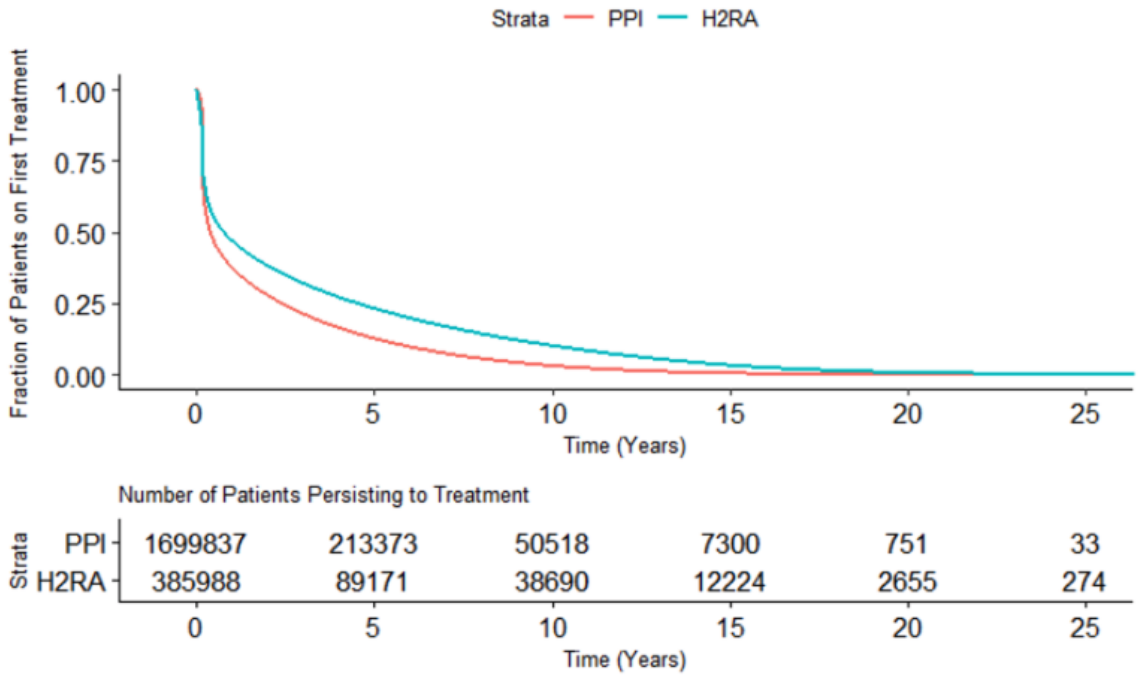


Figure 4.4 Persistence to original treatment course for proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) initiators



4.13 Supplementary Materials

Supplementary Table 4.1 List of British National Formulary Codes for Proton Pump Inhibitors

British National Formulary Code	British National Formulary Header
01030500/05010103	Proton Pump Inhibitors/Broad-spectrum Penicillins
01030500/10010100	Proton Pump Inhibitors/Non-steroidal Anti-inflammatory Drugs
01030500/05010500	Proton Pump Inhibitors/Macrolides
1030500	Proton Pump Inhibitors

Supplementary Table 4.2 List of British National Formulary Codes for Histamine-2 Receptor Antagonists

British National Formulary Code	British National Formulary Header
1030100	H2 receptor antagonists
01030100/01010201	H2 receptor antagonists/Alginate preparations
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030100/01010202	H2 receptor antagonists/Indigestion remedies
01010201/01030100	Compound Alginate Preparations/H2-Receptor Antagonists
01010202/01030100	Indigestion Preparations/H2-Receptor Antagonists

Abbreviations: H2, Histamine-2.

Supplementary Table 4.3 Sex Stratified Indications for Individuals Newly Prescribed Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Indication	Male	Female
Proton Pump Inhibitor, n (%) (n = 1,699,837)	768,781 (45.2)	931,056 (54.8)
Evidence-based indication, n (%)§	342,934 (44.6)	397,243 (42.7)
Dyspepsia	141,072	175,759
Gastroprotection	132,637	155,723
Gastro-oesophageal reflux disease	73,683	84,722
Peptic ulcer disease	31,416	18,823
Helicobacter pylori infection	19,001	22,429
Barrett's oesophagus	2,724	1,456
Zollinger-Ellison syndrome	17	7
Non-evidence based gastroprotection, n (%)	165,252 (21.5)	198,740 (21.3)
Off-label indication, n (%)§	97,248 (12.6)	156,343 (16.8)
Stomach pain	85,628	146,087
Gastritis or duodenitis	17,091	18,817
No recorded indication, n (%)	163,347 (21.2)	178,730 (19.2)
Histamine-2 Receptor Antagonists, n (%) (n=385,988)	167,683 (43.4)	218,305 (56.6)
Evidence-based indication, n (%)§	77,482 (46.2)	97,354 (44.6)
Dyspepsia	49,650	63,087
Gastroprotection	16,809	24,541
Gastro-oesophageal reflux disease	14,151	19,329
Peptic ulcer disease	8,834	5,619
Helicobacter pylori infection	1,127	1,399
Barrett's oesophagus	80	57
Zollinger-Ellison syndrome	S*	S*
Non-evidence based gastroprotection, n (%)	22,644 (13.5)	28,832 (13.2)
Off-label indication, n (%)§	29,227 (17.4)	43,204 (19.8)
Stomach pain	24,765	39,423
Gastritis or duodenitis	6,315	6,781
No recorded indication, n (%)	38,330 (22.9)	48,915 (22.4)

§ Indication categories are not mutually exclusive.

S* Numbers <5 are not displayed, as per the confidentially practices of the Clinical Practice Research Datalink.

Supplementary Table 4.4 Changes in Prescribing Intensity Over 5-Year Intervals for Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Interval	Proton Pump Inhibitor IRR (95% CI)	Histamine-2 Receptor Antagonists IRR (95% CI)
1990-1994	1.47 (1.39 – 1.54)	0.79 (0.76 – 0.81)
1995-1999	1.14 (1.13 – 1.16)	0.90 (0.90 – 0.91)
2000-2004	1.07 (1.06 – 1.08)	0.87 (0.87 – 0.87)
2005-2009	1.01 (1.01 – 1.01)	0.86 (0.84 – 0.87)
2010-2014	0.99 (0.99 – 1.00)	0.97 (0.95 – 0.99)
2015-2018	0.97 (0.97 – 0.97)	1.05 (1.05 – 1.05)

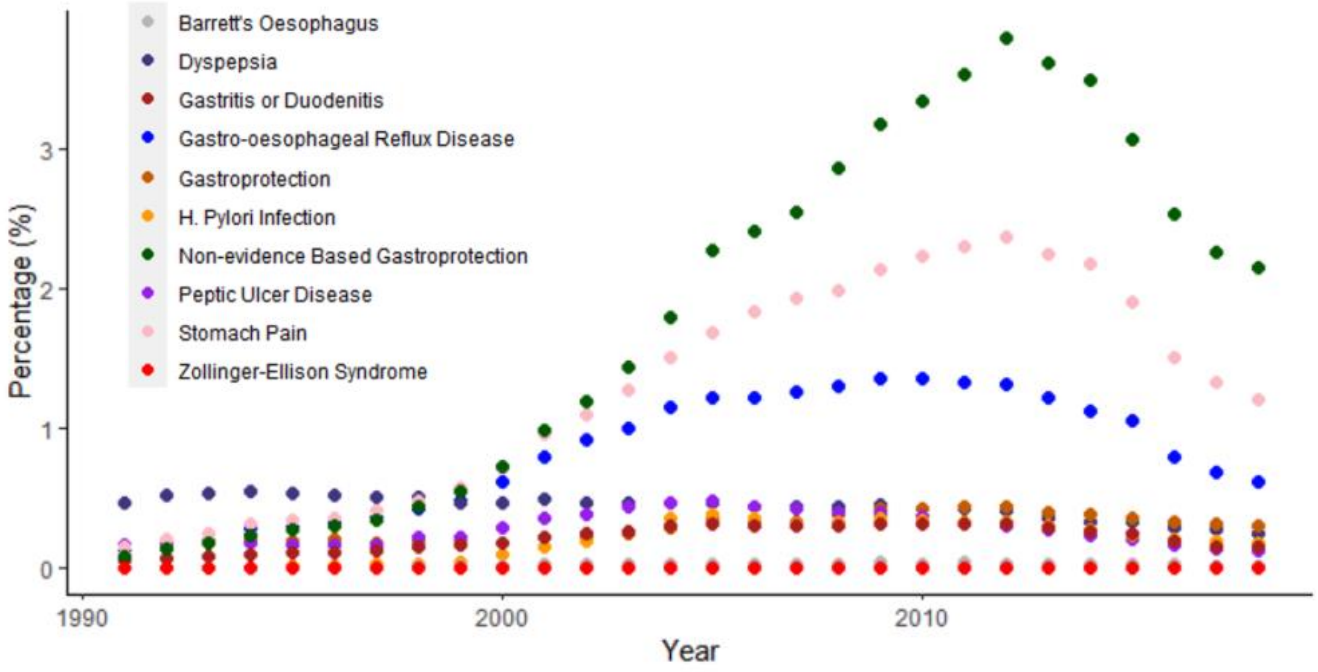
Abbreviations: IRR: Incidence rate ratio; CI: confidence interval.

Supplementary Table 4.5 Reason for Discontinuation of Initial Acid Suppressant Treatment Course Under Alternate Grace Periods

Reason for Discontinuation	Proton Pump Inhibitors (n=1,699,837)	Histamine-2 Receptor Antagonists (n=385,988)
7 Day Grace Period †		
Switch to other class	31,818 (1.9)	111,100 (28.8)
Treatment gap > 7 days	1,020,369 (60.0)	147,753 (38.3)
Administrative Censoring	647,650 (38.1)	127,135 (32.9)
60 Day Grace Period ‡		
Switch to other class	54,783 (3.2)	135,039 (35.0)
Treatment gap > 60 days	778,676 (45.8)	103,837 (26.9)
Administrative Censoring	866,378 (51.0)	147,112 (38.1)

† median (interquartile range) duration of first treatment course for PPI users and H2RA users was 66 (36 to 560) and 149 (38 to 1,479) days, respectively.
‡ median (interquartile range) duration of first treatment course for PPI users and H2RA users was 231 (89 to 1,097) and 381 (91 to 1,785) days, respectively.

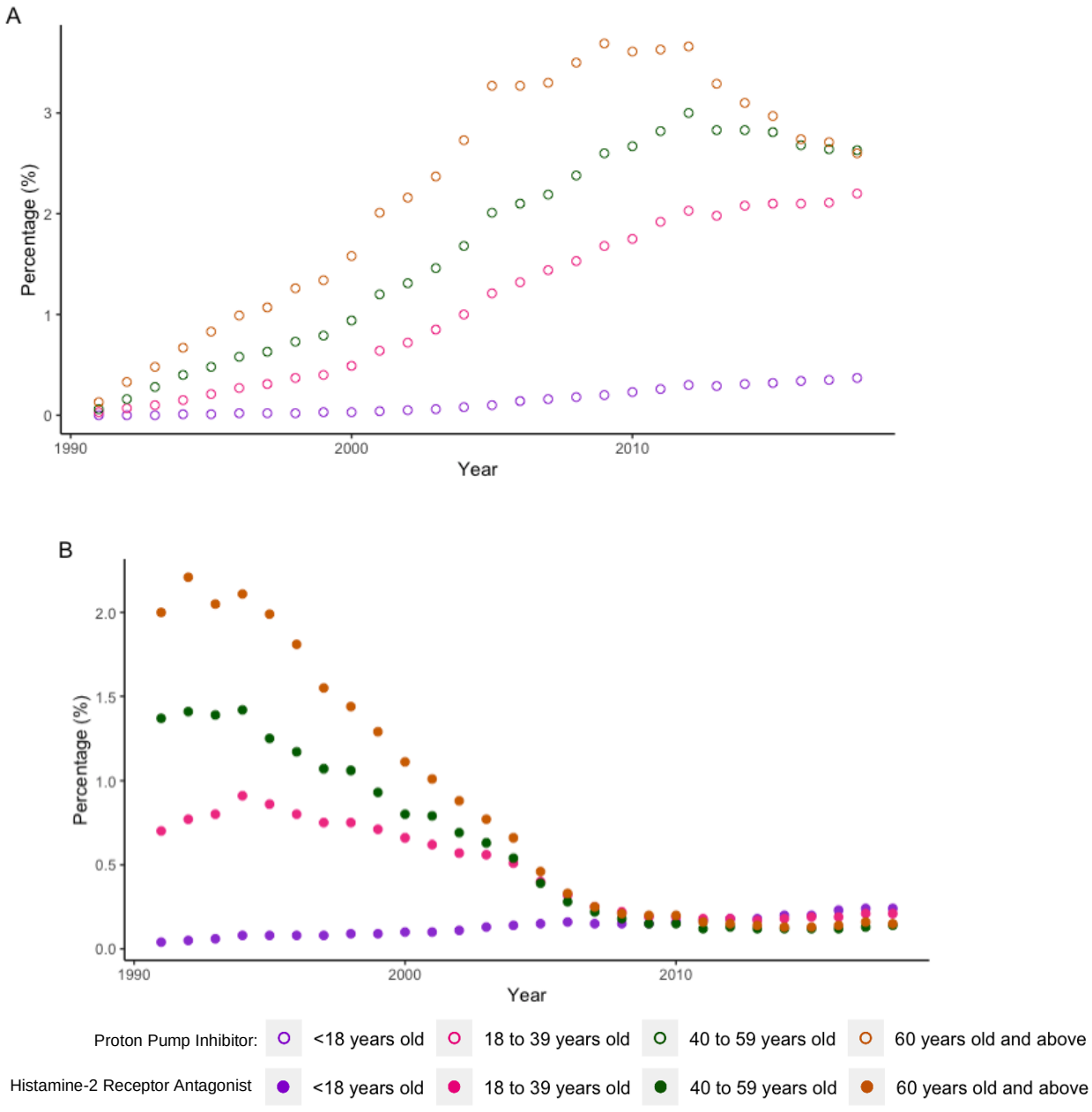
Supplementary Figure 4.1 Incidence of Indications for Proton Pump Inhibitors and Histamine-2 Receptor Antagonists Over Time



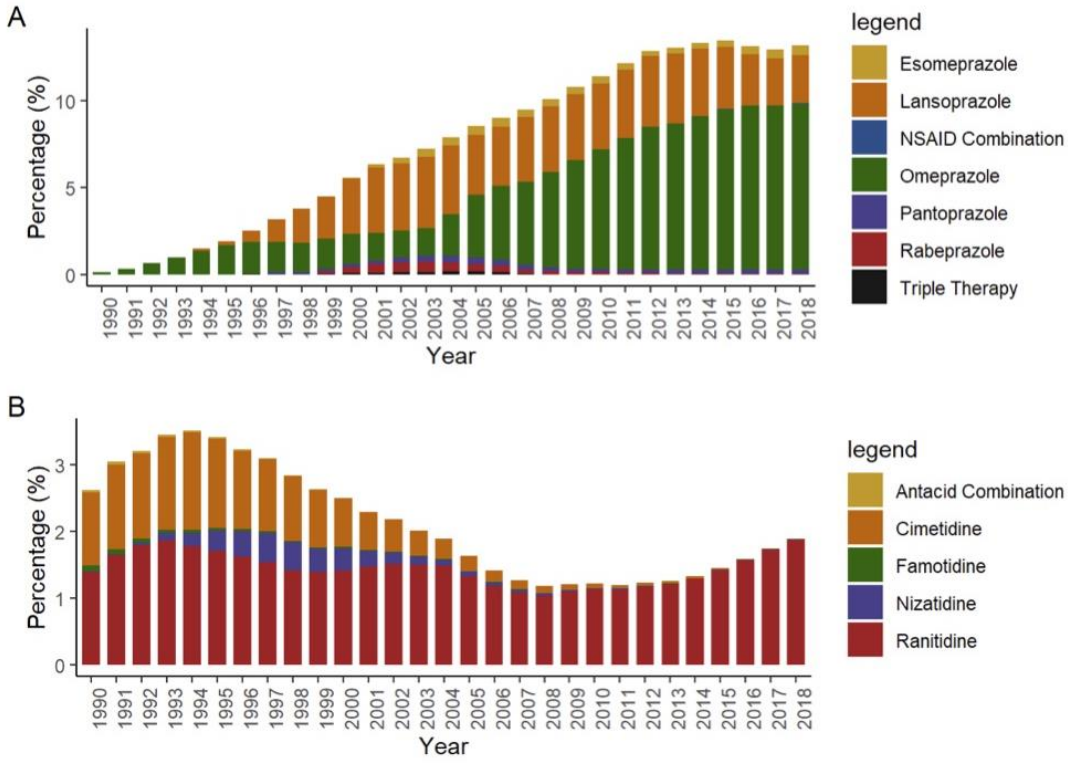
Supplementary Figure 4.2 Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users

Supplementary Figure 4.3 Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users

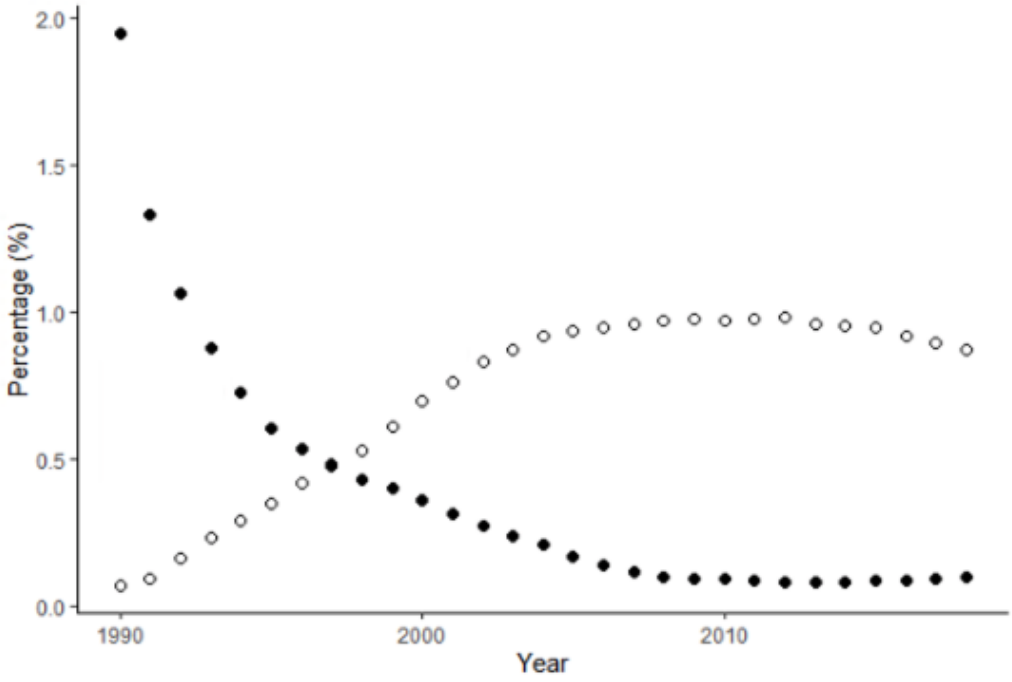
Supplementary Figure 4.4 Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use in New Users



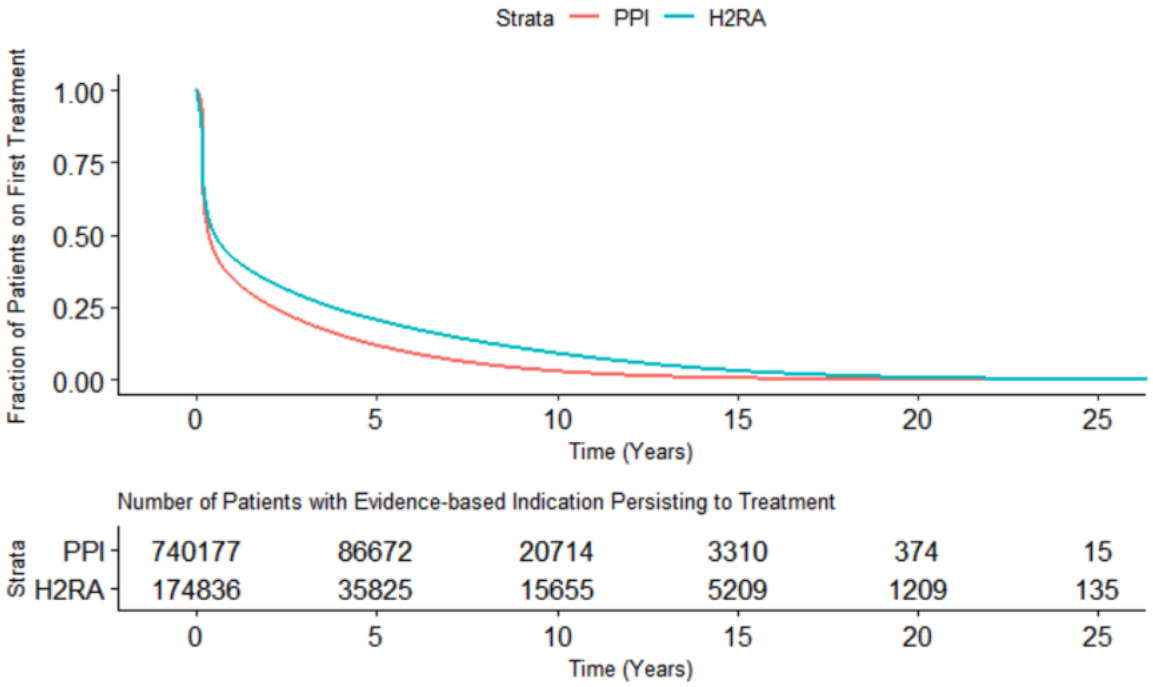
Supplementary Figure 4.5 Prevalence of A) Proton Pump Inhibitor Prescriptions and B) Histamine-2 Receptor Antagonist Prescriptions Stratified by Individual Drug Type



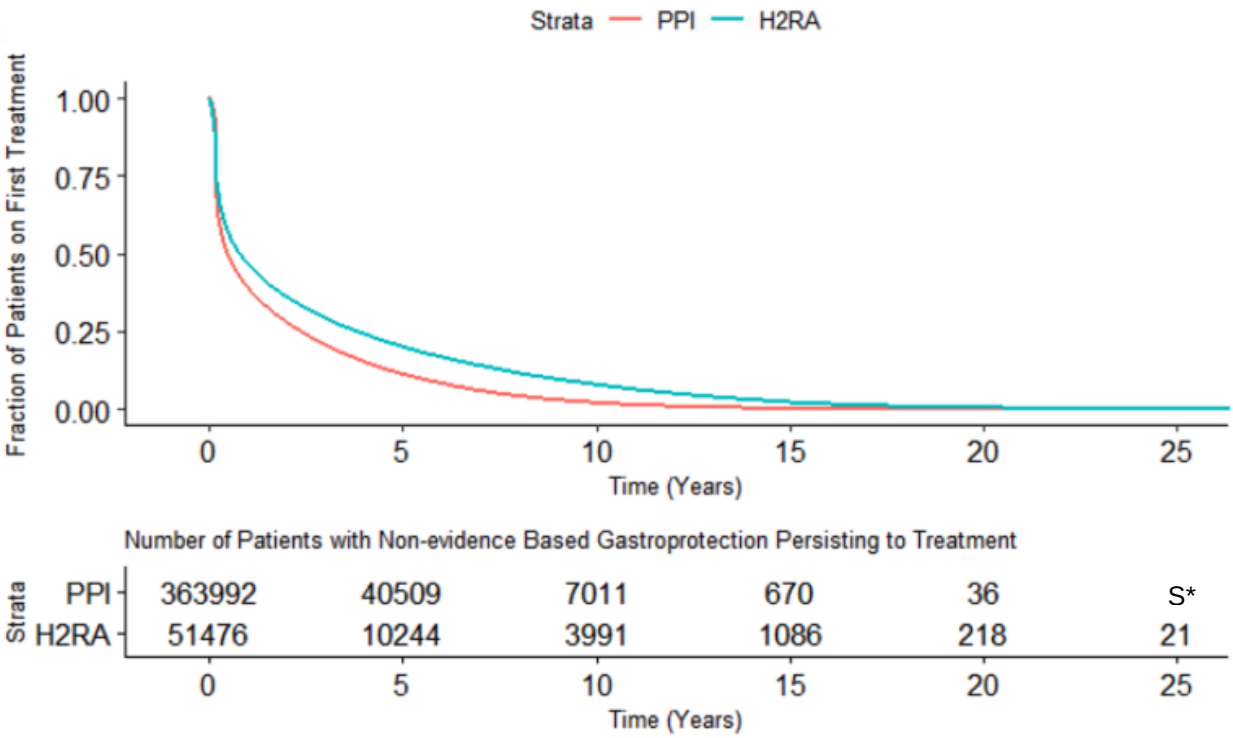
Supplementary Figure 4.6 Prescribing Intensity of Proton Pump Inhibitors and Histamine-2 Receptor Antagonists



