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Complete List of Authors:	Abrahami, Devin; Lady Davis Institute for Medical Research, Centre for Clinical Epidemiology; McGill University, Epidemiology, Biostatistics, and Occupational Health McDonald, Emily; McGill University Health Centre, General Internal Medicine; McGill University, Experimental Medicine Schnitzer , Mireille; Université de Montréal, Pharmacy Azoulay, Laurent; Lady Davis Institute for Medical Research, Centre for Clinical Epidemiology; McGill University, Epidemiology, Biostatistics, and Occupational Health
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Trends in Acid Suppressant Drug Prescriptions in Primary Care in the United Kingdom: A Population Based Cross Sectional Study

Devin Abrahami[1,2], Emily G. McDonald[3,4], Mireille Schnitzer[5], Laurent Azoulay [1,2,6]

[1] Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Canada

[2] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada

[3] Division of General Internal Medicine, Department of Medicine, McGill University Health Centre

[4] Division of Experimental Medicine, McGill University, Montreal Canada

[5] Faculty of Pharmacy, Université de Montréal, Montréal, Québec, Canada

[6] Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada

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Address for correspondence:

Dr Laurent Azoulay

Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital

3755 Cote Sainte-Catherine Road, H425.1

Montreal, Quebec, Canada H3T 1E2

Telephone: (514) 340-8222 Ext. 28396

Fax: (514) 340-7564

Email: laurent.azoulay@mcgill.ca

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ABSTRACT

Objective: To examine proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA) prescribing patterns over a 30-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 United Kingdom Clinical Practice Research Datalink.

Participants: Within a cohort of 14,242,329 patients registered in the Clinical Practice Research Datalink, 3,027,383 patients were prescribed at least one PPI or H2RA from January 1, 1990 to December 31, 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 Clinical Practice Research Datalink 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 0.2-14.2%, while H2RA prevalence remained low (range: 1.2-3.4%). PPI prescribing intensity increased by 16% per year from 1990-1999 and remained unchanged for the remainder of the study period. H2RA prescribing intensity initially decreased from 1990 to 2009 but increased by 5% per year from 2010-2018.

Conclusions: While PPI prevalence has been increasing over time, its prescribing intensity has begun to level off. Notwithstanding their efficacy, PPIs are associated with a number of adverse

effects not attributed to H2RAs, whose prescribing intensity has recently increased. Thus, H2RAs remain a valuable treatment option for individuals with gastric conditions.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Largest and most comprehensive study to date describing trends of acid suppressant drugs over a 30-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 asses patient adherence
- We did not have data on prescriptions recorded in hospital, by specialists, or from over the counter

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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] While both drug classes have been used for over three decades, PPIs have been shown to have superior efficacy in reducing stomach acid compared to H2RAs.[1] Nonetheless, both drug classes are among the top 25 most prescribed medications in the hospital setting in the United Kingdom (UK).[3]

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.[4-8] Indeed, the number of individuals using PPIs has been increasing significantly since their introduction in 1988.[9] In England alone, more than 50 million PPI prescriptions were dispensed in 2015.[10] In contrast, there is limited information on the older drug class, H2RAs, with regards 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 7] recent evidence suggests that long-term use, beyond the recommended 4-8 week duration for most conditions, may be associated with adverse health outcomes. These include enteric infections such as *Clostridium difficile,* osteoporotic fractures, acute interstitial nephritis, dementia, pneumonia, gastric cancer, and more recently, increased intestinal colonization with multidrug resistant organisms.[10-16] 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.[17] These new guidelines emphasize an annual review to determine ongoing need, and to use the lowest dose of PPI on an as-needed basis for symptom

relief.[17] Prescribing patterns of PPI usage 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 utilization study was to determine the prescribing patterns of PPIs and H2RAs in UK primary care over a 30-year period.

METHODS

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.[18 19] The CPRD contains information on demographics, diagnoses, procedures,[20] and prescription information based on the British National Formulary. The data are audited regularly, and diagnoses recorded in the CPRD have been extensively validated.[21 22]

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 19_119RA) and by the Research Ethics Board of the Jewish General Hospital. All authors had access to the study data and reviewed and approved the final manuscript.

Study Population

Using the CPRD, we identified a cohort of patients who were registered with a general practitioner from January 1, 1990 to December 31, 2018. We did not impose any age restrictions to evaluate 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 (January 1, 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 (December 31, 2018).

Exposure Definition

We identified all PPIs and H2RAs prescriptions within the study period using the British National Formulary (**Supplementary 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.

Statistical Analysis

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 either 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, 19-39, 40-59, ≥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 within the study period. To determine new use, individuals prescribed acid suppressants were required to have at least one year of

medical history in the CPRD prior to their first prescription. Similarly, patients in the CPRD were required to have at least one year of follow-up to contribute to the denominator. Individuals co-prescribed 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.

Indications for use

Indications for use among new users was inferred using Read codes recorded at any time prior to the first prescription. Indications were classified as evidence-based (dyspepsia, gastroprotection, gastroesophageal reflux disease, peptic ulcer disease, Helicobacter pylori infection, Barrett's oesophagus, and Zollinger-Ellison syndrome), off-label (stomach pain and gastritis or duodenitis), non-evidence based gastroprotection, and no recorded indication.[2] To define individuals using acid suppressant drugs for gastroprotection, we considered individuals prescribed 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 co-prescription for NSAIDs or dual antiplatelet therapy, but without a risk factor, were assumed to be using acid suppressants for non-evidence based gastroprotection.