Supplementary Figure 4.7 Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Evidence-based Indications for Use

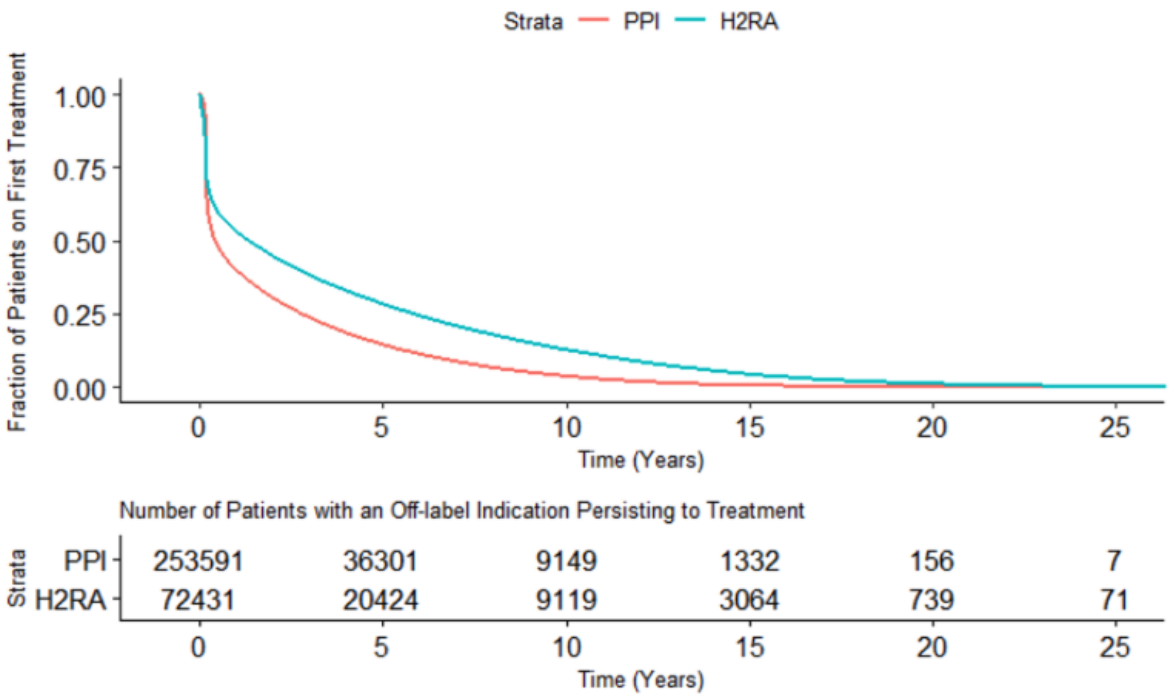


Supplementary Figure 4.8 Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Non-evidence Based Gastroprotection

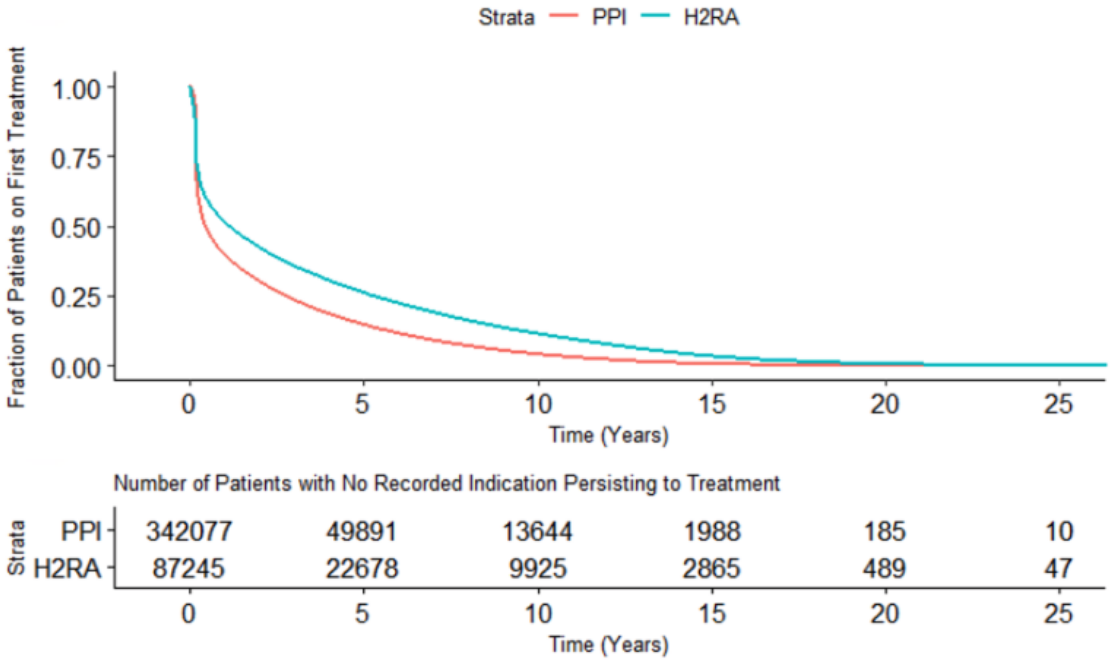


S* Numbers <5 are not displayed, as per the confidentially practices of the Clinical Practice Research Datalink.

Supplementary Figure 4.9 Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Off-label Indications for Use



Supplementary Figure 4.10 Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with No Recorded Indication for Use



Chapter 5. Trends in Prescribing Patterns of Proton Pump Inhibitors Surrounding New Guidelines

5.1 Preface

In Chapter four, we observed that one in every five patients in the CPRD were prescribed at least one acid suppressant drug from 1990 to 2018. We illustrated a high PPI prevalence, which has been increasing over time, but a constant PPI prescribing intensity over the past 15 years. In contrast, H2RA prevalence was low throughout the study period, but its intensity has begun to slightly increase over the past five years. Importantly, this study showed that in addition to the overprescribing burden of PPIs, H2RAs are being similarly overprescribed, with more than 20% of adults having no recorded indication for H2RA use. The high prevalence of PPIs in recent years, and the number of patients without an evidence-based indication for use, appears to contradict the most recent guidelines published by NICE in 2014. These guidelines recommend a minimum yearly assessment of ongoing need for treatment, with low-dose PPIs or H2RAs encouraged as an alternative to high-dose PPIs.[21] Thus, one would expect PPI prevalence and intensity to decrease following publication of the guidelines. However, given the cross-sectional nature of Objective 1, this study was not designed to specifically address the impact of the guidelines on PPI use. To date, it remains unclear whether these guidelines have led to a meaningful change in physician prescribing in the UK. Evaluating the effectiveness of existing programs is an important first step to address the burden of overprescribing. Thus, the second objective of this thesis was to determine whether the 2014 NICE PPI guidelines changed physician prescribing patterns in clinical practice. This paper was published in *Annals of Epidemiology* 55 (2021): 24-26 as a short research report.[169]

5.2 Title Page

Trends in Prescribing Patterns of Proton Pump Inhibitors Surrounding New Guidelines

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5.3 Abstract

Purpose: The purpose of this study was to examine whether the latest National Institute for Health and Care Excellence proton pump inhibitor (PPI) guidelines changed physician prescribing patterns in clinical practice.

Methods: Using data from the United Kingdom Clinical Practice Research Datalink, we calculated monthly PPI prescribing rates in adults by dividing the number of PPI prescriptions by the number of patients in each calendar month. Using these rates, we conducted an interrupted time-series analysis to compare PPI prescription rates before (September 2010-August 2014) and after (September 2014-August 2018) guideline publication, estimating a slope and level change using segmented autoregression.

Results: In the preguideline period, monthly PPI prescription rate increased by 46.9 (95% confidence interval (CI): 40.8 to 53.0) prescriptions per 100,000 persons. Following guideline publication, there was no immediate change in the monthly PPI prescribing rate (137.6, 95% CI: -36.7 to 311.9 prescriptions per 100,000 persons), but there was a modest attenuation of the change in monthly rate (-23.9, 95% CI: -14.0 to -33.6 prescriptions per 100,000 persons). However, the predicted rates mirror the observed rates after guideline publication, suggesting limited changes.

Conclusions: Despite efforts to minimize the overprescribing of PPIs, there was little meaningful change in clinical practice following the 2014 National Institute for Health and Care Excellence recommendations.

Keywords: Proton pump inhibitors, deprescribing, guidelines, policy, quasi-experimental

5.4 Introduction

Proton pump inhibitors (PPIs) are commonly prescribed for gastric conditions, including peptic ulcer disease and gastroesophageal reflux disease [1]. In recent years, there has been growing concern that PPIs are overprescribed, frequently without an evidence-based indication, for an inappropriately long duration, or without a reassessment for ongoing necessity [2,3]. As a result of this medication overuse, and given the potential adverse effects associated with PPI use [1,4], the United Kingdom National Institute for Health and Care Excellence (NICE) established new treatment guidelines in 2014 to improve the treatment of gastric conditions and reduce PPI prescribing [5,6]. These guidelines recommend a minimum yearly reassessment of the ongoing need for PPI treatment, with recommendations to step down, switch, or stop treatment when no longer indicated [6]. To date, no studies have investigated the trends of PPI prescribing patterns with respect to the implementation of these new guidelines. Thus, our objective was to investigate whether prescribing patterns changed following the most recent NICE guidelines to elucidate whether the guidelines had an impact on physician prescribing patterns in clinical practice.

5.5 Materials and Methods

Using data from the United Kingdom Clinical Practice Research Datalink, we assembled a cohort of 8,631,066 adults (≥18 years old) from September 1, 2010 to August 31, 2018. Using this cohort, we calculated monthly PPI prescribing rates by dividing the number of PPI prescriptions by the number of patients in the Clinical Practice Research Datalink in each calendar month. To investigate whether this rate was influenced by patients switching between PPI types, we quantified the monthly prevalence of switching by dividing the number of patients with a PPI switch by the number of patients prescribed PPIs in that month.

To determine whether PPI prescribing rates changed after the publication of the NICE guidelines in 2014 [6], we conducted an interrupted time-series analysis [7,8]. This analysis compared PPI prescription rates preguideline (September 2010-August 2014) and postguideline (September 2014-August 2018) publication. This timeframe was selected as there were no PPI warnings issued by the European Medicines Agency or updated treatment guidelines in the preguideline and postguideline periods, thus limiting the impact of confounding from other interventions. Using the data in the preguideline period, we fit an unadjusted segmented autoregression model to project PPI prescribing rates after September 2014; this approximated what would have been observed in the absence of the guidelines. This allowed for the estimation of both the short-term difference of the rate (level) and change in rate (i.e., difference in slopes) in the postguideline period [7,8]. We compared the characteristics of the patients in the preguideline and postguideline periods to determine if the underlying population characteristics changed after the publication of the guidelines. To assess heterogeneity, we repeated the analysis stratifying by age (<60 and ≥60 years old) and sex. The study protocol was approved by the Independent

Scientific Advisory Committee of the Clinical Practice Research Datalink (protocol 19_119RA) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

5.6 Results

The observed and predicted PPI prescribing rates are illustrated in Figure 1. In the preguideline period, the monthly PPI prescription rate increased by 46.9 (95% confidence interval (CI): 40.8-53.0) prescriptions per 100,000 persons. After the guideline publication, there was no immediate (level) change in the monthly PPI prescribing rate (137.6, 95% CI: -36.7 to 311.9 prescriptions per 100,000 persons), but there was a modest attenuation of the change in monthly rate (slope) (-23.9, 95% CI: -14.0 to -33.6 prescriptions per 100,000 persons). However, extrapolation of the null model (green line, Fig. 1) indicates that the predicted rates closely mirror the observed rates after guideline publication, suggesting limited changes in prescribing patterns after guideline publication. Finally, the modest attenuation in rate was not driven by patients switching between PPI types in any given month, as the prevalence of switching was minimal throughout the study period (2.02%) and was lower in the postguideline period than that in the preguideline period (1.95% vs. 2.30%, respectively).

There were no population age differences in the preguideline and postguideline periods (mean age 64.7 and 64.3 years, respectively). While there was an attenuation of the change in monthly rate in individuals less than 60 (-11.5, 95% CI: -16.6 to -6.43 prescriptions per 100,000 persons), which was not observed in the elderly population (-8.78, 95% CI: -19.0 to 1.41 prescriptions per 1000,000 persons); given that the CIs overlap, we cannot conclude heterogeneity in prescription changes in accordance with age. There were also no statistically significant short-term differences of the monthly rates (level changes) in accordance with age. There were also no statistically significant short-term differences of the monthly rates (level changes) in accordance with age (<60 years old: 97.5, 95% CI: -2.20 to 197.2 prescriptions per 100,000 persons; ≥60 years old -51.1, 95% CI: -288.5 to 186.3 prescriptions per 100,000 persons). There were no population

sex differences in the pre and postguideline periods (55% female). There were also no short-term differences in monthly prescribing rates (male: 106.5, 95% CI: -54.1 to 267.1 prescriptions per 100,000 persons; female: 165.0, 95% CI: -23.5 to 353.5 prescriptions per 100,000 persons) or changes in monthly rates (male: -20.0, 95% CI: -29.1 to -10.9 prescriptions per 100,000 persons; females: -27.3, 95% CI: -37.7 to -16.9 prescriptions per 100,000 persons) in accordance to sex.

5.7 Conclusions

This interrupted time-series analysis investigated PPI prescription patterns after the publication of the most recent NICE guidelines for PPI use. At best, the guidelines may have led to a modest attenuation of the increase in the rate of monthly PPI prescriptions. However, as it is likely that this attenuation would have been observed in the absence of the new guidelines, there was little meaningful change in clinical practice after the publication of the guidelines. This study is limited by its ecological design and was unable to assess whether the guidelines affected individual-level changes in prescribing.

Overall, despite efforts to combat the overprescribing of PPIs, projections of physician prescribing patterns using data before the 2014 NICE recommendations were not meaningfully different from the observed patterns following the guidelines. Thus, while it appears that general practitioners in the United Kingdom are now prescribing PPIs at a slower rate, other interventions in addition to guidelines are likely needed to combat the overprescribing of PPIs.

5.8 Acknowledgements

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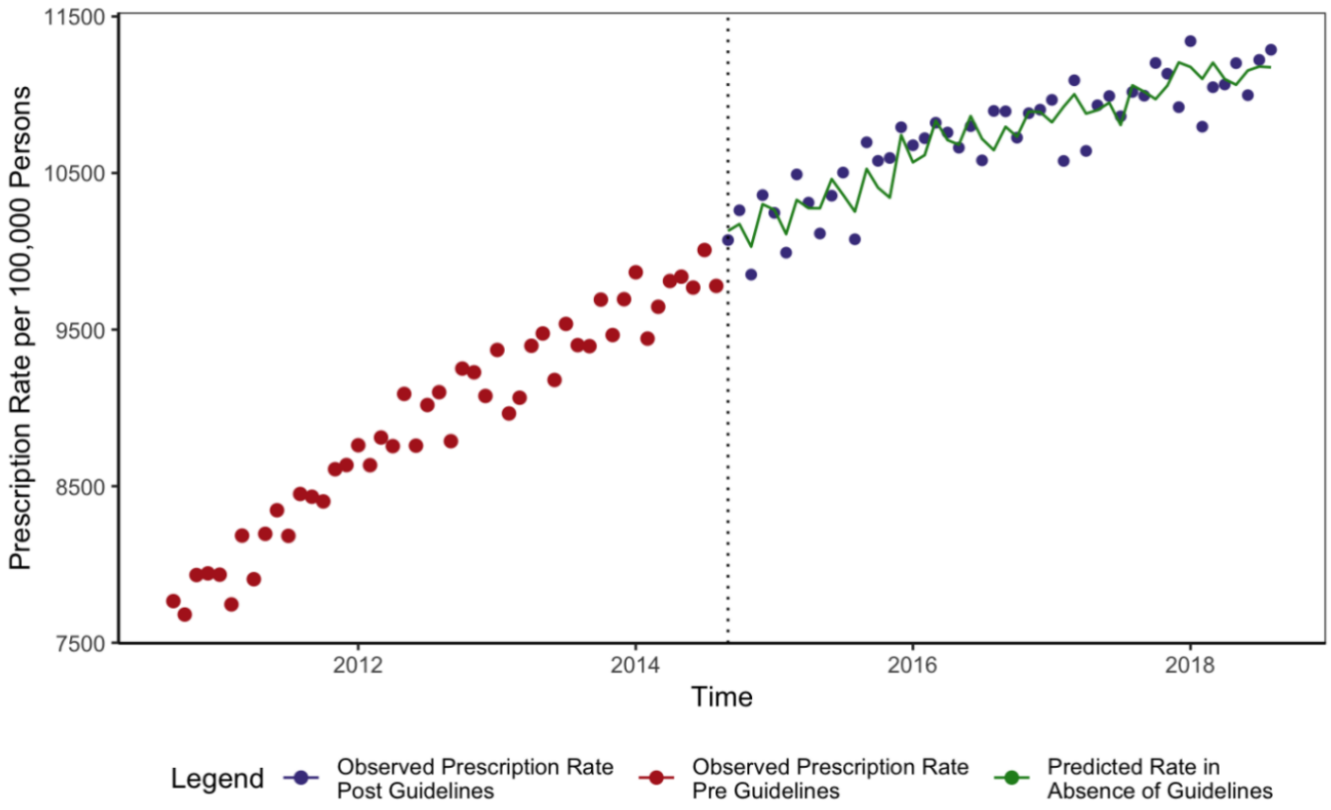
5.10 Figure Legend

Figure 5.1 Observed and predicted monthly prescribing rates of proton pump inhibitors in the United Kingdom before and after the publication of the National Institute for Health and Care Excellence guidelines in September 2014.

5.11 Figure

Figure 5.1 Observed and predicted monthly prescribing rates of proton pump inhibitors in the United Kingdom before and after the publication of the National Institute for Health and Care Excellence guidelines in September 2014.



Chapter 6. Proton Pump Inhibitors and Risk of Gastric Cancer: A Population-based Cohort Study

6.1 Preface

As illustrated by the interrupted time series analysis in the previous chapter, current deprescribing initiatives in the UK have not succeeded at closing the gap between PPI prescribing recommendations and physician behaviours in clinical practice. Whether or not stronger deprescribing initiatives should be implemented partially depends on the overall safety profile of a drug. To date, it is well established that the use of PPIs is associated with several adverse health outcomes, including enteric infections such as *Clostridiodes difficile*, acute interstitial nephritis, hypomagnesaemia, and increased intestinal colonization with multidrug-resistant organisms. What is less well known is whether PPIs are associated with an increased risk of gastrointestinal malignancies. While several previous observational studies have been conducted to determine whether PPIs are associated with gastric cancer risk, these studies had important methodological flaws, which limit their conclusions. This includes lack of an active comparator, which can introduce confounding by indication, and other time-related biases such as immortal time and time-window bias. These biases can significantly alter a study's conclusion and make interpretation of results difficult. Moreover, results were highly heterogeneous, with relative risks ranging from 1.01 to 3.61. Thus, it remains unclear whether gastric cancer risk must be considered as an adverse health outcome when prescribing PPIs. Given the severity of gastric cancer, should an association exist, this would be an important consideration for both physicians and patients when choosing to initiate PPI therapy. Thus, the third objective of this thesis was to determine whether the use of PPIs, when compared with the use of H2RAs, is associated with an increased risk of incident gastric cancer. This paper was published in *Gut* [epub ahead of print].[170]

6.2 Title Page

Proton Pump Inhibitors and Risk of Gastric Cancer: Population-based Cohort Study

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6.3 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 United Kingdom Clinical Practice Research Datalink, we conducted a population-based cohort study using a new-user active comparator design. From January 1, 1990, to April 30, 2018, we identified 973,281 new users of PPIs and 193,306 new users of H2RAs. Cox proportional hazards models were fit to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of gastric cancer, and the number needed to harm was estimated using the Kaplan-Meier method. The models were weighted using standardized 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: 1.45, 95% CI: 1.06-1.98). The number needed to harm was 2,121 and 1,191 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.

6.4 Summary Box

6.4.1 What is already known about this subject?

- Previous observational studies suggest that the use of proton pump inhibitors is associated with an increased risk of gastric cancer, a disease with poor survival.
- However, all previous studies were limited by important methodological shortcomings, which may lead to an exaggeration of the reported risk between the use of proton pump inhibitors and gastric cancer.

6.4.2 What are the new findings?

- The use of proton pump inhibitors is associated with a 45% increased risk of gastric cancer compared with the use of histamine-2 receptor antagonists.
- Gastric cancer risk increased with cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation.

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

- In light of the overuse of proton pump inhibitors, physicians should regularly reassess the necessity of ongoing treatment.

6.5 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.[1-3] 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 colonization with multi-drug 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 hypergastrinemia, 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 (hazard ratio [HR]: 1.01, 95% confidence interval [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.

6.6 Methods

6.6.1 Data Source

This study was conducted using the United Kingdom (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.[26 27] Recorded data includes patient characteristics, medical diagnoses, prescriptions, and lifestyle characteristics. Cancer diagnoses have been previously validated, with positive predictive values for gastroesophageal cancers as high as 96%.[28-31]

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 20_076) and by the Research Ethics Board of the Jewish General Hospital.

6.6.2 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 minimize 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, **Supplementary Tables 1** and **2**), from January 1, 1990 (first full year of PPI and H2RA availability) through April 30, 2018. At cohort entry, all patients were required to be at least 40 years old and have at least one 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 (i.e., 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 (**Supplementary Figure 1**). Finally, the cohort was restricted to patients with at least one year of follow-up after cohort entry (i.e., one year lag period) to allow for a latency time-window and minimize detection bias and reverse causality.[33]

6.6.3 Exposure Definition

All patients were followed starting one year after cohort entry until an incident diagnosis of gastric cancer (identified using Read codes, **Supplementary Table 3**), one year after switching between the study drug classes [i.e., switch from PPI to H2RA or vice versa to account for the one-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 (April 30, 2019), whichever occurred first. Patients were considered continuously exposed from cohort entry, regardless of treatment termination, as this exposure definition aligns with the hypothesized biological mechanism (i.e., an irreversible effect of PPIs on gastric cancer development that persists even after treatment discontinuation).

6.6.4 Potential Confounders

We considered a wide range of potential confounders, all measured on or before cohort entry. These included demographic and lifestyle variables, such as age (modelled as a continuous variable using a cubic spline model to account for a possible non-linear relation with the outcome),[34] sex, alcohol-related disorders (alcohol dependency, alcoholic cirrhosis of the liver, alcoholic hepatitis, hepatic failure), smoking status, and body mass index. The potential confounders also included comorbidities, such as atrial fibrillation, anemia, cancer (excluding non-melanoma skin cancer), congestive heart failure, gastric metaplasia, hypercholesterolemia, hypertension, venous thromboembolism, chronic kidney disease, stroke, hernia, gastrointestinal bleeding, dialysis, and gastric surgery. We considered approved indications for acid suppressant drug use (Barrett's

esophagus, *Helicobacter pylori* infection [identified by either a diagnosis or a prescription for triple therapy], gastroesophageal reflux disease, peptic ulcer disease, dyspepsia) and off-label indications (gastritis or duodenitis and stomach pain). We considered each indication separately, as there are some variations in the guidelines by indication.[35] Finally, we included the use of the following drugs: metformin, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors, which have been associated with a decreased risk of gastric cancer,[36-38] antiplatelets, dual antiplatelets, selective serotonin reuptake inhibitors (SSRIs), anticoagulants, and steroids, which may cause bleeding, and synthetic prostaglandin analogs, which are older drugs used to manage gastric conditions.[6] The aforementioned variables were selected based on a thorough review of the literature, which identified variables meeting the traditional definition of a confounder, measures of general health status, and opportunities for interaction with health care providers (which may increase detection).[39]

6.6.5 Statistical Analysis

The models were weighted using standardized mortality ratio weights estimated using calendar time-specific propensity scores. [40 41] 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,[4] changes in gastric cancer incidence,[42] heterogeneity in covariate definitions during the study period. Calendar-time specific propensity scores may result in better confounding control compared to a single propensity score model.[41] 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)).[40] This upweights the comparator patients (i.e., H2RA users) to represent the treated population (i.e., PPI users). Covariate balance was assessed before and after weighting using standardized differences, with differences of less than 0.10 indicative of good balance.[43]

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 pseudocopulation 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.[44]

6.6.6 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 World Health Organization defined daily dose (**Supplementary Table 4**).[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.[34] 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 possible 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.

6.6.7 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 (i.e., 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 standardized mortality ratio weights with stabilized inverse probability of censoring weights to account for censoring from drug switching during follow-up[46 47] and to account for the competing risk of death (**Supplementary Method 1**).[48] Fourth, as certain H2RAs (such as ranitidine), have recently been found to be contaminated with N-nitrosodimethylamine (NDMA), a probable carcinogen,[49] we repeated the analysis with follow-up truncated on December 31, 2017, which is before the time NDMA contaminants were found.[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 (**Supplementary Method 2**).[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 (**Supplementary Method 3**).[51] All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

6.6.8 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.

6.7 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 one-year lag period. There were 1,166 incident gastric cancer events in the PPI cohort, which generated a crude incidence rate of 23.9 (95% CI: 22.5-25.3) 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: 22.6-29.2) 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 hypercholesteremia, chronic kidney disease, and *Helicobacter 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 (standardized 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% versus 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: 1.14-1.57). 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: 1.06-1.98). 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 three years after treatment initiation) (**Figure 2**). The number needed to harm was 2,121 and 1,191 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 (**Supplementary 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 *Helicobacter pylori* infection to 3.0 (1.3, 6.0) years for Barrett's esophagus. The median (Q1, Q3) cumulative duration for H2RA users was 55 (30, 159) days, with minimal variation between the median value across the indications (range 30 to 92 days).

All PPI molecules were associated with elevated HRs for gastric cancer (ranging from 1.19 to 1.48; **Supplementary Table 5**). While the point estimates increased with age (Supplementary **Table 6**), and females had a slightly higher HR than males (**Supplementary 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 gastroesophageal disease (HR: 1.38, 95% CI: 0.59-3.22) and peptic ulcer disease (HR: 1.53, 95% CI: 0.49-4.92) (**Supplementary 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 for all strata were largely overlapping (**Supplementary Table 9**).

Figure 3 summarizes the results of the primary and sensitivity analyses (shown in detail in **Supplementary Tables 10** to **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 (**Supplementary Table 15**).

6.8 Discussion

6.8.1 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: 1.06-1.98) compared with new users of H2RAs, with a number needed to harm of 2,121 and 1,191 for five and 10 years after treatment initiation, respectively. 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.

6.8.2 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 gastric cancer.[52 53] Thus, our study represents an important addition by minimizing 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,[9 10 17] which may have introduced survival bias and confounding,[54] important time-related biases[9-11 14-16 20] such as immortal-time bias and time-window bias,[23-25] and failure to account for cancer latency.[11 13] 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 hypergastrinemia (elevated secretion of gastrin from G-cells), as gastrin secretion is inhibited by acidity.[21] Gastrin is considered a potent growth factor, which may induce hyperplasia.[22] Second, long-term PPI use may lead to changes in the gut microbiome, including reduced microbial diversity.[55 56] Changes to the gut microbiota have been shown to contribute to an increased risk of gastric cancer.[57] Third, although disputed, chronic suppression of acid secretion by PPIs may be associated with atrophic gastritis (chronic inflammation of the stomach mucous membrane),[58 59] which is one of the main precursors to gastric cancer;[60] although not all studies have reported this association.[61] 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,[6] and are associated with lower gastrin levels (i.e., less likely to induce hypergastrinemia).[21] Thus, from a theoretical biological perspective, H2RAs are less likely to be associated with an increased risk of gastric cancer than PPIs.

6.8.3 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.[54] Third, the comparator group consisted of patients prescribed H2RAs, an active comparator that likely

minimized 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.

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;[62] 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 versus non-cardia) as this information is not consistently recorded in the CPRD. Fourth, some secondary analyses may be underpowered, and should not be overinterpreted. Finally, given the observational nature of this study, residual confounding remains possible. While confounding from calendar time explained most of the observed difference between the crude and adjusted estimates,[4 42] we cannot rule out 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,[63] 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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Competing Interest Statement: SS participated in advisory meetings or as a guest speaker for Atara 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 organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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 analyzed and interpreted the data. EGM and AB 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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Data Sharing: No additional data available.

Transparency: The guarantor (LA) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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6.11 Figure Legends

Figure 6.1 Study flow chart describing the construction of the proton pump inhibitor and histamine-2 receptor antagonist cohorts.

Figure 6.2 Weighted Kaplan-Meier curve illustrating the cumulative incidence of gastric cancer in patients newly prescribed proton pump inhibitors and histamine-2 receptor antagonists.

Figure 6.3 Forest plot summarizing the results of primary and sensitivity analyses, with weighted hazard ratios and 95% confidence intervals for the association between use of proton pump inhibitors and gastric cancer, compared with the use of histamine-2 receptor antagonists.

Figure 6.4 Graphical summary highlighting the main findings of the association between the use of proton pump inhibitors and gastric cancer, compared with the use of histamine-2 receptor antagonists.

6.12 Tables and Figures

Table 6.1 Baseline Characteristics of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Users Before and After Weighting

	Before Weighting			After Weighting *		
Characteristic	**PPI**	**H2RA**	**ASD**	**PPI**	**H2RA**	**ASD**
Total	973,281	198,306		973,281	972,083	
Age (mean, SD)	60.4 (13.0)	60.4 (13.1)	0.00	60.4 (13.0)	60.4 (28.9)	0.00
Male	438,592 (45.1)	85,505 (43.1)	0.04	438,592 (45.1)	436,521 (44.9)	0.00
Alcohol related disorders	55,957 (5.8)	7,912 (4.0)	0.08	55,957 (5.8)	56,352 (5.8)	0.00
Smoking Status						
Current	260,166 (26.7)	50,856 (25.7)	0.03	260,166 (26.7)	259,094 (26.7)	0.00
Former	141,467 (14.5)	20,490 (10.3)	0.13	141,467 (14.5)	142,286 (14.6)	0.00
Never	538,106 (55.3)	100,006 (50.4)	0.10	538,106 (55.3)	537,236 (55.3)	0.00
Missing	33,542 (3.5)	26,954 (13.6)	0.37	33,542 (3.5)	33,467 (3.4)	0.00
Body mass index						
<25 kg/m^2	361,873 (37.2)	67,314 (33.9)	0.07	361,873 (37.2)	362,379 (37.3)	0.00
25-29.9 kg/m^2	326,240 (33.5)	58,226 (29.4)	0.09	326,240 (33.5)	325,379 (33.5)	0.00
≥30 kg/m^2	177,306 (18.2)	27,732 (14.0)	0.12	177,306 (18.2)	176,823 (18.2)	0.00
Missing	107,862 (11.1)	45,034 (22.7)	0.31	107,862 (11.1)	107,502 (11.1)	0.00
Atrial fibrillation	34,778 (3.6)	6,037 (3.0)	0.03	34,778 (3.6)	35,576 (3.7)	0.00
Anemia	89,930 (9.2)	14,860 (7.5)	0.06	89,930 (9.2)	90,836 (9.3)	0.00
Cancer	81,000 (8.3)	13,416 (6.8)	0.06	81,000 (8.3)	82,457 (8.5)	0.01
Congestive heart failure	21,292 (2.2)	6,372 (3.2)	0.06	21,292 (2.2)	21,920 (2.3)	0.00
Gastric metaplasia	293 (0.0)	55 (0.0)	0.00	293 (0.0)	371 (0.0)	0.00
Hypercholesterolemia	293,279 (30.1)	33,809 (17.1)	0.31	293,279 (30.1)	292,404 (30.1)	0.00
Hypertension	311,466 (32.0)	51,441 (25.9)	0.14	311,466 (32.0)	310,451 (31.9)	0.00
Venous thromboembolism	44,121 (4.5)	7,944 (4.0)	0.03	44,121 (4.5)	44,645 (4.6)	0.00
Chronic kidney disease	54,247 (5.6)	4,044 (2.0)	0.19	54,247 (5.6)	55,217 (5.7)	0.00
Stroke	49,495 (5.1)	10,105 (5.1)	0.00	49,495 (5.1)	50,673 (5.2)	0.01
Hernia	32,113 (3.3)	7,586 (3.8)	0.03	32,113 (3.3)	33,737 (3.5)	0.01
Gastro-intestinal bleeding	85,760 (8.8)	13,108 (6.6)	0.08	85,760 (8.8)	85,927 (8.8)	0.00
Dialysis	794 (0.1)	304 (0.2)	0.02	794 (0.1)	807 (0.1)	0.00
Gastric surgery	2,678 (0.3)	645 (0.3)	0.01	2,678 (0.3)	2,854 (0.3)	0.00
Barrett's Esophagus	2,928 (0.3)	79 (0.0)	0.06	2,928 (0.3)	3,627 (0.4)	0.01
Helicobacter pylori infection	20,440 (2.1)	982 (0.5)	0.14	20,440 (2.1)	20,935 (2.2)	0.00
Gastro-esophageal reflux disease	86,985 (8.9)	17,461 (8.8)	0.00	86,985 (8.9)	90,581 (9.3)	0.01
Peptic ulcer disease	29,358 (3.0)	8,623 (4.4)	0.07	29,358 (3.0)	29,795 (3.1)	0.00
Dyspepsia	169,147 (17.4)	60,869 (30.7)	0.32	169,147 (17.4)	173,000 (17.8)	0.01
Gastritis	41,343 (4.3)	11,094 (5.6)	0.06	41,343 (4.3)	42,142 (4.3)	0.00
Stomach pain	273,864 (28.1)	58,350 (29.4)	0.03	273,864 (28.1)	277,733 (28.6)	0.01
Metformin	56,972 (5.9)	6,286 (3.2)	0.13	56,972 (5.9)	57,053 (5.9)	0.00
Non-steroidal anti-inflammatory drugs	692,208 (71.1)	123,534 (62.3)	0.19	692,208 (71.1)	689,062 (70.9)	0.01
Antiplatelets	231,359 (23.8)	37,483 (18.9)	0.12	231,359 (23.8)	232,216 (23.9)	0.00
Dual antiplatelets	67,206 (6.9)	9,164 (4.6)	0.10	67,206 (6.9)	68,440 (7.0)	0.01
Cyclooxygenase-2 inhibitors	82,509 (8.5)	8,622 (4.4)	0.17	82,509 (8.5)	82,734 (8.5)	0.00
Prostaglandin analogues	1,564 (0.2)	1,101 (0.6)	0.07	1,564 (0.2)	1,692 (0.2)	0.00
Selective serotonin reuptake inhibitors	216,197 (22.2)	28,459 (14.4)	0.20	216,197 (22.2)	216,694 (22.3)	0.00
Anticoagulants	37,461 (3.9)	6,718 (3.4)	0.02	37,461 (3.9)	38,322 (3.9)	0.00
Steroids	155,048 (15.9)	27,031 (13.6)	0.06	155,048 (15.9)	156,362 (16.1)	0.00
Year of cohort entry						
1990 - 1994	7,839 (0.8)	33,809 (17.1)	0.59	7,839 (0.8)	7,857 (0.8)	0.00
1995 - 1999	36,611 (3.8)	50,456 (25.4)	0.65	36,611 (3.8)	36,711 (3.8)	0.00
2000 - 2004	148,408 (15.3)	62,201 (31.4)	0.39	148,408 (15.3)	148,453 (15.3)	0.00
2005 - 2009	327,938 (33.7)	30,027 (15.1)	0.44	327,938 (33.7)	328,102 (33.8)	0.00
2010 - 2018	452,485 (46.5)	21,813 (11.0)	0.85	452,485 (46.5)	450,960 (46.4)	0.00

Abbreviations: ASD, absolute standardized difference; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; SD, standard deviation.
Before weighting: counts (percentages), unless otherwise stated; After weighting: count, rounded to the nearest whole number, (percentages), unless otherwise stated.
* Pseudo-population created by applying standardized mortality ratio weights from calendar time-specific propensity scores.

Table 6.2 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared with the Use of Histamine-2 Receptor Antagonists

	Events	Person-years	Incidence rate (95% CI) *	Crude HR	Calendar-year weighted HR (95% CI)	Marginal HR (95% CI) †
H2RAs (n=198,306)	244	947,418	25.8 (22.6 to 29.2)	1.00	1.00 [Reference]	1.00 [Reference]
PPIs (n=973,281)	1,166	4,887,771	23.9 (22.5 to 25.3)	0.92	1.34 (1.14 to 1.57)	1.45 (1.06 to 1.98)
Cumulative duration of proton pump inhibitors						
<2 years	861	3,830,738	22.5 (21.0 to 24.0)	0.82	1.21 (1.03 to 1.42)	1.33 (0.96 to 1.83)
2-3.9 years	140	518,719	27.0 (22.7 to 31.8)	1.16	1.65 (1.31 to 2.07)	1.88 (1.33 to 2.65)
≥4 years	165	538,314	30.7 (26.2 to 35.7)	1.47	2.09 (1.67 to 2.62)	2.40 (1.68 to 3.45)
Cumulative omeprazole dose equivalents						
<14,600 mg	886	3,933,697	22.5 (21.1 to 24.1)	0.83	1.22 (1.04 to 1.43)	1.33 (0.97 to 1.83)
14,600-28,199 mg	147	502,892	29.2 (24.7 to 34.4)	1.27	1.81 (1.45 to 2.26)	2.05 (1.46 to 2.89)
≥29,200 mg	143	451,182	29.5 (24.7 to 34.9)	1.39	2.03 (1.60 to 2.58)	2.34 (1.62 to 3.37)
Time since proton pump inhibitor initiation						
<2 years	293	892,171	32.8 (29.2 to 36.8)	0.94	1.63 (1.17 to 2.29)	1.25 (0.69 to 2.28)
2-3.9 years	334	1,404,884	23.8 (21.3 to 26.5)	0.81	1.24 (0.92 to 1.67)	1.32 (0.79 to 2.19)
≥4 years	539	2,590,716	20.8 (19.1 to 22.6)	0.98	1.26 (1.01 to 1.56)	1.82 (1.09 to 3.02)

Abbreviations: CI, confidence interval; HR, hazard ratio; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

* Crude incidence rate per 100,000 person-years.

† Weighted using standardized mortality ratio weights.

Figure 6.1 Study flow chart describing the construction of the proton pump inhibitor and histamine-2 receptor antagonist cohorts

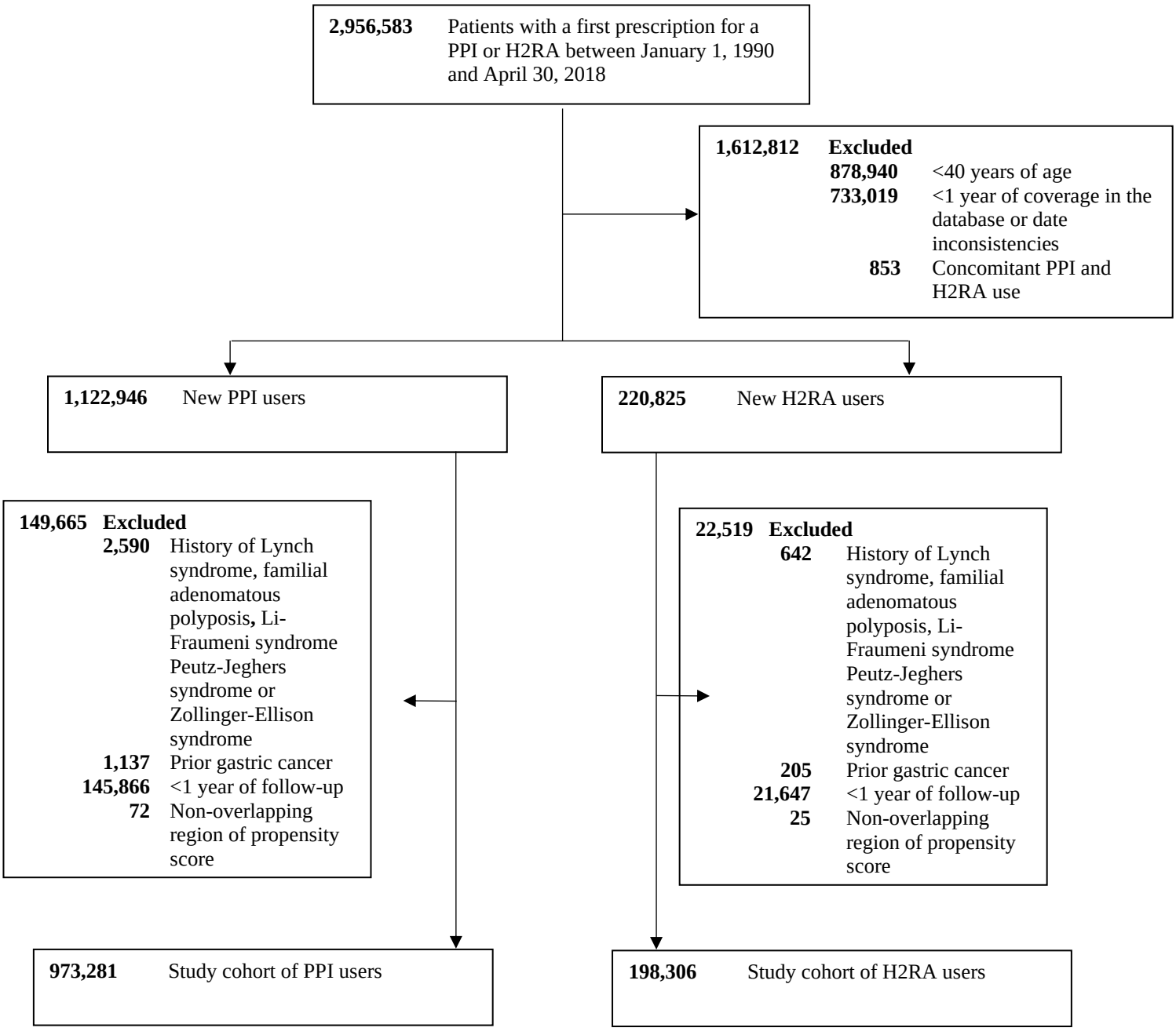
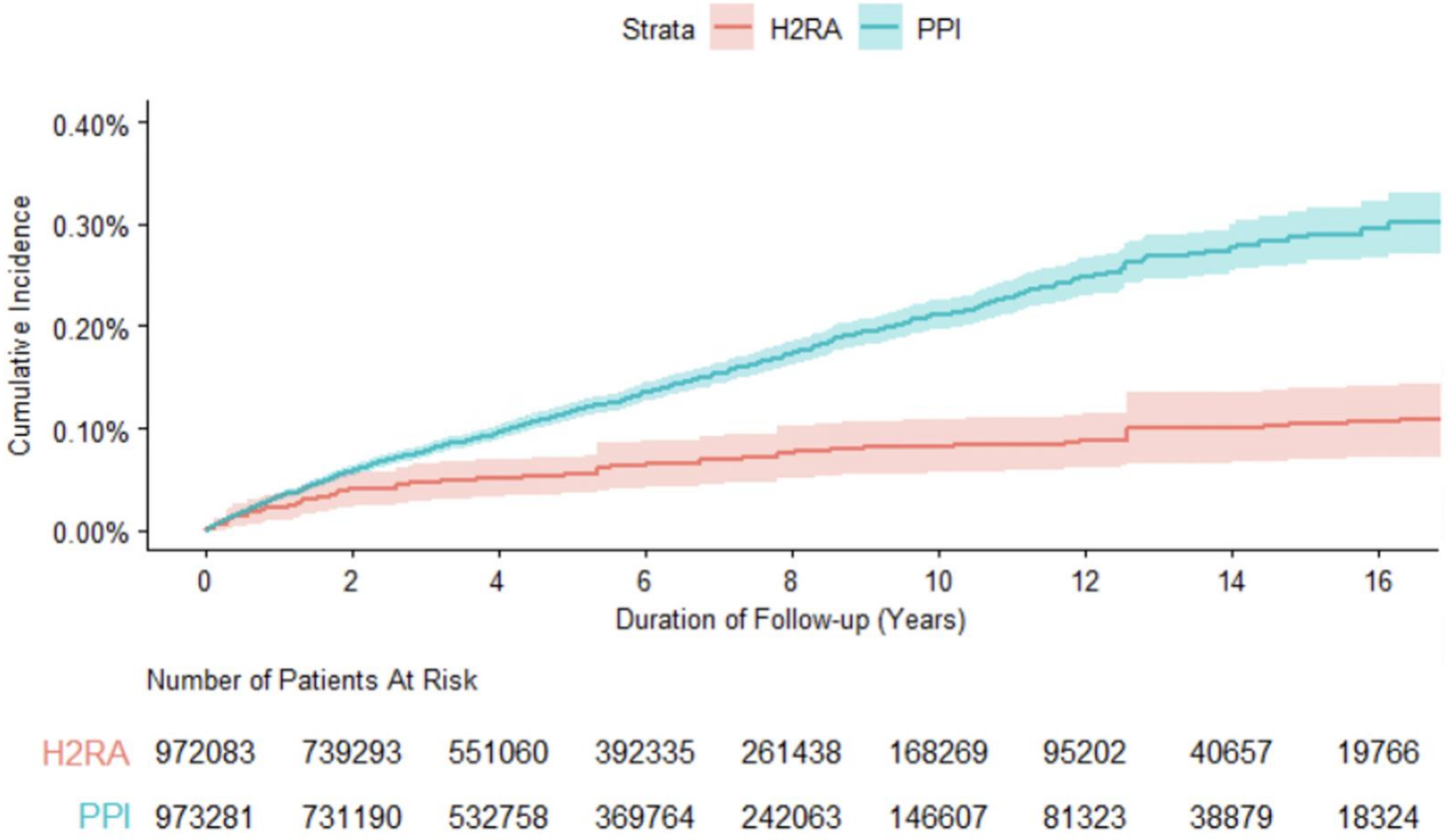
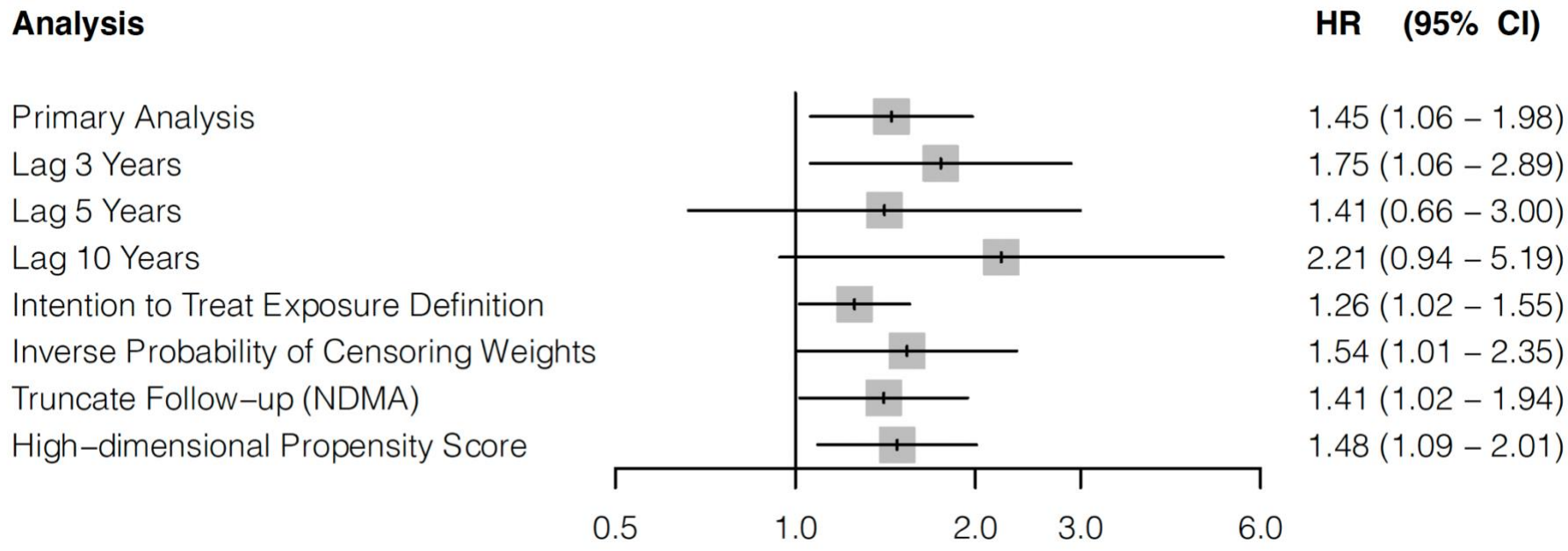


Figure 6.2 Weighted Kaplan-Meier curve illustrating the cumulative incidence of gastric cancer in patients newly prescribed proton pump inhibitors and histamine-2 receptor antagonists



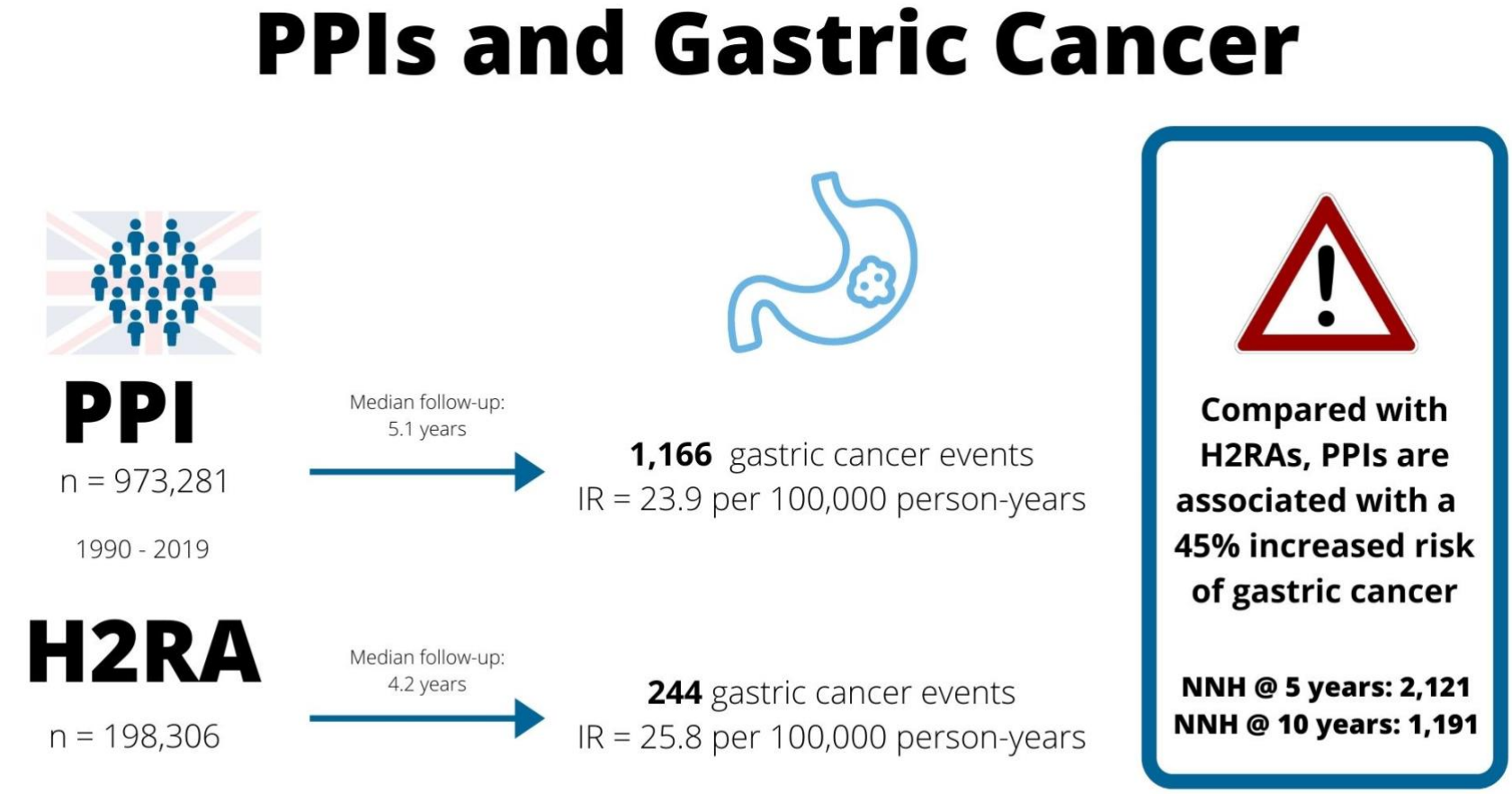
Follow-up starts one year after cohort entry.
Curves are weighted using standardized mortality ratio weights: PPI patients are given a weight of 1, while H2RA patients are upweighted by the odds of the treatment probability.

Figure 6.3 Forest plot summarizing the results of primary and sensitivity analyses, with weighted hazard ratios and 95% confidence intervals for the association between use of PPIs and gastric cancer, compared with the use of H2RAs



Abbreviations: HR: hazard ratio; CI: confidence interval; NDMA: N-Nitrosodimethylamine.

Figure 6.4 Graphical summary highlighting the main findings of the association between the use of proton pump inhibitors and gastric cancer, compared with the use of histamine-2 receptor antagonists.



Abbreviations: PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist; IR, incidence rate; NNH, number needed to harm

6.13 Supplementary Material

Supplementary Table 6.1 List of British National Formulary Codes for Proton Pump Inhibitors

British National Formulary Code	British National Formulary Header
01030500/05010103	Proton Pump Inhibitors/Broad-spectrum Penicillins
01030500/10010100	Proton Pump Inhibitors/Non-steroidal Anti-inflammatory Drugs
01030500/05010500	Proton Pump Inhibitors/Macrolides
1030500	Proton Pump Inhibitors

Supplementary Table 6.2 List of British National Formulary Codes for Histamine-2 Receptor Antagonists

British National Formulary Code	British National Formulary Header
1030100	H2 receptor antagonists
01030100/01010201	H2 receptor antagonists/Alginate preparations
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030100/01010202	H2 receptor antagonists/Indigestion remedies
01010201/01030100	Compound Alginate Preparations/H2-Receptor Antagonists
01010202/01030100	Indigestion Preparations/H2-Receptor Antagonists

Abbreviations: H2, Histamine-2.

Supplementary Table 6.3 Gastric Cancer Read Codes Used to Define Events	
Read Code	**Read Term**
B11y100	Malignant neoplasm of posterior wall of stomach NEC
B11y000	Malignant neoplasm of anterior wall of stomach NEC
B110000	Malignant neoplasm of cardiac orifice of stomach
B11..11	Gastric neoplasm
B110100	Malignant neoplasm of cardio-oesophageal junction of stomach
B110111	Malignant neoplasm of gastro-oesophageal junction
B113.00	Malignant neoplasm of fundus of stomach
B111.00	Malignant neoplasm of pylorus of stomach
B117.00	Malignant neoplasm, overlapping lesion of stomach
B11..00	Malignant neoplasm of stomach
B11yz00	Malignant neoplasm of other specified site of stomach NOS
B11y.00	Malignant neoplasm of other specified site of stomach
B11z.00	Malignant neoplasm of stomach NOS
B115.00	Malignant neoplasm of lesser curve of stomach unspecified
B116.00	Malignant neoplasm of greater curve of stomach unspecified
B114.00	Malignant neoplasm of body of stomach
B111000	Malignant neoplasm of prepylorus of stomach
B112.00	Malignant neoplasm of pyloric antrum of stomach
B110.00	Malignant neoplasm of cardia of stomach
B111100	Malignant neoplasm of pyloric canal of stomach
B111z00	Malignant neoplasm of pylorus of stomach NOS
B110z00	Malignant neoplasm of cardia of stomach NOS

Abbreviations: NEC, Neuroendocrine carcinoma; NOS, not otherwise specified.

Supplementary Table 6.4 Defined Daily Dose of Proton Pump Inhibitors	
Proton Pump Inhibitor Type	**Defined Daily Dose***
Omeprazole	20 mg
Esomeprazole	30 mg
Rabeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg

*All doses are equivalent to 1 Defined Daily Dose.

Supplementary Table 6.5 Crude and Adjusted HRs for the Association Between the Use of Specific Types of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists

Exposure	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonists	244	947,418	25.8 (22.6-29.2)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor type ‡						
Esomeprazole	17	78,412	21.7 (12.6-34.7)	0.86	1.15 (0.70-1.89)	1.25 (0.72-2.16)
Lansoprazole	426	1,685,920	25.3 (22.9-27.8)	0.98	1.37 (1.15-1.63)	1.48 (1.10-2.01)
Omeprazole	661	2,867,210	23.1 (21.3-24.9)	0.88	1.34 (1.13-1.58)	1.45 (1.03-2.02)
Pantoprazole	22	102,816	21.4 (13.4-32.4)	0.86	1.10 (0.71-1.71)	1.19 (0.73-1.95)
Rabeprazole	40	150,378	26.6 (19.0-36.2)	1.07	1.34 (0.95-1.89)	1.44 (0.96-2.15)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100,000 person-years.

† Weighted using standardized mortality ratio weights.

‡ Combination users contributed 0 events and 3,035 person-years of follow-up.

Supplementary Table 6.6 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Age)

	Age < 65	**Age 65-74**	**Age ≥ 75**
Events	431	491	488
Person-Years	3,907,039	1,191,102	737,049
Crude incidence rate (95% CI) *	11.0 (10.0-12.1)	41.2 (37.7-45.0)	66.2 (60.5-72.4)
Crude HR			
Histamine-2 receptor antagonists	1.00	1.00	1.00
Proton pump inhibitors	0.77	1.02	1.00
			p-interaction: 0.18
Adjusted HR (95% CI) †			
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.27 (0.69-2.33)	1.42 (0.84-2.40)	1.71 (1.04-2.81)
			p-interaction: 0.75

Abbreviations: HR, hazard ratio; CI, confidence interval.
* Per 100,000 person-years.
†Weighted using standardized mortality ratio weights.

Supplementary Table 6.7 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Sex)

	Male	Female
Events	854	556
Person-Years	2,591,410	3,243,779
Crude Incidence Rate (95% CI)*	33.0 (30.8-35.2)	17.1 (15.7-18.6)
Crude HR		
Histamine-2 receptor antagonists	1.00	1.00
Proton pump inhibitors	0.87	0.98
		p-interaction: 0.43
Adjusted HR (95% CI) †		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.25 (0.84-1.88)	1.91 (1.22-3.00)
		p-interaction: 0.17

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100,000 person-years.

†Weighted using standardized mortality ratio weights.

Supplementary Table 6.8 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists Stratified by Approved Indication at Baseline

Indication *	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) †
Gastroesophageal reflux disease						
Histamine-2 receptor antagonists	20	78,410	25.5 (15.6-39.4)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	106	484,578	21.9 (17.9-26.5)	0.86	1.23 (0.71-2.13)	1.38 (0.59-3.22)
Peptic ulcer disease						
Histamine-2 receptor antagonists	21	40,570	51.8 (32.0-79.1)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	90	161,650	55.7 (44.8-68.4)	1.06	1.38 (0.77-2.48)	1.53 (0.48-4.92)
Dyspepsia						
Histamine-2 receptor antagonists	97	292,664	33.1 (26.9-40.4)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	270	954,590	28.3 (25.0-31.9)	0.86	1.19 (0.90-1.56)	1.12 (0.69-1.85)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Barrett's esophagus and *Helicobacter pylori* generated few events with unstable estimates.

† Per 100,000 person-years.

‡Weighted using standardized mortality ratio weights.

Supplementary Table 6.9 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists Stratified by Category of Calendar Year

Calendar Year	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
1990-1994					
Histamine-2 receptor antagonists	88	221,998	39.6 (31.8-48.8)	1.00	1.00 [Reference]
Proton pump inhibitor	21	61,313	34.3 (21.2-52.4)	0.89	0.95 (0.58-1.56)
1995-1999					
Histamine-2 receptor antagonists	83	282,105	29.4 (23.4-36.5)	1.00	1.00 [Reference]
Proton pump inhibitor	89	305,308	29.2 (23.4-35.9)	1.06	1.07 (0.78-1.46)
2000-2004					
Histamine-2 receptor antagonists	54	280,498	19.3 (14.5-25.1)	1.00	1.00 [Reference]
Proton pump inhibitor	315	1,143,684	27.5 (24.6-30.8)	1.57	1.43 (1.04-1.98)
2005-2009					
Histamine-2 receptor antagonists	9	114,596	7.9 (3.6-14.9)	1.00	1.00 [Reference]
Proton pump inhibitor	515	1,999,341	25.8 (23.6-28.0)	3.43	2.55 (1.21-5.38)
2010-2018					
Histamine-2 receptor antagonists	10	48,221	20.7 (9.9-38.1)	1.00	1.00 [Reference]
Proton pump inhibitor	226	1,378,125	16.4 (14.3-18.7)	0.82	0.87 (0.45-1.71)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100,000 person-years.

† Weighted using standardized mortality ratio weights.

Supplementary Table 6.10 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Different Lag Periods)

Length of Lag Period	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) †
3 years						
Histamine-2 receptor antagonists	136	649,219	20.9 (17.6 to 24.8)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	671	3,235,785	20.7 (19.2 to 22.4)	0.99	1.28 (1.05 to 1.56)	1.75 (1.06 to 2.89)
5 years						
Histamine-2 receptor antagonists	102	441,939	23.1 (18.8 to 28.0)	1.00	1.00	1.00 [Reference]
Proton pump inhibitors	435	2,047,297	21.2 (19.3 to 23.3)	0.91	1.21 (0.96 to 1.52)	1.41 (0.66 to 3.00)
10 years						
Histamine-2 receptor antagonists	36	36,462	24.4 (17.1 to 33.8)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	95	490,853	19.4 (15.7 to 23.7)	0.78	1.00 (0.67 to 1.49)	2.21(0.94 to 5.19)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100,000 person-years.

† Weighted using standardized mortality ratio weights.

Supplementary Table 6.11 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Intention-to-treat Exposure Definition) *

Exposure	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonists	493	1,760,954	28.0 (25.6-30.6)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1,256	5,275,112	23.8 (22.5-25.2)	0.82	1.12 (0.99-1.26)	1.26 (1.02-1.55)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Did not censor on switch from PPI to H2RA or H2RA to PPI.

† Per 100,000 person-years.

‡Weighted using standardized mortality ratio weights.

Supplementary Table 6.12 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Adjustment for IPCW)

Exposure	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonists	244	1,253,913	19.5 (17.1-22.1)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1,166	6,360,764	18.3 (17.3-19.4)	0.93	1.41 (1.20-1.66)	1.54 (1.01-2.35)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100,000 person-years.

† Weighted using standardized mortality ratio weights and inverse probability of censoring weights for death and switching.

Supplementary Table 6.13 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Truncate Follow-up for Possible NDMA Contaminant)*

Exposure	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Calendar-year weighted HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonists	243	932,052	26.1 (22.9-29.6)	1.00	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1,113	4,497,921	24.7 (23.3-26.2)	0.94	1.33 (1.14-1.56)	1.41 (1.02-1.94)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Follow-up truncated on December 31, 2017.

† Per 100,000 person-years.

‡Weighted using standardized mortality ratio weights.

Supplementary Table 6.14 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Gastric Cancer Compared to the Use of Histamine-2 Receptor Antagonists (HD-PS)*

Exposure	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonists	244	947,396	25.8 (22.6-29.2)	1.00	1.00 [Reference]
Proton pump inhibitors	1,166	4,887,522	23.9 (22.5-25.3)	0.92	1.48 (1.09-2.01)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Treatment weights created using predefined covariates listed in the manuscript and 200 empirically selected covariates from the HD-PS algorithm.

† Per 100,000 person-years.

‡Weighted using standardized mortality ratio weights.

Supplementary Table 6.15 Sensitivity Analysis Without Assumptions for Unmeasured Confounding

Risk ratio for unmeasured confounder and exposure association	Risk ratio for unmeasured confounder and outcome association								
	1.2	**1.3**	**1.5**	**1.8**	**2.0**	**2.5**	**3.0**	**4.0**	**5.0**
1.2	1.41 (1.03-1.93)	1.39 (1.02-1.90)	1.37 (1.00-1.87)	1.34 (0.98-1.83)	1.33 (0.97-1.82)	1.31 (0.95-1.78)	1.29 (0.94-1.76)	1.27 (0.93-1.73)	1.26 (0.92-1.72)
1.3	1.39 (1.02-1.9)	1.37 (1.00-1.87)	1.34 (0.98-1.83)	1.3 (0.95-1.78)	1.28 (0.94-1.75)	1.25 (0.91-1.71)	1.23 (0.9-1.68)	1.20 (0.88-1.64)	1.18 (0.86-1.61)
1.5	1.37 (1.00-1.87)	1.34 (0.98-1.83)	1.29 (0.94-1.76)	1.24 (0.90-1.69)	1.21 (0.88-1.65)	1.16 (0.85-1.58)	1.13 (0.82-1.54)	1.09 (0.80-1.49)	1.06 (0.78-1.45)
1.8	1.34 (0.98-1.83)	1.3 (0.95-1.78)	1.24 (0.90-1.69)	1.16 (0.85-1.59)	1.13 (0.82-1.54)	1.06 (0.78-1.45)	1.02 (0.75-1.39)	0.97 (0.71-1.32)	0.93 (0.68-1.28)
2.0	1.33 (0.97-1.82)	1.28 (0.94-1.75)	1.21 (0.88-1.65)	1.13 (0.82-1.54)	1.09 (0.80-1.49)	1.02 (0.74-1.39)	0.97 (0.71-1.32)	0.91 (0.66-1.24)	0.87 (0.64-1.19)
2.5	1.31 (0.95-1.78)	1.25 (0.91-1.71)	1.16 (0.85-1.58)	1.06 (0.78-1.45)	1.02 (0.74-1.39)	0.93 (0.68-1.27)	0.87 (0.64-1.19)	0.80 (0.58-1.09)	0.75 (0.55-1.03)
3.0	1.29 (0.94-1.76)	1.23 (0.90-1.68)	1.13 (0.82-1.54)	1.02 (0.75-1.39)	0.97 (0.71-1.32)	0.87 (0.64-1.19)	0.81 (0.59-1.1)	0.73 (0.53-0.99)	0.68 (0.49-0.92)
4.0	1.27 (0.93-1.73)	1.20 (0.88-1.64)	1.09 (0.80-1.49)	0.97 (0.71-1.32)	0.91 (0.66-1.24)	0.8 (0.58-1.09)	0.73 (0.53-0.99)	0.63 (0.46-0.87)	0.58 (0.42-0.79)
5.0	1.26 (0.92-1.72)	1.18 (0.86-1.61)	1.06 (0.78-1.45)	0.93 (0.68-1.28)	0.87 (0.64-1.19)	0.75 (0.55-1.03)	0.68 (0.49-0.92)	0.58 (0.42-0.79)	0.52 (0.38-0.71)

Supplementary Method 1. Inverse Probability of Censoring Weights

We used inverse probability of censoring weighting to assess the potential impact of differential censoring from drug switching (i.e. PPI users adding-on/switching to H2RAs, and vice versa) (1, 2), and to investigate death as a competing risk between PPI and H2RA users (3). This analysis was completed in three steps.

Step 1:

For both exposure groups, the follow-up period will be sudivided into one-year intervals. Inverse probability of censoring weights (IPCWs) were fit using logistic regression to predict the probability of remaining uncensored (i.e. not switching or adding on from PPI to H2RA and vice versa) at a given interval, conditional on the following variables, all measured in the previous interval: age, sex, alcohol related disorders (alcohol dependency, alcoholic cirrhosis of the liver, alcoholic hepatitis, hepatic failure), smoking status (current, former, never, unknown), body mass index, atrial fibrillation, anemia, cancer (excluding non-melanoma skin cancer), congestive heart failure, gastric metaplasia, hypercholesterolemia, hypertension, venous thromboembolism, chronic kidney disease, stroke, hernia, gastrointestinal bleeding, dialysis, gastric surgery, indications for acid suppressant drug use (approved indications: Barrett's esophagus, *Helicobacter pylori* infection, gastro-oesophageal reflux disease, peptic ulcer disease, dyspepsia; off-label indications: gastritis/duodenitis and stomach pain) and use of the following medications: metformin, non-steroidal anti-inflammatory drugs, antiplatelets, dual antiplatelets, cyclooxygenase-2 inhibitors, synthetic prostaglandin analogs, selective serotonin reuptake inhibitors, anticoagulants and steroids.

Step 2: We repeated step 1 by fitting a logistic regression model for remaining alive at a given interval (i.e. not having death as a competing event), using the same covariates as above.

Step 3: Using the fitted logistic models generated in Steps 1 and 2, we took the product of the weights (i.e. inverse of the probability of being uncensored from drug switching and from not dying) across all intervals for a given patient. We then stabilized the weight for each patient using intercept only models as the numerator. Unstable weights were truncated at the 0.5^{th} and 99.5^{th} percentile. For each patient, the stabilized IPCWs generated in steps 1 and 2 were multiplied along with the standardized mortality ratio weights used in the primary model to generate an overall weight. Thus, stabilized IPCWs and treatment weights were used to estimate the marginal hazard ratio of gastric cancer associated with the use of PPIs compared with H2RAs.

Supplementary Method 2. High-dimensional propensity-scores

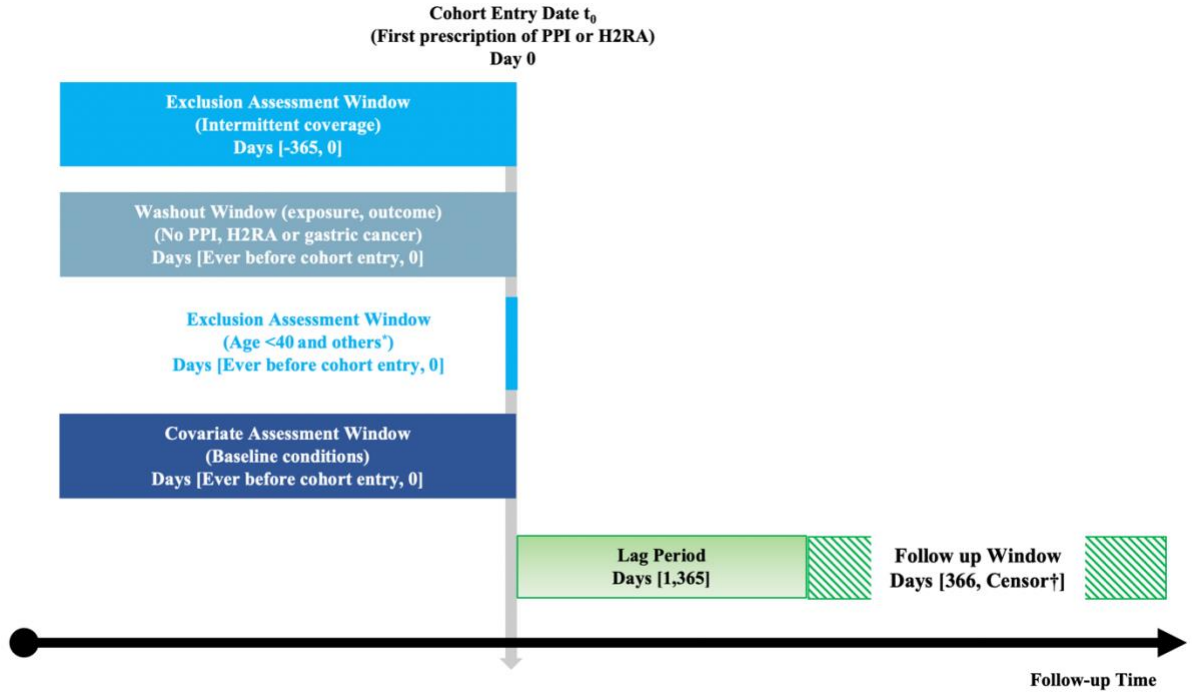
We used the high-dimensional propensity score (HD-PS) approach to reweigh our study population to investigate the impact of residual confounding. The HD-PS is a seven-step algorithm which empirically selects covariates from different data dimensions based on their prevalence and potential for confounding (4). The HD-PS represents an efficient means to control for confounding as adjustment is based on this summary score and not individual covariate values. The HD-PS model may also account for some unmeasured confounding, as the empirically selected variables may include proxies for unmeasured or unknown confounders (5).

Using the HD-PS algorithm, we empirically selected 200 covariates, in addition to the prespecified covariates listen in the manuscript and calendar year of cohort entry. Covariates were selected from five data dimensions, including prescriptions, procedures, diagnoses, disease history and administrative files. Propensity scores were then estimated using logistic regression as the predicted probability of receiving a PPI versus a H2RA, conditional on the empirically selected covariates, predefined covariates listed in the manuscript and calendar year of cohort entry. Using the estimated predicted probabilities, we reweighed the cohort using standardized mortality ratio weighting.(6) Patients exposed to PPIs were given a weight of 1, and patients exposed to H2RAs were given a weight of the odds of treatment probability (PS/[1-PS]) (6). Treatment weights were combined with IPCWs, and marginal hazard ratios for gastric cancer for users of PPIs compared to users of H2RAs were estimated.

Supplementary Method 3. Sensitivity analysis without assumptions

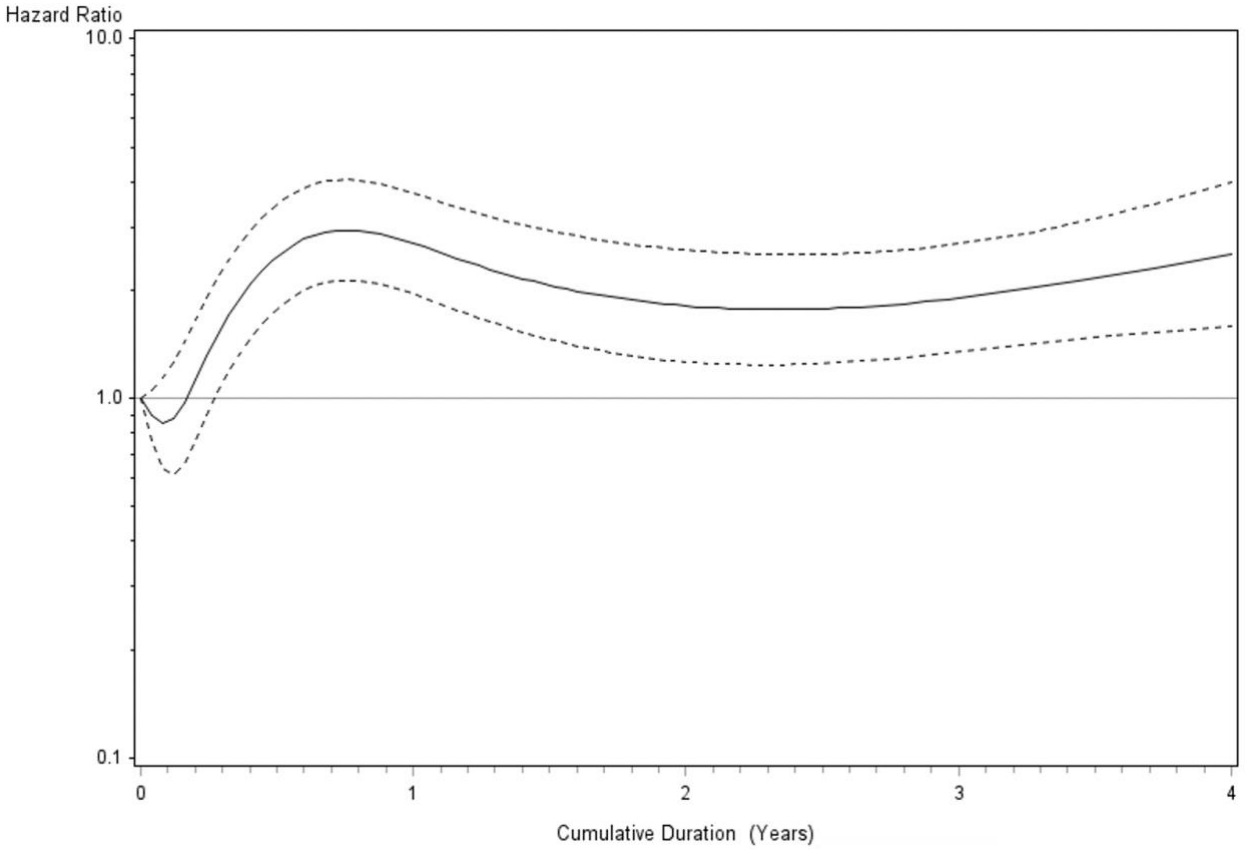
To assess the impact of residual confounding on the observed hazard ratio, we conducted a post-hoc sensitivity analysis using the model proposed by Ding and VanderWeele (7). This model is a flexible approach to dealing with unmeasured confounding as it does not impose assumptions on the unmeasured confounder(s). Instead, the model derives a joint bounding factor and a sharp inequality. For an unmeasured confounder to explain away the observed hazard ratio, the sensitivity analysis parameters must satisfy the inequality. Thus, to nullify the observed hazard ratio observed in this study (HR: 1.45, 95% CI: 1.06 – 1.98), an unmeasured confounder would need to be strongly associated with both the exposure and the outcome (supplementary table 17). Should the strength of the association between an unmeasured confounder and the outcome have a magnitude of 3.0, this confounder would also need to be associated with the exposure to a magnitude of 2.0 to nullify the observed hazard ratio.

Supplementary Figure 6.1 Cohort Construction



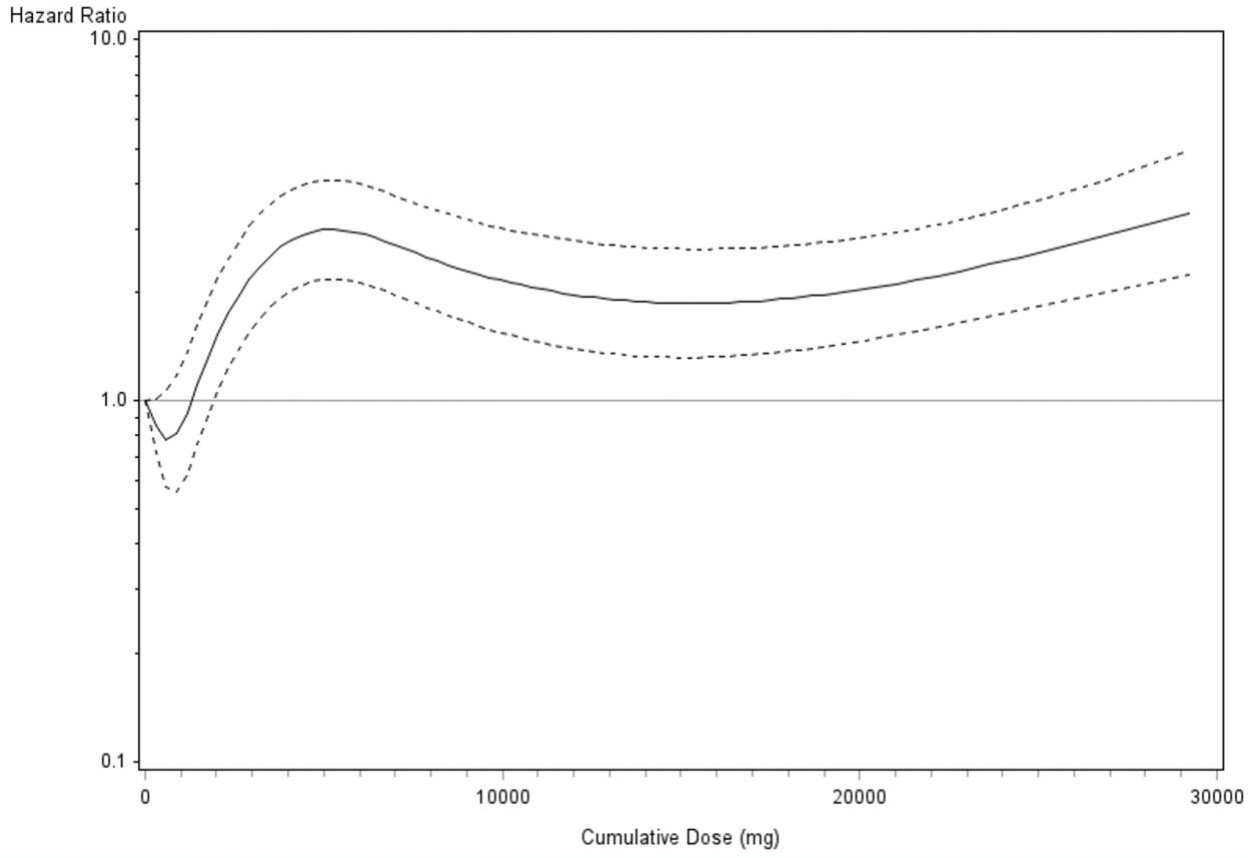
* Concomitant PPI and H2RA use, inherited cancer syndromes, less than 1 year of follow-up.
† Earliest of an incident diagnosis of gastric cancer, death from any cause, 1 year after switch between study drugs, end of registration, last collection date, or end of the study period (April 30, 2019), whichever occurs first.
Abbreviations: PPI: proton pump inhibitor; H2RA: histamine-2 receptor antagonist.

Supplementary Figure 6.2 Restricted Cubic Spline of Cumulative Duration of Proton Pump Inhibitor Use



Smooth restricted cubic spline curve using 5 knots of weighted hazard ratio of gastric cancer disease (solid line) and 95% confidence limits (dashed lines) as function of cumulative duration of proton pump inhibitor use. Cumulative duration was truncated at 4 years of use because of few events.

Supplementary Figure 6.3 Restricted Cubic Spline of Cumulative Dose of Proton Pump Inhibitor Use



Smooth restricted cubic spline curve using 5 knots of weighted hazard ratio of gastric cancer disease (solid line) and 95% confidence limits (dashed lines) as function of cumulative dose of proton pump inhibitor use. Cumulative dose was truncated at 29,200 mg of use, which is equivalent to 4 years of daily omeprazole 20 mg, because of few events.

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Chapter 7. Proton Pump Inhibitors and Risk of Colorectal Cancer: A Population-based Cohort Study

7.1 Preface

The last chapter illustrated that compared with H2RAs, use of PPIs is associated with a 45% increased risk of gastric cancer. The risk increased with increasing cumulative duration, dose, and time since initiation. This objective was designed to address limitations of previous observational studies, and included use of an active comparator, appropriate exposure definition, a lag period, and several sensitivity analyses to assess robustness. Given its robust design, the findings from this study are an important addition to the overall safety profile of PPIs. Yet, questions remain regarding the potential association with other gastrointestinal malignancies, including colorectal cancer. Previous observational studies have reported mixed findings, with relative risks ranging from 0.85 to 2.54. Moreover, no study has quantified the absolute risk of colorectal cancer, which is an important measure from a public health perspective. Given that colorectal cancer incidence is increasing among younger adults and this disease remains a leading cause of cancer death, identifying potential modifiable risk factors can have important implications. As existing studies are limited by small sample sizes, short durations of follow-up, and significant methodological shortcomings, an additional study is needed to better inform the safety profile of this popular drug class. These findings have potential to inform future PPI prescribing guidelines and deprescribing initiatives. Thus, the final objective of this thesis was to determine whether new users of PPIs are at an increased risk of colorectal cancer compared to new users of H2RAs. This paper was published in *Gut* [epub ahead of print].[171]

7.2 Title Page

Proton Pump Inhibitors and Risk of Colorectal Cancer: A Population-based Cohort Study

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June 15, 2021

7.3 Abstract

Objective: To determine whether proton pump inhibitors (PPIs) are associated with an increased risk of colorectal cancer, compared with histamine-2 receptor antagonists (H2RAs).

Design: The United Kingdom Clinical Practice Research Datalink was used to identify initiators of PPIs and H2RA from 1990 to 2018, with follow-up until 2019. Cox proportional hazards models were fit to estimate marginal hazard ratios (HRs) and 95% confidence intervals (CIs) of colorectal cancer. The models were weighted using standardized mortality ratio weights using calendar time-specific propensity scores. Prespecified secondary analyses assessed associations with cumulative duration, cumulative dose, and time since treatment initiation. The number needed to harm was calculated at five and 10 years of follow-up.

Results: The cohort included 1,293,749 and 292,387 initiators of PPIs and H2RAs, respectively, followed for a median duration of 4.9 years. While the use of PPIs was not associated with an overall increased risk of colorectal cancer (HR: 1.02, 95% CI: 0.92 to 1.14), HRs increased with cumulative duration of PPI use (<2 years, HR: 0.93, 95% CI: 0.83 to 1.04; 2-4 years, HR: 1.45, 95% CI: 1.28 to 1.60; ≥4 years, HR: 1.60, 95% CI: 1.42 to 1.80). Similar patterns were observed with cumulative dose and time since treatment initiation. The number needed to harm was 5,343 and 792 for five and 10 years of follow-up, respectively.

Conclusion: While any use of PPIs was not associated with an increased risk of colorectal cancer compared with H2RAs, prolonged use may be associated with a modest increased risk of this malignancy.

7.4 Summary Box

7.4.1 What is already known about this subject?

- Previous observational studies present conflicting evidence regarding the association between proton pump inhibitor use and colorectal cancer incidence.
- Previous studies have been limited by small sample sizes, short durations of follow-up, and other methodological shortcomings.

7.4.2 What are the new findings?

- The results of this study suggest that any use of proton pump inhibitors is not associated with an increased risk of colorectal cancer.
- However, prolonged durations of use of proton pump inhibitors may be associated with a modest increased risk of colorectal cancer.

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

- Given that proton pump inhibitors are commonly overprescribed for inappropriately long durations, this study highlights the need to reassess the need for ongoing treatment regularly.

7.5 Introduction

Proton pump inhibitors (PPIs) are commonly prescribed drugs indicated for several gastric conditions, including peptic ulcer disease, gastroesophageal reflux disease, and Barrett's esophagus.[1 2] Histamine-2 receptor antagonists (H2RAs), an alternative class of acid suppressant drugs, are indicated for similar conditions, although they are less effective at lowering stomach acid levels compared to PPIs.[1] Recent evidence suggests that PPIs are commonly overprescribed, either in patients without an evidence-based indication for use or longer durations than necessary.[3] This is particularly relevant as several observational studies have associated the use of PPIs with different adverse health outcomes, including gastrointestinal malignancies such as colorectal cancer.[4-13]

Hypergastrinemia may be induced by prolonged use of PPIs,[14] which in turn, may be associated with the development of colorectal cancer, as hypergastrinemia has been shown to promote the proliferation of both normal and malignant colonic and rectal cancer cells *in vitro*.[15-20] While animal models suggest that hypergastrinemia leads to adenoma progression, an important precursor to colorectal cancer,[21] the association between PPI use and adenomatous polyps has not been shown consistently in humans.[22] To date, several observational studies that investigated the association between PPI use and colorectal cancer have generated conflicting findings (relative risks ranging from 0.85 to 2.54) and had important methodological shortcomings.[4-13] Major sources of bias in the existing literature include confounding by indication, the inclusion of prevalent users, and latency bias.[23-25] These conclusion-altering biases can lead to spurious and exaggerated associations in both directions, limiting the conclusions drawn from these studies.

Given the conflicting observational evidence, it remains unclear whether the use of PPIs is associated with the incidence of colorectal cancer, a leading cause of cancer death with an

increasing incidence among younger adults.[26] [27] Additional studies are needed to better inform the safety profile of this widely prescribed drug class. Thus, the objective of this large population-based cohort study is to determine whether the use of PPIs, when compared with the use of H2RAs, is associated with an increased risk of colorectal cancer.

7.6 Methods

7.6.1 Data Source

We used data from the United Kingdom (UK) Clinical Practice Research Datalink (CPRD), a large, computerized database of longitudinal primary care records of over 15 million patients.[28] [29] The CPRD contains information on medical diagnoses and procedures, prescription details including dose and quantity, laboratory values, and lifestyle characteristics, including smoking and body mass index (BMI). The data have been extensively validated, generating high positive predictive values and high sensitivities for various diagnoses, including colorectal cancer.[30-36] Indeed, the sensitivity, specificity, and positive predictive value of colorectal cancer have been estimated at above 90% in several studies.[33-35] Moreover, when assessing the validity of 183 different diagnoses, a median of 89% of cases were confirmed using additional internal or external data.[36]

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 21_000341) and by the Research Ethics Board of the Jewish General Hospital.

7.6.2 Study Population

We used a new-user, active comparator design to compare patients newly treated with PPIs (including all available in the UK: esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole; **Supplementary Table 1**) with patients newly treated with H2RAs (including all available in the UK: cimetidine, famotidine, nizatidine, or ranitidine; **Supplementary Table 2**). We selected H2RAs as the comparator group because they represent a clinically relevant group used in similar indications as PPIs and thus should minimize confounding by indication. Cohort entry was defined as the date of this first prescription of either a PPI or H2RA from January 1,

1990, through April 30, 2018. To be included in the cohort, patients were required to be at least 18 years of age and have at least one year of medical information in the CPRD before cohort entry; the latter served as a washout period to ensure new use of PPIs and H2RAs. We excluded patients for whom a PPI and an H2RA were prescribed concomitantly at cohort entry and those with a history of Zollinger-Ellison syndrome (a rare indication for PPI use)[1] or cystic fibrosis, which is known to increase the risk of early-onset colorectal cancer,[37] at any time on or before cohort entry. We also excluded patients with a history of colorectal cancer (i.e., to exclude prevalent cases) or rare inherited cancer syndromes (familial adenomatous polyposis, Lynch syndrome, Li Fraumeni syndrome, Peutz-Jeghers syndrome, or Cowden syndrome),[38-41] at any time on or before cohort entry. Finally, to allow for a sufficient latency period and minimize detection bias and reverse causality, the cohort was restricted to patients with at least one year of follow-up after cohort entry (i.e., one year lag period).[42]

7.6.3 Exposure Definition

Patients were considered continuously exposed to their cohort entry drug (i.e., first of either PPI or H2RA prescription) starting one year after cohort entry until the end of follow-up. This exposure definition, which does not consider treatment termination, aligns with the hypothesized biological mechanism (i.e., adenoma progression from prolonged PPI use would progress even following treatment discontinuation). Thus, patients were followed starting one year after cohort entry until an incident diagnosis of colorectal cancer (identified using Read codes, **Supplementary Table 3**, one year after switching between the study drug classes [i.e., switch from PPI to H2RA or vice versa to account for the one-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 (April 30, 2019), whichever occurred first. **Supplementary Figure 1** illustrates a schematic of this exposure definition.

7.6.4 Potential Confounders

We considered the following potential confounders, all measured on or before cohort entry: age (modelled as a continuous variable using a cubic spline model to account for a possible non-linear relation with the outcome),[43] sex, alcohol-related disorders, smoking status (current, former, never), BMI, type 2 diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, cancer (other than nonmelanoma skin cancer), Crohn's disease, ulcerative colitis, other inflammatory bowel disease, gastrointestinal polyps, cholecystectomy, and solid organ transplant. We also considered the indication for acid suppressant drug use (approved indications: peptic ulcer disease, gastroesophageal reflux disease, dyspepsia, *Helicobacter pylori* infection, and Barrett's oesophagus; off-label indications: gastritis/duodenitis and stomach pain). We also included the following drugs previously associated with colorectal cancer incidence, measured at any time before cohort entry: hormone replacement therapy, aspirin, other non-steroidal anti-inflammatory drugs, statins, bisphosphonates, and use of synthetic prostaglandin analogues, which are older drugs used to manage gastric conditions.[1] Finally, we included measures of health-seeking behaviours, such as mammographic screening, prostate-specific antigen testing, colorectal cancer screening, and influenza vaccination.

7.6.5 Statistical Analysis

We used calendar time-specific propensity scores to reweigh our study population.[44] Using multivariable logistic regression, we estimated propensity scores within 5-year calendar bands at cohort entry (1990-1994, 1995-1999, 2000-2004, 2005-2009, 2010-2018) as the predicted probability of receiving a PPI versus an H2RA conditional on the covariates listed above. Calendar

time-specific propensity scores were chosen to account for temporal changes in the prescribing of acid suppressants and colorectal cancer incidence during the study period.[3 45] Patients in non-overlapping regions of the propensity score distributions were trimmed from the analysis. Using the propensity scores, treatment weights were assigned using standardized mortality ratio weights. Thus, PPI initiators were given a weight of 1, while H2RA initiators were given a weight of the odds of the treatment probability (propensity score / (1-propensity score)).[46] This weight functions to upweight the comparator patients (i.e., H2RA users) to represent the treated population (i.e., PPI users). We assessed covariate balance using standardized differences, with differences of less than 0.10 considered acceptable.[47]

Incident rates of colorectal cancer, with 95% confidence intervals (CIs) based on the Poisson distribution, were calculated for each exposure group. Weighted Kaplan-Meier curves were plotted to display the cumulative incidence of colorectal cancer over the follow-up period for PPI and H2RA users. Weighted Cox proportional hazards models were fit to estimate marginal hazard ratios (HRs) of colorectal cancer with 95% CIs using robust variance estimators. This marginal HR is a population-level estimate that described the average treatment effect in the treated; the average causal effect of treatment in the PPI cohort.[46 48] Finally, we calculated the number needed to harm at five and 10 years of follow-up using the Kaplan-Meier method.[49]

7.6.6 Secondary Analyses

We performed five secondary analyses. The first analysis assessed duration- and dose-response relations according to cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation. Cumulative duration was defined by summing the durations of each PPI prescription from cohort entry until the time of the event defining risk set. Given the different potencies of various PPIs, cumulative dose was defined using defined daily doses, a

standardized unit of drug consumption defined by the World Health Organization (**Supplementary Table 4**).[50] Individual PPI molecules were converted to omeprazole equivalents, and the cumulative dose was calculated by summing the dose of each prescription from cohort entry until the risk set. According to the defined daily dose, a patient prescribed a 30-day course of 30-mg of esomeprazole has equivalent usage to a patient prescribed a 30-day course of 20-mg omeprazole. Finally, time since treatment initiation was defined as the time between cohort entry and the risk set. HRs for these secondary exposures were estimated using time-dependent Cox proportional hazards models using predefined categories (<2 years, 2-4 years, and ≥4 years), and cumulative duration and dose were also modelled flexibly using restricted cubic spline models.[43] Second, we stratified by type of PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, or combinations) to determine whether there were any molecule-specific effects. Third, to determine if the association varies by cancer type, we repeated the primary analysis by stratifying on colon versus rectal cancer. Fourth, we considered whether there is effect measure modification by sex, age (<40, 40-59, and ≥60 years), history of inflammatory bowel disease (including ulcerative colitis and Crohn's disease), gastrointestinal polyps, and aspirin use. Age, sex, inflammatory bowel disease, and gastrointestinal polyp history are strong nonmodifiable risk factors for colorectal cancer, while aspirin use has been associated with a decreased risk of colorectal cancer.[51-56] For these analyses, we included an interaction term in the primary model between exposure status and these variables. Finally, we calculated HRs according to the most common approved indications at baseline (gastroesophageal reflux disease, peptic ulcer disease, and dyspepsia).

7.6.7 Sensitivity Analyses

We conducted six sensitivity analyses to assess the robustness of our findings. First, we repeated the primary analysis by increasing the exposure lag period to three, five, and 10 years, as there are uncertainties regarding the optimal length of the latency window. These analyses were restricted to patients with at least three, five, and 10 years of follow-up, respectively. Second, to address the impact of informative censoring, we did not censor patients who switched between drug classes (i.e., an intention-to-treat exposure definition). Third, as an alternative method to investigate the impact of informative censoring, we used stabilized inverse probability of censoring weights to account for censoring from switching between drug classes during follow-up,[57 58] and to account for the competing risk of death from any cause.[59] Censoring weights were calculated using two separate logistic regression models within one-year intervals, with one estimating the probability of remaining uncensored from a drug switch and the other estimating the probability of not dying (**Supplementary Method 1**). Fourth, as certain H2RAs have recently been found to be contaminated with a probable carcinogen [N-nitrosodimethylamine (NDMA)],[60] we repeated the analysis with follow-up truncated on December 31, 2017, which is before the time NDMA contaminants were found.[60] Fifth, to investigate the impact of residual confounding, we repeated the analysis using the high-dimensional propensity score (HD-PS) approach to calculate treatment weights (**Supplementary Method 2**).[61] For this analysis, we considered all predefined covariates listed above, along with 200 empirically selected covariates from the HD-PS algorithm. Finally, we investigated the potential impact of detection bias from differential screening uptake using inverse probability of screening weighting, estimated within two-year intervals (**Supplementary Method 3**).[62] All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC) and R Version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

7.6.8 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.

7.7 Results

The cohort included 1,293,749 and 292,387 initiators of PPIs and H2RAs, respectively (**Figure 1**). Over a median duration of 4.9 years of follow-up (including the one-year post-cohort entry latency period), there were 6,759 incident colorectal cancer events among PPI users versus 1,264 events among H2RA users. The corresponding crude incidence rates of colorectal cancer were 105.5 (95% CI 103.0 to 108.0) and 87.7 (95% CI: 82.9 to 92.7) per 100,000 person-years among PPI and H2RA users, respectively.

Table 1 shows the baseline characteristics of PPI and H2RA users before and after weighting. Before weighting, the exposure groups were similar in age, sex, history of inflammatory bowel disease, and cancer. PPI users were more likely to be former smokers, obese, use nonsteroidal anti-inflammatory drugs and statins, and have type 2 diabetes and hypertension, but were less likely to have dyspepsia compared to H2RA users. PPI users were also more likely to be screened for colorectal cancer and have a history of prostate-specific antigen testing. After weighting, the exposure groups were well-balanced on all study covariates, with all standardized differences below 0.10. During the follow-up period, 52.8% of H2RA users added-on or switched to PPIs, while 7.7% of PPI users added-on or switched to H2RAs.

Table 2 shows the results of the primary and secondary analyses. After adjusting for treatment weights, any use of PPIs was not associated with colorectal cancer incidence, compared with the use of H2RAs (HR: 1.02, 95% CI: 0.92 to 1.14). The cumulative incidence of colorectal cancer was similar in both exposure groups (**Supplementary Figure 2**). In secondary analyses, there was a gradual increase in risk with increasing cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation (**Table 2**). The risk was most elevated in the highest categories of use for all exposure definitions (≥4 years cumulative duration, HR:

1.60, 95% CI: 1.42 to 1.80; ≥29,200 mg omeprazole dose equivalents, HR: 1.58, 95% CI: 1.39 to 1.78; ≥4 years since treatment initiation, HR: 1.19, 95% CI: 1.03 to 1.34) and consistently elevated in the restricted cubic spline models (**Supplementary Figures 3** and **4**). The number needed to harm at five years of follow-up was 5,343 patients, and at 10 years of follow-up was 792 patients. There was no evidence of molecule-specific effects (**Supplementary Table 5**), and there was no difference in risk when stratifying by colon versus rectal cancer (**Supplementary Table 6**). The association between PPI use and colorectal cancer was modified by sex (male HR: 0.90, 95% CI 0.78 to 1.04; female HR: 1.22, 95% CI 1.04 to 1.45, **Supplementary Table 7**), but was not modified by age, history of inflammatory bowel disease, gastrointestinal polyps or aspirin use (**Supplementary Tables 8 to 11**). The HR was slightly elevated among patients with dyspepsia at baseline, although the CIs across indications largely overlapped (**Supplementary Table 12**).

The sensitivity analyses generated highly consistent results (**Figure 2, Supplementary Tables 13** to **18**). Overall, the HRs ranged from 0.97 for the intention-to-treat exposure definition to 1.24 for the screening analysis. The screening rate in the PPI and H2RA cohorts was 55.4 and 20.0 per 1,000 person-years, respectively.

7.8 Discussion

7.8.1 Principal Findings

In this large population-based cohort study, we assessed whether initiators of PPIs are at an increased risk of colorectal cancer compared with initiators of H2RAs. While any use of PPIs was not associated with an increased risk of colorectal cancer, there was evidence of a duration-response relation, with elevated relative risks with increasing duration, dose, and time since initiation. The number needed to harm was 5,343 and 792 for five and 10 years of follow-up, respectively. The association was modified by sex, with female PPI initiators at an increased risk of colorectal cancer compared to males. The results remained largely consistent across several sensitivity analyses, although adjustment for screening led to a slight increase in the HR, as colorectal screening is an interventional procedure that decreases the risk of colorectal cancer.[63]

7.8.2 Comparison with Previous Studies

The existing evidence on the association between the use of PPIs and overall colorectal cancer risk has been inconsistent, with relative risks ranging from 0.85 to 2.54 (**Supplementary Table 19**).[4-13] While the overall results of our study are in line with some of the previous studies,[4 5 8-12] few studies found evidence of duration-response relation.[5 11 13] However, there are important methodologic differences between our study and the previous literature, which may explain some of the discrepant findings. First, while some studies assessed the effect of H2RAs on colorectal cancer risk (relative risks ranging from 0.80 to 2.10),[6 7 12] no study used H2RAs as an active comparator. Comparing PPI users to the general population may lead to spurious associations from confounding by indication.[23] The previous studies were also limited by other important biases, such as the inclusion of prevalent users, time-related biases like time-window and immortal-time bias, and failure to account for cancer latency.[24 25 64 65] In light of these conclusion-altering biases,

it is difficult to interpret the existing literature.

The existing biological evidence on the association between PPI use and colorectal cancer is limited. Indeed, chronic suppression of acid through PPI use can induce hypergastrinemia,[14] which has been associated with increased proliferation of normal and malignant colonic and rectal cancer cells *in vitro*.[15-20] However, our findings suggest that for most PPI users who are using PPIs as a short-term treatment, this does not amount to a meaningful increase in the risk of colorectal cancer. Moreover, there is no consensus in the literature as to whether hypergastrinemia leads to adenoma progression.[21 22] While we did not find an increased risk of colorectal cancer from any PPI use, our findings do support the aforementioned biological hypothesis, in that there was a modest increased risk of colorectal cancer among patients prescribed PPIs for increasing durations. Thus, it remains possible that prolonged hypergastrinemia over an extended period may lead to increased colorectal cancer risk among long-term PPI users. This association may also be explained by changes to the gut microbiome induced through PPI use,[66 67] which can alter colorectal cancer susceptibility and progression.[68]

7.8.3 Strengths and Limitations of this Study

This study has several strengths. First, to our knowledge, this is the largest study with the longest potential follow-up conducted to date. Second, contrary to previous studies, we used an active comparator for our analyses, minimizing confounding by indication and presenting a clinically meaningful comparison. Third, our new-user study design eliminated the biases associated with the inclusion of prevalent users, such as survival bias and confounding. This active comparator new-user study design also minimizes the possibility of immortal time bias, as person-time at risk starts after the initiation of treatment.[69] Fourth, we used propensity score-weighted models, which ensured that baseline confounders were well-balanced between our study groups.

Finally, we present measures of absolute risk, which are important in understanding the potential burden of colorectal cancer in patients using PPIs.

This study has certain limitations that need to be considered. First, there may be some exposure misclassification, as the CPRD captures prescriptions issued by general practitioners and does not contain data on specialist prescriptions or over-the-counter use. However, in the UK, general practitioners are responsible for the long-term care of gastric disorders,[70] and patients with underlying disease, for whom moderate-to-long-term treatment is indicated, are financially incentivized to receive prescriptions from their general practitioner rather than from over-the-counter. Nonetheless, we expect any potential exposure misclassification to be non-differential between the exposure groups. It was also not possible to measure treatment adherence, although this is unlikely to be differential between the exposure groups. Second, we were unable to stratify the outcome according to cancer stage or tumour site (colon vs rectal or left- vs right-sided colon), as these variables are not available in the CPRD. This would have been useful to understand whether any observed increased risk of colorectal cancer was a result of increased detection. Third, the prevalence of screening may be underestimated in this cohort.[71] Finally, as with all observational studies, residual confounding from unknown or unmeasured confounders is possible, including family history, diet, or ethnicity. We attempted to minimize the impact of residual confounding using an active comparator and a wide variety of potential confounders in our propensity score models. Moreover, the results from the HD-PS analysis, which included an additional 200 covariates, which may be proxies for unknown or unmeasured confounders,[61] generated highly consistent findings.

In summary, the results of this study suggest that while any use of PPIs is not associated with an increased risk of colorectal cancer compared with the use of H2RAs, prolonged use might

be associated with an increased risk of this malignancy. Though the absolute risk of colorectal cancer is low at the individual level, given the high prevalence of PPI use, this increased risk could translate to a significant excess number of colorectal cancer cases at the population level. In light of this risk, PPIs should be deprescribed in patients for whom treatment is no longer indicated, and physicians should closely monitor patients that require long-term PPI treatment.

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Competing Interest Statement: SS participated in advisory meetings or as a guest speaker for Atara 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 three years; no other relationships or activities that could appear to have influenced the submitted work.

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 analyzed and interpreted the data. EGM and AB provided clinical expertise. DA wrote the manuscript, and all authors critically revised the manuscript. LA supervised the study and is the guarantor. All authors approved the final version of the manuscript and agree to be accountable for the accuracy of the work.

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Data Sharing: No additional data available.

Transparency: The guarantor (LA) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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7.11 Figure Legends

Figure 7.1 Study flow chart illustrating the construction of the proton pump inhibitor and histamine-2 receptor antagonist cohorts

Figure 7.2 Forest plot summarizing the results of the primary and sensitivity analyses, with weighted hazard ratios and 95% confidence intervals for the association between use of proton pump inhibitors and colorectal cancer, compared with the use of histamine-2 receptor antagonists.

Figure 7.3 Graphical summary highlighting the main findings of the association between the use of proton pump inhibitors and colorectal cancer, compared with the use of histamine-2 receptor antagonists.

7.12 Tables and Figures

Table 7.1 Baseline Characteristics of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Users Before and After Weighting

	Before Weighting			After Weighting *		
Characteristic	**PPI**	**H2RA**	**ASD**	**PPI**	**H2RA**	**ASD**
Total	1,293,749	292,387		1,293,749	1,294,713	
Age (mean, SD)	52.6 (17.6)	50.3 (18.3)	0.12	52.6 (17.6)	52.6 (37.3)	0.00
Male	583,401 (45.1)	125,897 (43.1)	0.04	583,401 (45.1)	589,773 (45.6)	0.01
Alcohol related disorders	72,658 (5.6)	11,746 (4.0)	0.07	72,658 (5.6)	73,068 (5.6)	0.00
Smoking Status						
Current	286,577 (22.2)	72,347 (24.7)	0.06	286,577 (22.2)	289,184 (22.3)	0.00
Former	366,403 (28.3)	51,301 (17.6)	0.27	366,403 (28.3)	365,923 (28.3)	0.00
Never	593,370 (45.9)	130,113 (44.5)	0.03	593,370 (45.9)	592,021 (45.7)	0.00
Missing	47,399 (3.7)	38,626 (13.2)	0.35	47,399 (3.7)	47,585 (3.7)	0.00
Body mass index						
<25 kg/m^2	428,551 (33.1)	99,667 (34.1)	0.02	428,551 (33.1)	431,364 (33.3)	0.00
25-29.9 kg/m^2	399,316 (30.9)	78,045 (26.7)	0.09	399,316 (30.9)	396,685 (30.6)	0.00
≥30 kg/m^2	290,289 (22.4)	45,218 (15.4)	0.18	290,289 (22.4)	289,311 (22.4)	0.00
Missing	175,593 (13.6)	69,457 (23.8)	0.26	175,593 (13.6)	177,353 (13.7)	0.00
Type 2 diabetes	76,125 (5.9)	9,429 (3.2)	0.13	76,125 (5.9)	76,388 (5.9)	0.00
Hypertension	315,352 (24.4)	53,032 (18.1)	0.15	315,352 (24.4)	316,400 (24.4)	0.00
Coronary artery disease	136,300 (10.5)	32,677 (11.2)	0.02	136,300 (10.5)	137,106 (10.6)	0.00
Chronic obstructive pulmonary disorder	88,909 (6.9)	25,219 (8.6)	0.07	88,909 (6.9)	89,933 (7.0)	0.00
Cancer	77,844 (6.0)	13,209 (4.5)	0.07	77,844 (6.0)	79,864 (6.2)	0.01
Crohn's disease	5,115 (0.4)	885 (0.3)	0.02	5,115 (0.4)	5,404 (0.4)	0.00
Ulcerative colitis	7,865 (0.6)	1,484 (0.5)	0.01	7,865 (0.6)	8,336 (0.6)	0.00
Other inflammatory bowel disease	2,349 (0.2)	394 (0.1)	0.01	2,349 (0.2)	2,492 (0.2)	0.00
Gastrointestinal polyps	16,170 (1.3)	2,068 (0.7)	0.06	16,170 (1.3)	16,034 (1.2)	0.00
Cholecystectomy	35,359 (2.7)	7,716 (2.6)	0.01	35,359 (2.7)	36,162 (2.8)	0.00
Solid organ transplant	1,191 (0.1)	698 (0.2)	0.04	1,191 (0.1)	1,272 (0.1)	0.00
Peptic ulcer disease	31,715 (2.5)	9,978 (3.4)	0.06	31,715 (2.5)	32,459 (2.5)	0.00
Gastroesophageal reflux disease	115,880 (9.0)	24,378 (8.3)	0.02	115,880 (9.0)	119,752 (9.3)	0.01
Dyspepsia	232,197 (18.0)	89,299 (30.5)	0.30	232,197 (18.0)	239,284 (18.5)	0.01
Helicobacter pylori infection	29,269 (2.3)	1,606 (0.6)	0.15	29,269 (2.3)	30,665 (2.4)	0.01
Barrett's Esophagus	2,923 (0.2)	86 (0.0)	0.06	2,923 (0.2)	3,305 (0.3)	0.01
Gastritis/duodenitis	58,373 (4.5)	18,877 (6.5)	0.09	58,373 (4.5)	59,573 (4.6)	0.00
Stomach pain	405,117 (31.3)	95,561 (32.7)	0.03	405,117 (31.3)	413,004 (31.9)	0.01
Hormone replacement therapy	158,233 (12.2)	33,504 (11.5)	0.02	158,233 (12.2)	158,046 (12.2)	0.00
Aspirin	234,232 (18.1)	40,567 (13.9)	0.12	234,232 (18.1)	233,410 (18.0)	0.00
Other nonsteroidal anti-inflammatory drugs	882,495 (68.2)	170,674 (58.4)	0.21	882,495 (68.2)	878,900 (67.9)	0.01
Statins	247,703 (19.2)	24,229 (8.3)	0.32	247,703 (19.2)	248,201 (19.2)	0.00
Bisphosphonates	42,257 (3.3)	3,644 (1.3)	0.14	42,257 (3.3)	43,548 (3.4)	0.01
Prostaglandin analogues	1,595 (0.1)	1,153 (0.4)	0.05	1,595 (0.1)	1,710 (0.1)	0.00
Mammographic screening	296,749 (22.9)	45,178 (15.5)	0.19	296,749 (22.9)	298,034 (23.0)	0.00
Prostate-specific antigen test	113,480 (8.8)	9,807 (3.4)	0.23	113,480 (8.8)	113,427 (8.8)	0.00
Colorectal cancer screening	116,028 (9.0)	9,384 (3.2)	0.24	116,028 (9.0)	117,518 (9.1)	0.00
Influenza vaccination	502,581 (38.9)	86,798 (29.7)	0.19	502,581 (38.9)	506,735 (39.1)	0.01
Year of cohort entry						
1990 - 1994	9,318 (0.7)	44,492 (15.2)	0.56	9,318 (0.7)	9,331 (0.7)	0.00
1995 - 1999	45,318 (3.5)	69,634 (23.8)	0.62	45,318 (3.5)	45,395 (3.5)	0.00
2000 - 2004	189,891 (14.7)	92,139 (31.5)	0.41	189,891 (14.7)	189,804 (14.7)	0.00
2005 - 2009	426,895 (33.0)	48,367 (16.6)	0.39	426,895 (33.0)	427,304 (33.0)	0.00
2010 - 2018	622,327 (48.1)	37,755 (12.9)	0.83	622,327 (48.1)	622,881 (48.1)	0.00

Abbreviations: ASD, absolute standardized difference; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist; SD, standard deviation.

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

* Pseudo-population created by applying standardized mortality ratio weights.

Table 7.2 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared with the Use of Histamine-2 Receptor Antagonists

	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonist (n=292,387)	1,264	1,440,977	87.7 (82.9 to 92.7)	1.00	1.00 [Reference]
Proton pump inhibitor (n=1,293,749)	6,759	6,406,425	105.5 (103.0 to 108.0)	1.23	1.02 (0.92 to 1.14)
Cumulative duration of proton pump inhibitors					
<2 years	4,961	5,248,111	94.5 (91.9 to 97.2)	1.09	0.93 (0.83 to 1.04)
2-4 years	836	574,744	145.5 (135.8 to 155.7)	1.72	1.45 (1.28 to 1.65)
≥4 years	962	583,570	164.8 (154.6 to 175.6)	1.85	1.60 (1.42 to 1.80)
Cumulative omeprazole dose equivalents					
<14,600 mg	5,120	5,356,848	95.6 (93.0 to 98.2)	1.11	0.94 (0.84 to 1.05)
14,600-29,200 mg	839	556,726	150.7 (140.7 to 161.3)	1.77	1.50 (1.32 to 1.70)
≥29,200 mg	800	492,851	162.3 (151.3 to 174.0)	1.80	1.58 (1.39 to 1.78)
Time since proton pump inhibitor initiation					
<2 years	1,206	1,182,062	102.0 (96.3 to 108.0)	1.13	0.87 (0.69 to 1.10)
2-4 years	1,795	1,844,488	97.3 (92.9 to 102.0)	1.15	0.92 (0.74 to 1.13)
≥4 years	3,758	3,379,875	111.2 (107.7 to 114.8)	1.30	1.19 (1.03 to 1.34)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights

Figure 7.1 Study flow chart illustrating the construction of the proton pump inhibitor and histamine-2 receptor antagonist cohorts

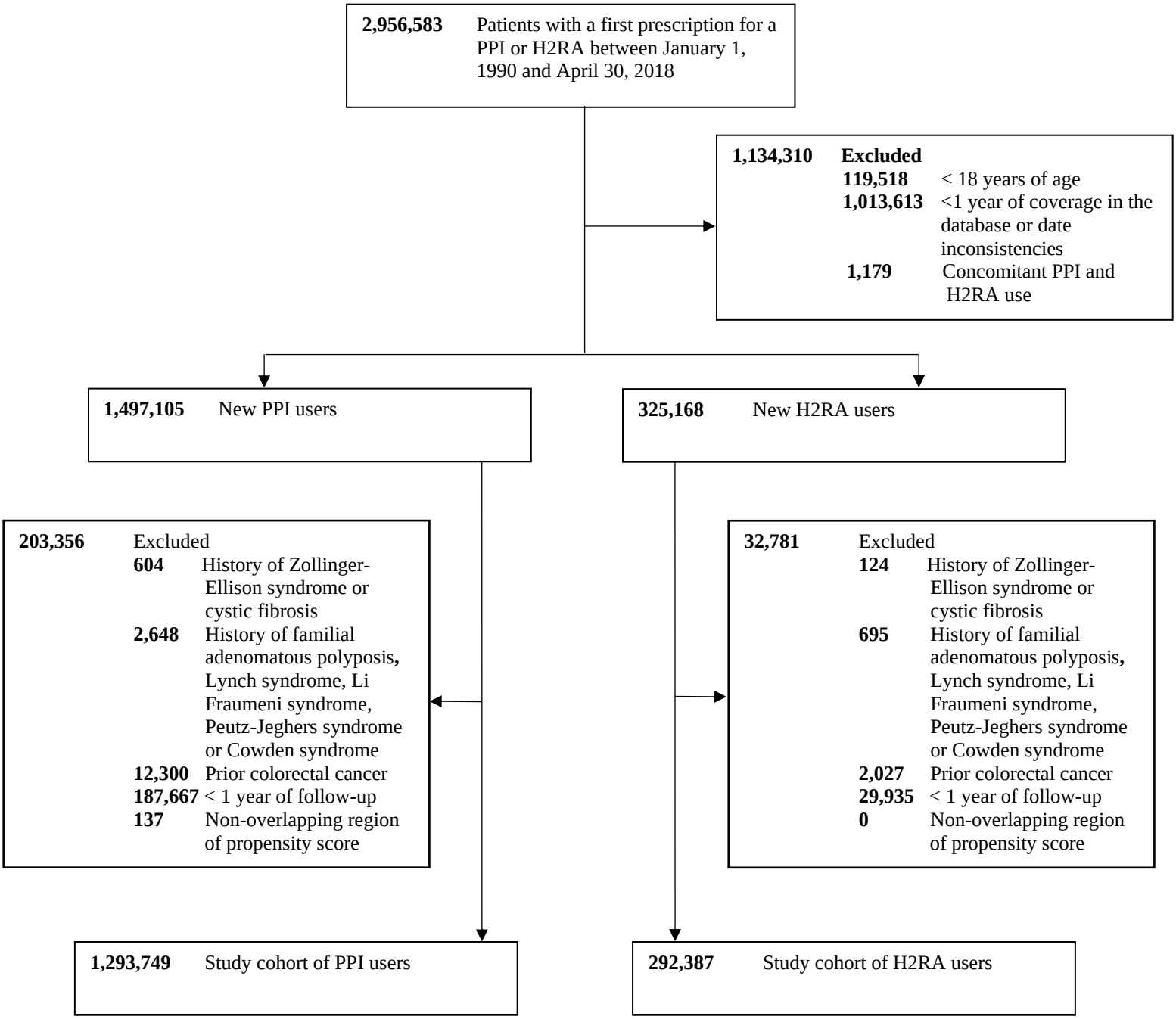
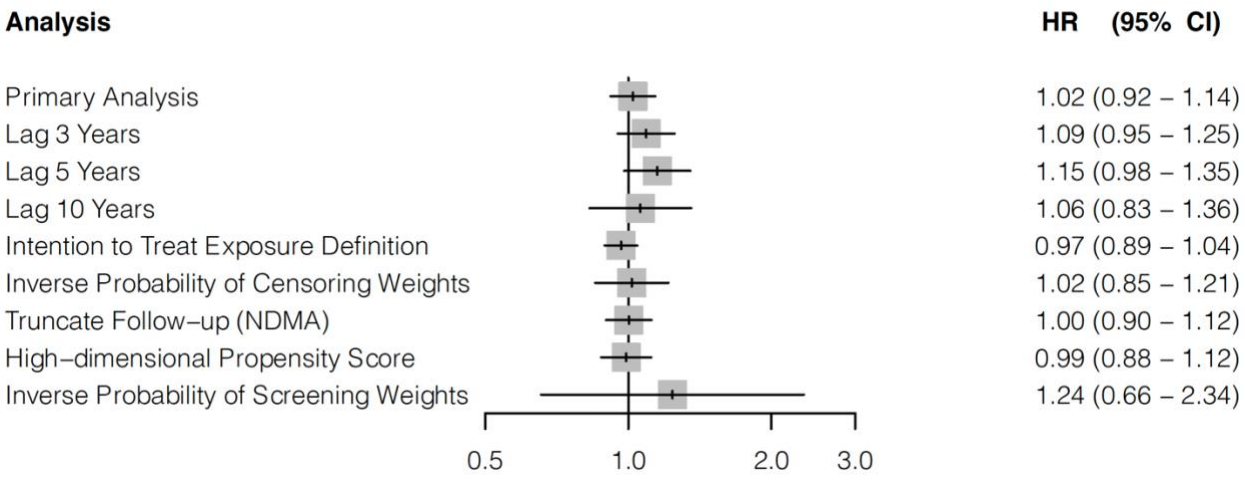


Figure 7.2 Forest plot summarizing the results of the primary and sensitivity analyses, with weighted hazard ratios and 95% confidence intervals for the association between use of proton pump inhibitors and colorectal cancer, compared with the use of histamine-2 receptor antagonists



Abbreviations: HR: hazard ratio; CI: confidence interval; NDMA: N-Nitrosodimethylamine

7.13 Supplementary Material

Supplementary Table 7.1 List of British National Formulary Codes for Proton Pump Inhibitors

British National Formulary Code	British National Formulary Header
01030500/05010103	Proton Pump Inhibitors/Broad-spectrum Penicillins
01030500/10010100	Proton Pump Inhibitors/Non-steroidal Anti-inflammatory Drugs
01030500/05010500	Proton Pump Inhibitors/Macrolides
1030500	Proton Pump Inhibitors

Supplementary Table 7.2 List of British National Formulary Codes for Histamine-2 Receptor Antagonists

British National Formulary Code	British National Formulary Header
1030100	H2 receptor antagonists
01030100/01010201	H2 receptor antagonists/Alginate preparations
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030100/01010202	H2 receptor antagonists/Indigestion remedies
01010201/01030100	Compound Alginate Preparations/H2-Receptor Antagonists
01010202/01030100	Indigestion Preparations/H2-Receptor Antagonists

Abbreviations: H2, Histamine-2

Supplementary Table 7.3 Colorectal Cancer Read Codes Used to Define Events

Read Code	Read Term
B13..00	Malignant neoplasm of colon
B141.00	Malignant neoplasm of rectum
B133.00	Malignant neoplasm of sigmoid colon
B134.00	Malignant neoplasm of caecum
B141.12	Rectal carcinoma
B131.00	Malignant neoplasm of transverse colon
B141.11	Carcinoma of rectum
B130.00	Malignant neoplasm of hepatic flexure of colon
B13z.11	Colonic cancer
B132.00	Malignant neoplasm of descending colon
B136.00	Malignant neoplasm of ascending colon
B902500	Neoplasm of uncertain behaviour of rectum
B137.00	Malignant neoplasm of splenic flexure of colon
B902400	Neoplasm of uncertain behaviour of colon
B134.11	Carcinoma of caecum
B140.00	Malignant neoplasm of rectosigmoid junction
B13z.00	Malignant neoplasm of colon NOS
B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
B13y.00	Malignant neoplasm of other specified sites of colon
B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
B138.00	Malignant neoplasm, overlapping lesion of colon
B1z0.11	Cancer of bowel
BB5N100	[M]Adenocarcinoma in adenomatous polposis coli
BB5N.00	[M]Adenomatous and adenocarcinomatous polyps of colon
BB5L100	[M]Adenocarcinoma in adenomatous polyp
BB5L.00	[M]Adenomatous and adenocarcinomatous polyps
BB5L300	[M]Adenocarcinoma in multiple adenomatous polyps

Abbreviations: NOS, not otherwise specified.

Supplementary Table 7.4 Defined Daily Dose of Proton Pump Inhibitors

Proton Pump Inhibitor Type	Defined Daily Dose*
Omeprazole	20 mg
Esomeprazole	30 mg
Rabeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg

*All doses are equivalent to 1 Defined Daily Dose

The dose of each PPI prescription was defined according to the World Health Organization defined daily dose and converted into omeprazole equivalents.[1] This allows for PPIs with different potencies to be compared. According to the defined daily dose, a patient prescribed a 30-day course of 30-mg of esomeprazole is equivalent to a patient prescribed a 30-day course of 20-mg omeprazole.

Supplementary Table 7.5 Crude and Adjusted HRs for the Association Between the Use of Specific Types of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists

	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonist	1,264	1,440,977	87.7 (82.9 to 92.7)	1.00	1.00 [Reference]
Proton pump inhibitor type					
Esomeprazole	94	103,912	90.5 (73.1 to 110.7)	1.02	0.81 (0.64 to 1.01)
Lansoprazole	2,407	2,174,265	110.7 (106.3 to 115.2)	1.28	1.04 (0.93 to 1.15)
Omeprazole	3,878	3,791,049	102.3 (99.1 to 105.6)	1.20	1.03 (0.91 to 1.15)
Pantoprazole	161	134,210	120.0 (102.1 to 140.0)	1.34	1.06 (0.88 to 1.27)
Rabeprazole	214	199,263	107.4 (93.5 to 122.8)	1.21	0.92 (0.78 to 1.08)
Combinations	5	3,726	134.2 (43.6 to 313.2)	1.53	1.24 (0.51 to 2.99)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights

Supplementary Table 7.6 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Stratified by Colorectal Cancer Type)

Cancer Type *	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Colon					
Histamine-2 receptor antagonists	852	1,440,977	59.1 (55.2 to 63.2)	1.00	1.00 [Reference]
Proton pump inhibitor	4,895	6,406,425	76.4 (74.3 to 78.6)	1.32	1.00 (0.88 to 1.14)
Rectal					
Histamine-2 receptor antagonists	408	1,440,977	28.3 (25.6 to 31.2)	1.00	1.00 [Reference]
Proton pump inhibitor	1,834	6,406,425	28.6 (27.3 to 30.0)	1.03	1.07 (0.87 to 1.30)

Abbreviations: CI, confidence interval; HR, hazard ratio; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor

* Other colorectal cancer types generated 33 events

† Per 100,000 person-years

‡Weighted using standardized mortality ratio weights

Supplementary Table 7.7 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Sex)

	Male	**Female**
Events	4,338	3,685
Person-Years	3,526,065	4,321,337
Crude Incidence Rate (95% CI) *	123.0 (119.4 to 126.7)	85.3 (82.5 to 88.1)
Crude HR		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.19	1.27 p-interaction: 0.28
Adjusted HR (95% CI) †		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	0.90 (0.78 to 1.04)	1.22 (1.04 to 1.45) p-interaction: 0.01

Abbreviations: HR, hazard ratio; CI, confidence interval

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights

Supplementary Table 7.8 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Age)

	Age < 40	**Age 40-59**	**Age ≥ 60**
Events	151	1,806	6,066
Person-Years	2,074,653	3,128,625	2,644,124
Crude Incidence Rate (95% CI) *	7.3 (6.2 to 8.5)	57.7 (55.1 to 60.5)	229.4 (223.7 to 235.3)
Crude HR			
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.08	1.22	1.01 p-interaction: 0.05
Adjusted HR (95% CI) †			
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	0.77 (0.40 to 1.48)	1.08 (0.84 to 1.40)	0.97 (0.85 to 1.09) p-interaction: 0.56

Abbreviations: HR, hazard ratio; CI, confidence interval
* Per 100,000 person-years
†Weighted using standardized mortality ratio weights

Supplementary Table 7.9 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Gastrointestinal Polyps)

	Gastrointestinal Polyps	No Gastrointestinal Polyps
Events	176	7,847
Person-Years	80,435	7,766,967
Crude Incidence Rate (95% CI) *	218.8 (187.7 to 253.6)	101.0 (98.8 to 103.3)
Crude HR		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	0.91	1.23
		p-interaction: 0.20
Adjusted HR (95% CI) †		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.22 (0.59 to 2.54)	1.02 (0.91 to 1.14)
		p-interaction: 0.63

Abbreviations: HR, hazard ratio; CI, confidence interval
* Per 100,000 person-years
† Weighted using standardized mortality ratio weights

Supplementary Table 7.10 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Inflammatory Bowel Disease)

	Inflammatory Bowel Disease	**No Inflammatory Bowel Disease Inflammatory Bowel Disease**
Events	92	7,931
Person-Years	78,948	7,768,454
Crude Incidence Rate (95% CI) *	116.5 (93.9 to 142.9)	102.1 (99.9 to 104.4)
Crude HR		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	0.98	1.23 p-interaction: 0.44
Adjusted HR (95% CI) †		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.06 (0.26 to 4.29)	1.02 (0.92 to 1.14) p-interaction: 0.96

Abbreviations: HR, hazard ratio; CI, confidence interval

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights

Supplementary Table 7.11 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Aspirin Use)

	Aspirin History	No Aspirin History
Events	2,491	5,532
Person-Years	1,249,495	6,597,907
Crude Incidence Rate (95% CI) *	199.4 (191.6 to 207.3)	83.8 (81.7 to 86.1)
Crude HR		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.19	1.14
		p-interaction: 0.58
Adjusted HR (95% CI) †		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.10 (0.91 to 1.34)	0.98 (0.86 to 1.12)
		p-interaction: 0.33

Abbreviations: HR, hazard ratio; CI, confidence interval

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights

Supplementary Table 7.12 Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists Stratified by Approved Indication at Baseline

Indication *	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Gastroesophageal reflux disease					
Histamine-2 receptor antagonists	114	110,811	102.9 (84.9 to 123.6)	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	687	626,438	109.7 (101.6 to 118.2)	1.08	0.95 (0.66 to 1.36)
Peptic ulcer disease					
Histamine-2 receptor antagonists	90	48,255	186.5 (150.0 to 229.3)	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	320	176,638	181.2 (161.9 to 202.1)	0.98	0.91 (0.57 to 1.46)
Dyspepsia					
Histamine-2 receptor antagonists	378	446,774	84.6 (76.3 to 93.6)	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	1,316	1,284,222	102.5 (97.0 to 108.2)	1.24	1.27 (1.03 to 1.57)

Abbreviations: HR, hazard ratio; CI, confidence interval

* Barrett's esophagus and *H. pylori* generated few events with unstable estimates

† Per 100,000 person-years

‡ Weighted using standardized mortality ratio weights

Supplementary Table 7.13 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Different Lag Periods)

Length of lag period	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
3 years					
Histamine-2 receptor antagonist	882	1,000,052	88.2 (82.5 to 94.2)	1.00	1.00 [Reference]
Proton pump inhibitor	4,598	4,224,388	108.8 (105.7 to 112.0)	1.27	1.09 (0.95 to 1.25)
5 years					
Histamine-2 receptor antagonist	623	691,325	90.1 (83.2 to 97.5)	1.00	1.00 [Reference]
Proton pump inhibitor	3,069	2,671,337	114.9 (110.9 to 119.0)	1.31	1.15 (0.98 to 1.35)
10 years					
Histamine-2 receptor antagonist	257	242,346	106.0 (93.5 to 119.8)	1.00	1.00 [Reference]
Proton pump inhibitor	858	647,821	132.4 (123.7 to 141.6)	1.25	1.06 (0.83 to 1.36)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights

Supplementary Table 7.14 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Intention to Treat Exposure Definition) *

	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonist	2,589	2,565,103	100.9 (97.1 to 104.9)	1.00	1.00 [Reference]
Proton pump inhibitor	7,322	6,912,360	105.9 (103.5 to 108.4)	1.12	0.97 (0.89 to 1.04)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Did not censor on switch between drug classes

† Per 100,000 person-years

‡ Weighted using standardized mortality ratio weights

Supplementary Table 7.15 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (IPCW)

	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonist	1,264	1,892,953	66.8 (63.1 to 70.6)	1.00	1.00 [Reference]
Proton pump inhibitor	6,759	8,365,632	80.8 (78.9 to 82.7)	1.23	1.02 (0.85 to 1.21)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights and stabilized inverse probability of censoring weights for death and switching

Supplementary Table 7.16 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Truncate Follow-up for Possible NDMA Contaminant) *

	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonist	1,245	1,438,394	86.6 (81.8 to 91.5)	1.00	1.00 [Reference]
Proton pump inhibitor	6,269	6,372,752	98.4 (96.0 to 100.8)	1.15	1.00 (0.90 to 1.12)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Follow-up truncated on December 31, 2017

† Per 100,000 person-years

‡ Weighted using standardized mortality ratio weights

Supplementary Table 7.17 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (High-dimensional Propensity Score) *

	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonist	1,264	1,440,924	87.7 (83.0 to 92.7)	1.00	1.00 [Reference]
Proton pump inhibitor	6,758	6,406,237	105.5 (103.0 to 108.0)	1.23	0.99 (0.88 to 1.12)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Treatment weights created using predefined covariates listed in the manuscript and 200 empirically selected covariates from the high-dimensional propensity score algorithm

† Per 100,000 person-years

‡ Weighted using standardized mortality ratio weights

Supplementary Table 7.18 Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Inverse Probability of Screening Weights) *

	Events	Person-intervals	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonist	1,264	1,005,714	125.7 (118.8 to 132.8)	1.00	1.00 [Reference]
Proton pump inhibitor	6,759	4,478,253	150.9 (147.4 to 154.6)	1.20	1.24 (0.66 to 2.34)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Screening weights calculated within 2-year intervals

† Per 100,000 person-intervals

‡ Weighted using standardized mortality ratio weights and stabilized inverse probability of screening rates for colorectal screening

Supplementary Table 7.19 Summary of observational studies assessing the association between PPIs and colorectal cancer

First Author (Year)	Study Design	Study Size	Effect estimate (95% CI)	Main Limitation
Yang (2007)	Nested case-control	48,724	OR: 1.1 (0.7 to 1.9)	Confounding by indication Latency bias Prevalent users
Robertson (2007)	Nested case-control	61,479	OR: 1.11 (0.97 to 1.27)	Confounding by indication Prevalent users Time-window bias
Van Soest (2008)	Nested case-control	8,384	OR: 0.85 (0.63 to 1.16)	Confounding by indication Prevalent users
Chubak (2009)	Case-control	1,282	OR: 1.7 (0.8 to 4.0)	Confounding by indication Prevalent users Time-window bias
Lai (2013)	Nested case-control	3,989	OR: 2.54 (2.31 to 2.79)	Confounding by indication Latency bias Prevalent users Time-window bias
Hwang (2017)	Cohort	451,284	Low dose PPI HR: 0.96 (0.88 to 1.06) High dose PPI HR: 0.98 (0.78 to 1.24)	Confounding by indication Latency bias
Lei (2020)	Cohort	90,764	HR: 2.03 (1.56 to 2.63)	Confounding by indication Immortal time bias
Babic (2020)	Cohort	175,859*	HR: 0.89 (0.71 to 1.12)	Confounding by indication Prevalent users Self-reported exposure
Kuiper (2020)	Case-control	9,890	OR: 1.08 (0.97 to 1.21)	Confounding by indication Latency bias Prevalent users Time-window bias
Lee (2020)	Nested case-control	178,717	OR: 1.05 (0.99 to 1.12)	Confounding by indication Differential exclusion by case/control status

Abbreviations: OR: odds ratio; HR: hazard ratio, PPI: proton pump inhibitors.
*Combined from three separate cohorts.

Supplementary Method 1. Inverse Probability of Censoring Weights

We used inverse probability of censoring weighting to assess the potential impact of differential censoring from drug switching (i.e. PPI users adding-on or switching to H2RAs, and vice versa)[2] [3] and to investigate death as a competing risk between PPI and H2RA users.[4] This analysis was completed in three steps.

Step 1: For both exposure groups, the follow-up period was subdivided into one-year intervals. Within each interval, inverse probability of censoring weights (IPCWs) were fit, separately for the PPI and H2RA cohorts, using multivariable logistic regression within 5-year bands of calendar year to predict the probability of remaining uncensored (i.e. not switching or adding on from PPI to H2RA and vice versa). The models were conditional on the following variables, all measured in the previous interval: age, sex, alcohol related disorders (alcohol dependency, alcoholic cirrhosis of the liver, alcoholic hepatitis, hepatic failure), smoking status (current, former, never, unknown), body mass index, type 2 diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, cancer (other than nonmelanoma skin cancer), Crohn's disease, ulcerative colitis, other inflammatory bowel disease, polyps, cholecystectomy, solid organ transplant, indications for acid suppressant drug use (approved indications: Barrett's esophagus, *Helicobacter pylori* infection, gastro-oesophageal reflux disease, peptic ulcer disease, dyspepsia; off-label indications: gastritis/duodenitis and stomach pain) and use of the following medications: hormone replacement therapy, aspirin, other non-steroidal anti-inflammatory drugs, statins and bisphosphonates, and use of synthetic prostaglandin analogues and measures of health-seeking behaviour, including mammographic screening, prostate exams, colorectal cancer screening, and influenza vaccination.

Step 2: We repeated step 1 by fitting a multivariable logistic regression model for remaining alive at a given interval (i.e. not having death as a competing event), using the same covariates as above.

Step 3: Using the fitted logistic models generated in Steps 1 and 2, we took the product of the weights (i.e. inverse of the probability of being uncensored from drug switching and from not dying) across all intervals for a given patient. IPCWs were stabilized using intercept only models as the numerator, and truncated at the 0.5^{th} and 99.5^{th} percentile. These stabilized weights were combined with standardized mortality ratio weights for each patient to generate a final weight. Marginal hazard ratios of colorectal cancer associated with the use of PPIs compared with H2RAs were estimated using the final weights.

Supplementary Method 2. High-dimensional Propensity-scores

To investigate the impact of residual confounding, we reweighted our cohort using high-dimensional propensity scores (HD-PS). The HD-PS is a seven-step algorithm which empirically selects covariates from different data dimensions based on their prevalence and potential for confounding.[5] As the HD-PS is a summary score, it is an efficient way to control for a wide range of confounders. The HD-PS may also account for some unmeasured confounders, as the empirically selected covariates may include proxies for unknown or unmeasured confounders.[6]

Using the HD-PS algorithm, we empirically selected 200 covariates from five data dimensions: prescriptions, procedures, diagnoses, disease history and administrative files. Using multivariable logistic regression, conditional on the empirically selected and predefined covariates (including calendar year of cohort entry), we estimated the predicted probability of received a PPI versus an H2RA. Using these propensity score values we reweighted the cohort using standardized mortality ratio weighting, where exposed to PPIs were given a weight of 1, and patients exposed to H2RAs were given a weight of the odds of treatment probability (PS/[1-PS]).[7] For this analysis, we then combined the SMR weights with IPCWs, and marginal hazard ratios for colorectal cancer for users of PPIs compared to users of H2RAs were estimated using Cox proportional hazards models.

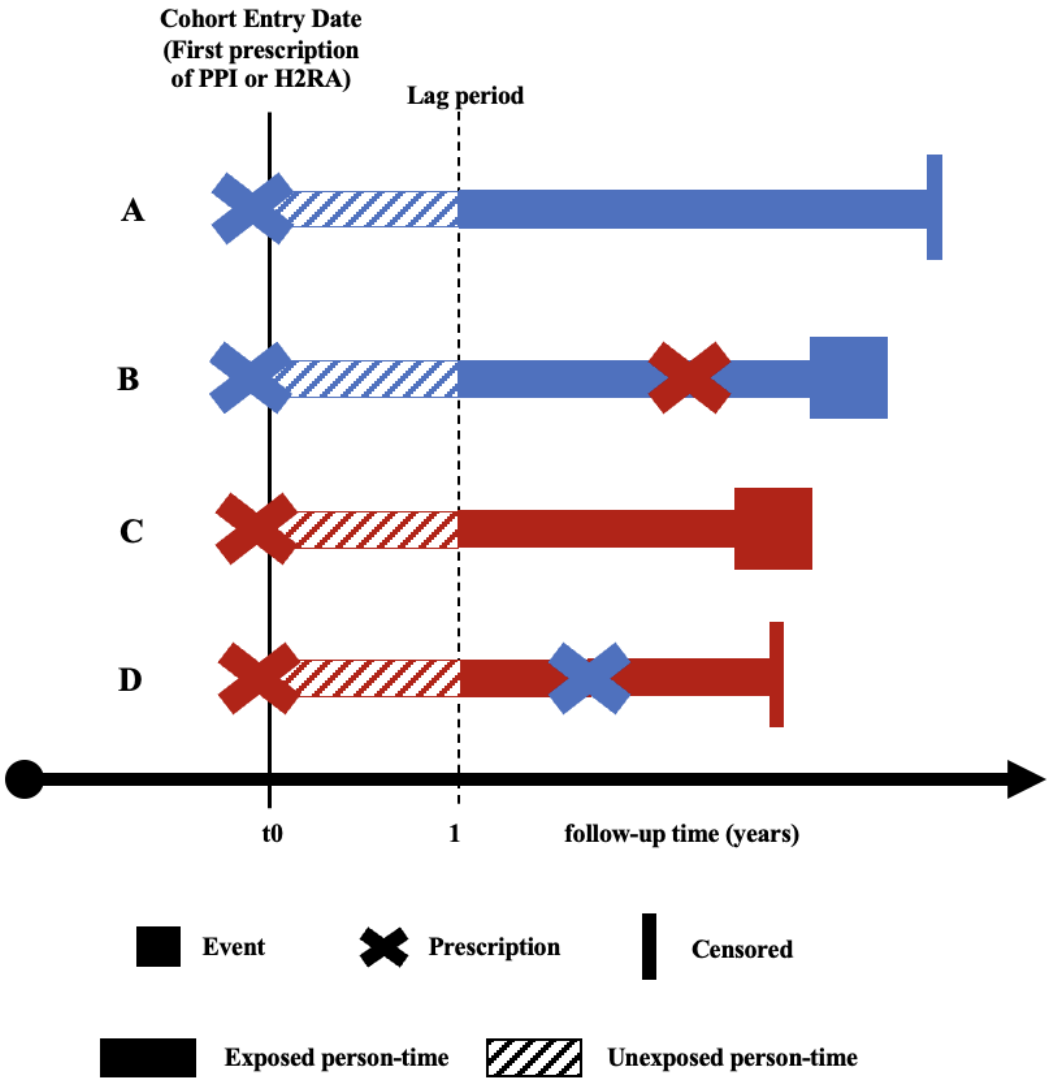
Supplementary Method 3. Inverse Probability of Screening Weights

To investigate the potential for detection bias from differential screening uptake between exposure groups, we used inverse probability of screening weights (IPSWs) to reweight our cohort.[8] For this analysis, the cohort was divided into 2-year intervals of follow-up. Within each interval, we estimated the predicted probability (P_{screen}) of colorectal screening (i.e., fecal occult blood testing or colon neoplasm screening) using multivariable logistic regression, conditional on the following covariates, all measured in the previous interval:

age, year of cohort entry, sex, alcohol-related disorders, smoking status (current, former, never), BMI, type 2 diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, cancer (other than nonmelanoma skin cancer), Crohn's disease, ulcerative colitis, other inflammatory bowel disease, polyps, cholecystectomy, and solid organ transplant. We also considered the indication for acid suppressant drug use (approved indications: peptic ulcer disease, gastroesophageal reflux disease, dyspepsia, *Helicobacter pylori* infection, and Barrett's oesophagus; off-label indications: gastritis/duodenitis and stomach pain). We also included the following drugs previously associated with colorectal cancer incidence, measured at any time before cohort entry: hormone replacement therapy, aspirin, other non-steroidal anti-inflammatory drugs, statins, bisphosphonates, and use of synthetic prostaglandin analogues, which are older drugs used to manage gastric conditions.[1] We also included measures of health-seeking behaviours, such as mammographic screening, prostate-specific antigen testing, influenza vaccination and the number of physician visits in the previous interval. Finally, we included the country, to account for differences in screening programs by region, and use of anticoagulants, which may be associated with closer patient monitoring.

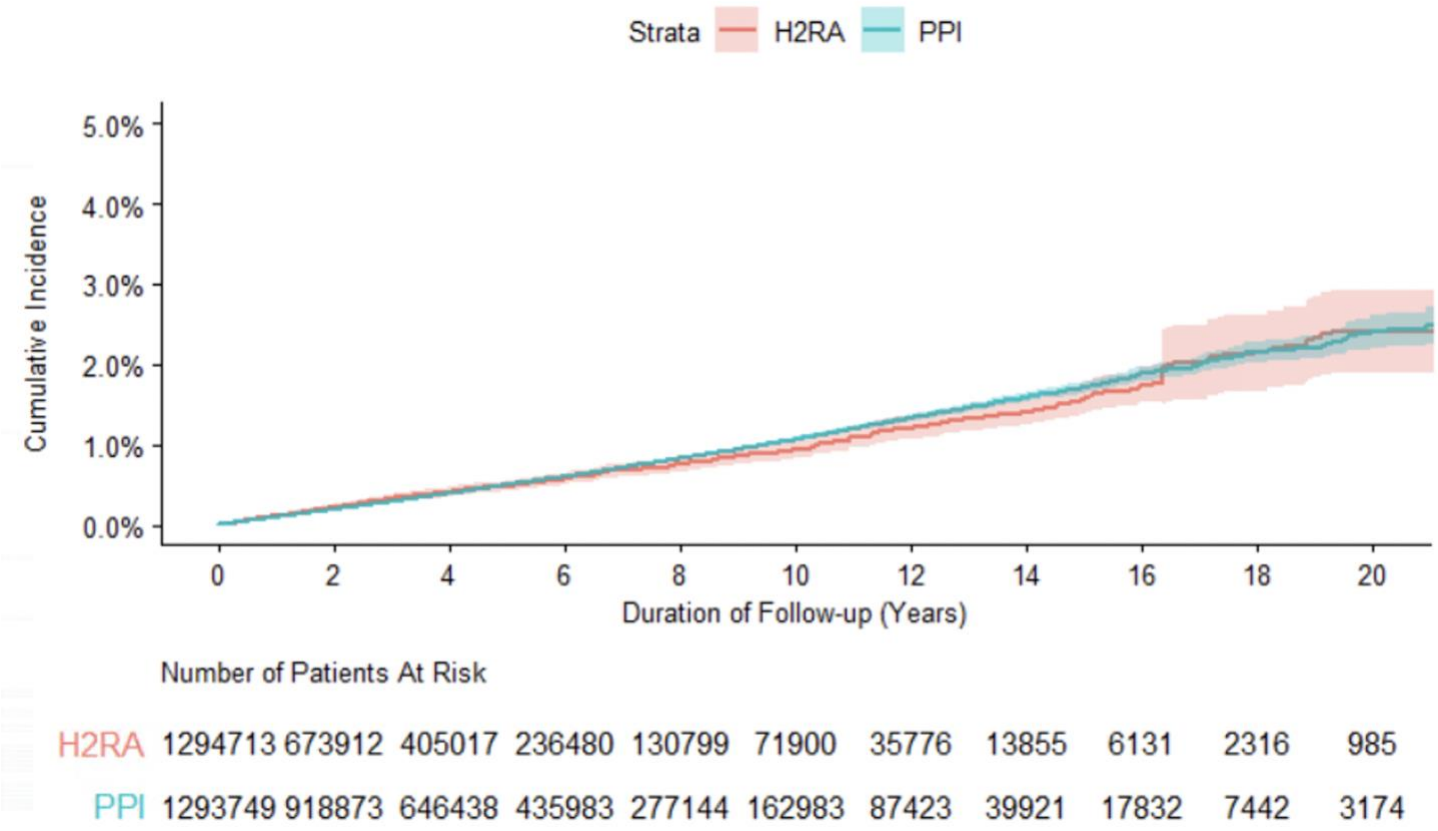
Any screening events that were considered diagnostic were not included. The weights were stabilized using the overall proportion of screening within the population (20%). Thus, patients who were screened were given a weight of $0.2/P_{screen}$, and patients who were not screened were given a weight of $0.8/(1- P_{screen})$.[8] Screening weights calculated at each interval were combined with standardized mortality ratio weights, and the overall weight was used to reweight the study cohort. Thus, marginal hazard ratios for colorectal cancer, adjusted for screening and treatment, were calculated using Cox proportional hazards models.

Supplementary Figure 7.1 Exposure Definition



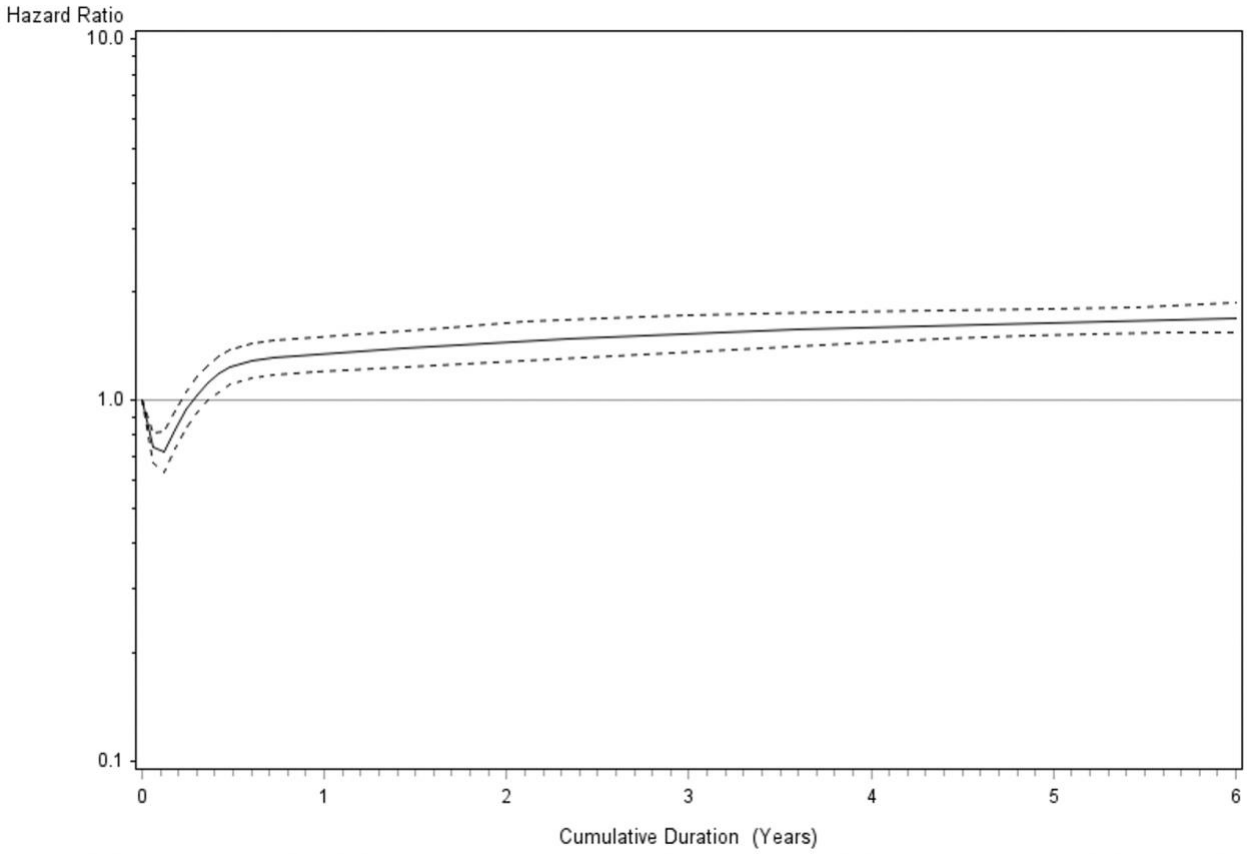
Supplementary figure 1 illustrates the exposure definition used to define incident PPI and H2RA users. Blue graphics represent PPIs, and red graphics represent H2RAs. Patients A and B enter the cohort as PPI users. Following the one-year lag period, illustrated by the dashed box, both patients contribute PPI exposed person-time to the analysis. When patient B switches to an H2RA (red X), they are considered exposed to PPIs for one additional year (lag period = one year). Thus, when patient B has an event, it is considered a PPI event. Patients C and D enter the cohort as H2RA users. Following the one year-lag period, they contribute person-time to the H2RA exposed group. Patient C has an event during follow-up, classified as an event for the comparator. Patient D switches to a PPI during follow-up (blue X) and thus contributes one additional year as an H2RA user before they are censored.

Supplementary Figure 7.2 Weighted Kaplan-Meier Curve of the Cumulative Incidence of Colorectal Cancer



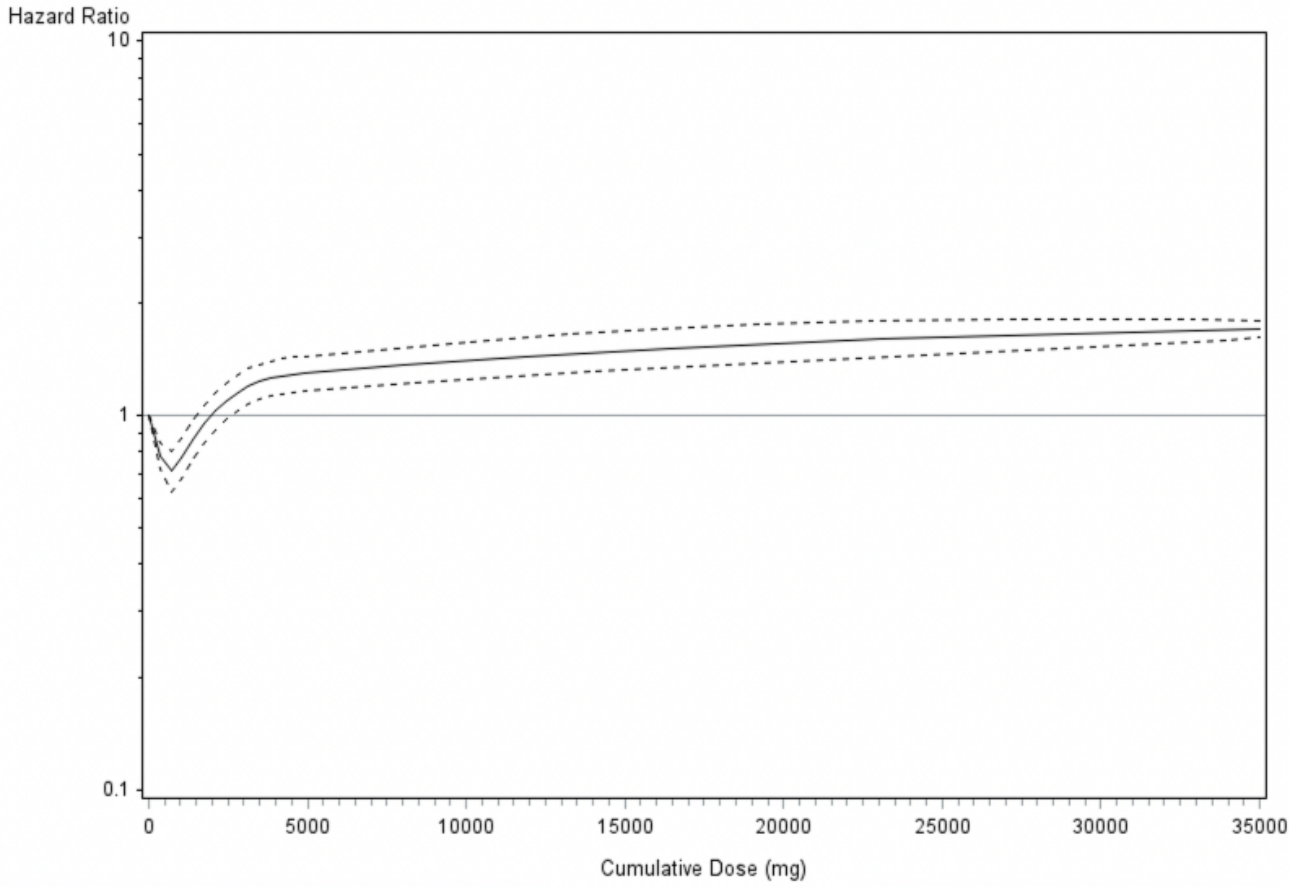
Follow-up starts one year after cohort entry
Curves are weighted using standardized mortality ratio weights

Supplementary Figure 7.3 Restricted Cubic Spline of Cumulative Duration of Proton Pump Inhibitor Use



Smooth restricted cubic spline curve of weighted hazard ratio of colorectal cancer disease (solid line) and 95% confidence limits (dashed lines) as function of cumulative duration of proton pump inhibitor use. Cumulative duration was truncated at six years of use because of few events.

Supplementary Figure 7.4 Restricted Cubic Spline of Cumulative Dose of Proton Pump Inhibitor Use



Smooth restricted cubic spline curve of weighted hazard ratio of colorectal cancer disease (solid line) and 95% confidence limits (dashed lines) as a function of cumulative omeprazole equivalents. Cumulative dose was truncated at 35,000 mg because of few events.

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Chapter 8. General Discussion

8.1 Summary of Findings

This thesis was designed to address the utilization and gastrointestinal cancer safety of PPIs. Given their growing popularity,[11] especially among patients who may not have an approved indication for use,[19 20 70] remaining safety signals need to be addressed in a timely manner to better inform patient care. Moreover, the contemporary data on H2RAs, an alternative class of drug used to manage gastric conditions is lacking. Addressing recent prescribing patterns of both classes of acid suppressant drugs is an important first step to determine the potential burden of any unanswered safety signals. While several deprescribing initiatives have been designed to curb unnecessary prescribing of PPIs,[17 21] the effectiveness of the latest UK guidelines had not been addressed before this thesis. Thus, it remained unclear if stronger initiatives were required. This is especially important in light of recent safety signals with gastric and colorectal cancer.[29-34]

The first manuscript in this thesis (Chapter 4) investigated the prescribing patterns of PPIs and H2RAs over a 29-year period among general practitioners in the UK.[168] This study found that from 1990 to 2018, more than 20% of adults registered in the CPRD were exposed to at least one acid suppressant drug. During the study period, PPI prevalence increased from 0.2% to 14.2%, while H2RA prevalence remained low at under 4%. However, prescribing intensity to PPIs has been constant over the past decade, whereas H2RA prescribing has begun to slightly increase. This study also illustrated that as many as one in five adults prescribed an acid suppressant drug have no recorded indication for use. Notwithstanding the popularity and efficacy of PPIs, there are several serious adverse effects associated with their use,[24-34] while H2RAs are more commonly associated with mild adverse events.[22] Thus, this study indicates that H2RAs remain a valuable treatment option for patients with gastric conditions. Nonetheless, given the high prevalence of

adults with no recorded indication for use of PPIs or H2RAs, physicians need to regularly reassess the need for ongoing acid suppressant treatment.

The second manuscript (Chapter 5) was designed to determine whether the 2014 NICE guidelines changed physician prescribing patterns in general practice.[21] Using an interrupted time-series analysis, we found no immediate change in PPI prescription rates in the post-guideline period (September 2014 to August 2018) compared to the pre-guideline period (September 2010 to August 2014).[169] While there was a modest attenuation of the change in the monthly PPI prescribing rate in the post-guideline period (-23.9 95% CI: -14.0 to -33.6),[169] the predicted rate using data from the pre-guideline period mirrored the observed rates in the post-guideline period. Overall, this suggests that publication of the 2014 NICE guidelines had a limited impact on physician behaviours. Thus, while these guidelines were developed in part to curb unnecessary PPI prescribing, other interventions in addition to the guidelines are likely required to combat the overprescribing of PPIs.

After observing increased utilization of PPIs, with minimal changes in prescribing following stricter guidelines, the third manuscript was designed to address open safety signals regarding the gastrointestinal cancer safety of PPIs. Thus, the objective of the third manuscript in this thesis (Chapter 6) was to determine whether the use of PPIs, when compared with the use of H2RAs, was associated with an increased risk of incident gastric cancer. Using a population-based cohort study with a new-user active comparator design, we identified 973,281 new users of PPIs and 193,306 new users of H2RAs, followed for a median follow-up of 5.0 years. After propensity score weighting using SMRWs, use of PPIs was associated with a 45% increased risk of gastric cancer (HR: 1.45, 95% CI: 1.06-1.98) compared with the use of H2RAs. The number needed to harm was 2,121 and 1,191 for five and 10 years after treatment initiation, respectively. In

secondary analyses, the risk increased with cumulative duration, dose, and time since treatment initiation. Overall, this study indicates that while the absolute risk of gastric cancer is low, patients newly prescribed PPIs are at an increased risk of gastric cancer compared to patients newly prescribed H2RAs. While PPIs have established clinical benefits when used according to evidence-based guidelines, physicians must regularly reassess the necessity of ongoing treatment, especially in patients who are prescribed PPIs in the long-term and for patients without an evidence-based indication for use.

Lastly, the fourth manuscript in this thesis (Chapter 7) was designed to determine whether PPIs are associated with an increased risk of colorectal cancer, compared with H2RAs. The cohort included 1,293,749 patients newly treated with PPIs and 292,387 patients newly treated with H2RAs from 1990 to 2018. Overall, any use of PPIs was not associated with an increased risk of colorectal cancer (HR: 1.02, 95% CI: 0.92 to 1.14). However, there was a dose-response relationship according to cumulative duration of PPI use (<2 years, HR: 0.93, 95% CI: 0.83 to 1.04; 2-4 years, HR: 1.45, 95% CI: 1.28 to 1.60; ≥4 years, HR: 1.60, 95% CI: 1.42 to 1.80), with similar patterns by increasing cumulative dose and time since initiation. The number needed to harm was 5,343 and 792 for five and 10 years of follow-up, respectively. Thus, while any use of PPIs was not associated with an overall increased risk of colorectal cancer, prolonged use may be associated with a modest increased risk of this malignancy. Given the high prevalence of PPI use in the general population, a small increased risk could translate to a significant excess number of colorectal cancer cases at the population level. In light of this risk, physicians should closely monitor patients that require long-term PPI treatment.

8.2 Clinical Implications

This thesis contributes to the existing literature on the utilization of acid suppressant drugs. Importantly we present new data regarding the prescribing patterns of H2RAs, a drug that has been understudied in recent years. While H2RAs are considerably less popular than PPIs, we observed almost 10 million H2RA prescriptions from 1990 to 2018. This highlights that H2RAs remain a valuable treatment option, and that PPIs have not completely supplanted use of H2RAs. Moreover, the increasing yearly prescribing intensity to H2RAs over the past five years suggests that they are gaining favour among general practitioners. The results from the utilizations study are consistent with a similar study using CPRD data with follow-up until 2014.[70] However, this study did not address the prescribing patterns of H2RAs. Thus, to our knowledge, this study is the first to show that H2RAs may be similarly overprescribed to PPIs. Indeed, we observed 22.6% of H2RA users had no recorded indication for use (20.1% of PPI users). This suggests that the *class* of acid suppressant drugs may be overprescribed, and physicians should regularly reassess the ongoing need for both PPI and H2RA treatment.

To our knowledge, this thesis was the first study to address the impact of the 2014 NICE PPI prescribing guidelines. The results suggest that the existing interventions are not adequately curbing the burden of PPI overprescribing. While other countries have implemented stricter PPI deprescribing initiatives, including updating treatment guidelines and targeted campaigns,[17 71] to our knowledge such a strategy has not been implemented in the UK. Given that the existing guidelines are not addressing the burden of PPIs, a targeted campaign through electronic medical records may be a more sufficient strategy. At minimum, patients who are taking acid suppressant drugs without an indication for use should be deprescribed. For all other patients prescribed PPIs, physicians may wish to consider alternative treatments like H2RAs, or treatment with a lower-

dose PPI; as indicated by the recent guidelines.[21] Future guidelines and other deprescribing initiatives may also target the overburden of H2RAs, and consider implications of acid suppressant drugs as a class.

8.2.1 Risk-benefit Profile

PPIs and H2RAs have been used to effectively manage the symptoms of gastric conditions, including peptic ulcer disease, gastroesophageal reflux disease, and dyspepsia, for several decades.[1-3] PPIs are potent acid suppressors, as they inhibit the final pathway of acid secretion in response to all three stimuli.[3 62] In contrast, H2RAs only block the effects of histamine, so they are considered less effective than PPIs.[63] Nonetheless, both classes of drugs are frequently prescribed in practice.[25 66 67 69] However, use of these drugs, especially in the long-term is not without risk.

Indeed, PPIs have been previously associated with enteric infections such as *Clostridiodes difficile*, acute interstitial nephritis, hypomagnesaemia, increased intestinal colonization with multidrug-resistant organisms.[24-28] In contrast, H2RAs have been associated with milder adverse events like headache and constipation,[22] with less evidence on serious outcomes like delirium and acute interstitial nephritis.[60 61] While several previous studies attempted to address the gastrointestinal cancer safety of PPIs,[39-50] these generated highly heterogenous findings, and had important methodological flaws, including time-related biases, failure to account for cancer latency and severe confounding by indication.[103 107-110] These conclusion-altering biases make it challenging to draw conclusions based on the existing evidence.

This thesis presents new information regarding the gastrointestinal safety of PPIs, as these two studies were deigned to specifically address the limitations of previous studies. Given that use of PPIs are associated with gastric cancer, and prolonged use may be associated with a modest increased risk of colorectal cancer, patients at a high risk of gastrointestinal malignancies may

consider treatment with H2RAs, or treatment with PPIs for the shortest duration possible. Moreover, physicians should be mindful when prescribing PPIs for the long-term, especially as most evidence-based indications suggest short durations of treatment.[2 13 14] While the absolute risk of both gastric and colorectal cancer remains low, given the burden of PPI overprescribing, these small increases in risk could translate to a large absolute increase in gastric and colorectal cancer cases in the population. Overall, while PPIs have established clinical benefits, their long-term efficacy is restricted to specific indications. In light of the potential harms associated with the use of PPIs outlined in this thesis, careful consideration regarding long-term acid suppressant treatment is required.

8.3 Strengths and Limitations

This thesis had several strengths. To our knowledge, the studies conducted were the largest and most comprehensive to date, as all studies considered the class of acid suppressant drugs and had up to 29 years of follow-up. Indeed, Objective 1 assessed the prescribing patterns of both PPIs and H2RAs from 1990 to 2018, which was the longest study conducted to date. Objective 2 was the first study conducted to assess the 2014 NICE guidelines, and had sufficiently long follow-up following the guidelines (four years) to assess the impact on physician prescribing. Objectives 3 and 4 were the largest studies with the longest potential follow-up, including over 1 million patients in each study cohort. Given the extensive sample size, each study was sufficiently powered, and able to investigate prescribing trends or cancer risk among important subgroups. Second, the CPRD, which was used in all four objectives, has been extensively validated in previous studies.[135 140-146] Diagnoses have been previously validated, and the CPRD population is representative of the general population in the UK.[56] Finally, each study was designed to specifically address limitations of the existing literature. Thus, Objective 1 was designed to provide a more comprehensive picture

on the utilization of the class of acid suppressant drugs, as prior literature was restricted to PPI use only. Finally, Objectives 3 and 4 minimized the impact of biases present in the existing literature by restricting the cohort to incident drug users, using an active comparator for all analyses, and using propensity score weights to deal with confounding.

This thesis also had some limitations. The prescriptions recorded in the CPRD are issued by general practitioners and not specialists, and there are no hospitalization or over-the-counter data. This may have slightly underestimated the prescribing rates presented in Objectives 1 and 2, and could have led to some exposure misclassification in Objectives 3 and 4. However, while this may slightly underestimate the burden of acid suppressant use, general practitioners are considered the gatekeepers to health in the UK, and are responsible for long-term patient care, including the management of gastric conditions.[137] Thus, we do not expect the rates to be vastly underestimated, and any misclassification from missing prescription data should be minimal. Similarly, it was not possible to measure adherence to treatment. Given that Objectives 1 and 2 did focused on physician behaviours, adherence was not relevant. While adherence could lead to some exposure misclassification in Objectives 3 and 4, there is no reason to expect differential adherence to PPIs versus H2RAs. Moreover, the exposure definition used in these two objectives was analogous to an intention-to-treat approach, which does not consider adherence or treatment termination. Second, it was not possible to stratify according to gastric cardia versus non-cardia cancer, or by colorectal cancer site, as this information is not consistently recorded in the CPRD. Finally, given the observational nature of these studies, residual confounding from unknown or unmeasured confounders is possible. While use of an active comparator and calendar time-specific propensity score models should minimize confounding, residual confounding cannot be ruled out.

8.4 Future Directions

While this thesis is an important addition to the literature, there are several remaining gaps that can be addressed in future works. First, the utilization patterns in Objectives 1 and 2 may only apply to the UK and should be investigated further in other study settings. This is especially important for recent prescribing patterns of H2RAs, which have been largely understudied. Second, an interrupted time series analysis at the level of individual practices will allow for inference beyond the population level and may be useful to target specific practices for new deprescribing initiatives. Third, while there have been several previous observational studies on the gastrointestinal cancer safety of PPIs, each had at least one major methodological flaw. Thus, future studies using appropriate methodology should be conducted in other settings to confirm the findings of Objectives 3 and 4. This may better inform regulatory action and changes to guidelines of PPIs, which should not be based on the results from any single study. Studies with greater detail on cancer-specific outcomes, such as cardia versus non-cardia gastric cancer should also be conducted, given that these cancer types have different risk profiles.[105] Moreover, there are other site-specific related cancers that need to be addressed in future studies, including esophageal, pancreatic and cholangiocarcinoma. Finally, future studies are also needed to better elucidate the mechanism by which use of PPIs increases the overall risk of gastric cancer, and long-term PPI use increases the risk of colorectal cancer, given that the existing mechanism are hypothetical.

8.5 Conclusions

This thesis presented data on the prescribing patterns of PPIs and H2RAs from 1990 to 2018, illustrating a high PPI prevalence, but increasing H2RA prescribing intensity. Both PPIs and H2RAs are overprescribed, and existing guidelines have been insufficient to combat the overprescribing burden of PPIs. There has been less discussion on the overuse of H2RAs, as this

has been largely understudied, especially in recent years. However, while H2RAs remain a valuable treatment option for patients with gastric conditions, caution regarding overprescribing needs to be applied to H2RAs, in addition to PPIs. Stronger deprescribing initiatives may be required in the future, especially in light of the associations with gastric and colorectal cancer observed in this thesis. Indeed, use of PPIs is associated with an increased risk of gastric cancer, and long-term PPI use is associated with an increased risk of colorectal cancer. Thus, despite their effectiveness when used for evidence-based indications, their use does carry a certain level of risk. At the very least, patients without a recorded indication for use, and long-term users without an indication for long-term use should be deprescribed. Given the high prevalence of PPI use, even a small increased risk of a malignancy can have important public health implications at the population level. Thus, physicians should closely monitor all patients prescribed PPIs in the long-term, and consider step down PPI therapy to a lower dose or on an 'as-needed' basis for patients with recurring symptoms.[21] At the minimum, all patients should be reassessed at yearly intervals to determine ongoing need for PPI treatment.

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