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 [e.g. 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 based 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 of use changed during the study period, we stratified the study period by decade (1990-1999, 2000-2009 and 2010-2018) and estimated incident rate ratios (IRRs) with 95% CIs using negative binomial regression, with log of follow-up time included as an offset variable.

Persistence

As there is some evidence that PPIs are being used for inappropriate durations,[4-8] 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 length of this grace period was changed to 7 and 60 days in a sensitivity analysis. We used Kaplan-Meier curves to graphically describe 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 as a function of follow-up time. All analyses described above were conducted with SAS version 9.4 (SAS institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

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.

RESULTS

Within a cohort of 14,242,329 patients 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, 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. At baseline, PPI users were slightly older than H2RA users, but there were no sex differences between the two groups. Only 48.4% and 54.1% 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 (19.4%) than the H2RA users (12.8%). About 18% of PPI and H2RA users did not have a recorded indication for use.

Figures 1 to 3 illustrate the overall, and 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 to 3.4%). PPIs and H2RAs were more commonly prescribed in adults at least 60 years old and in females. Patterns of use were similar among new users (**Supplementary Figures 1 and 2**), except for an increase in use of H2RAs among the paediatric population over the past decade (**Supplementary Figure 3**). Omeprazole was the most commonly prescribed PPI

during the study period, followed by lansoprazole (**Supplementary Figure 4**). 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 (**Supplementary Figure 4**).

Throughout the study period, the prescribing intensity of PPIs ranged from 0.68 per 1,000 person-years in 1990, increasing to a peak intensity of 9.78 per 1,000 person-years in 2012 (**Supplementary Figure 5**). In contrast, the prescribing intensity of H2RA use decreased over the study period from the highest intensity of 19.45 per 1,000 person-years in 1990, to the lowest intensity of 0.78 per 1,000 person-years in 2013. From 1990 to 1999, the prescribing intensity of PPI use increased yearly by 16% (IRR: 1.16, 95% CI: (1.16 to 1.16)), while the intensity of use remained constant from 2000 to 2009 (IRR: 1.01, 95% CI: 1.01 to 1.01) and 2010 to 2018 (IRR: 0.98, 95% CI: 0.98 to 0.98). In contrast, prescribing intensity of H2RAs decreased by 11% per year from 1990 to 1999 (IRR: 0.89, 95% CI: 0.89 to 0.90), 10% a year from 2000 to 2009 (IRR: 0.90, 95% CI: 0.90 to 0.90), but increased by 5% a year from 2010 to 2018 (IRR: 1.05, 95% CI: 1.05 to 1.05).

Within new users of PPIs (n=1,699,837) the median duration of the first treatment course was 144 days (interquartile range [IQR]: 59 to 870). 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 (2.1%) 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=385,988) was 279 days (IQR: 61 to 1,645). H2RA users were equally likely to discontinue use due to a treatment gap exceeding 30 days, administrative censoring, or because of a switch to a PPI. **Supplementary Table 3** presents duration of treatment and reasons for discontinuation under alternate grace

periods. **Figure 4** illustrates the time to discontinuation of both drug classes. While persistence to PPIs and H2RAs rapidly 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 one-year recommended duration.[17] Though persistence to the original treatment course decreased for both study drugs with time, 12.6% of PPI users and 23.1% of H2RA users persisted to their original treatment course after 5 years.

DISCUSSION

To our knowledge, this is the largest and most comprehensive study conducted to examine the prescribing patterns of both PPIs and H2RAs in the UK. Throughout the study period, 21.3% of the CPRD population received at least one acid suppressant drug. The overall prevalence of PPI prescribing has increased from 1990 to 2018, while the prevalence of H2RA remained low. Prescribing intensity to PPIs increased within the first decade of follow-up but remained consistent for the remainder of the study period. In contrast, H2RA prescribing intensity decreased from 1990 to 2009, but has begun to increase over the past 10 years.

The overall high prevalence of PPI use in the UK is consistent with a utilization study using CPRD data, but whose follow-up period ended at end of 2014.[9] Importantly, our study further contextualizes the landscape of prescribing acid suppressant drugs by 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,[23 24] they are generally well tolerated compared to PPIs, and are more commonly associated with mild adverse effects like headache and constipation,[23] not the serious adverse effects associated with use of PPIs.[10-16] Thus, H2RAs continue to represent an important treatment option for individuals with gastric conditions. Finally, to our knowledge, this is the first study to describe contemporary prescribing practices following the most recent NICE recommendations in 2014.[17]. Given that H2RA prescribing intensity has been increasing from 2010 to 2018, this may suggest a gradual shift in prescribing to favour H2RAs following the guidelines. Future studies should investigate the impact of the NICE recommendations more thoroughly.

Our study demonstrated a sex and age difference among PPI and H2RA prescribing patterns, whereby women 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,[25] this would lead to more frequent prescribing of acid suppressants to manage these symptoms. Given that the incidence of dyspepsia, the most common indication for PPIs and H2RAs, increases with age,[26] the patterns we observed with age were expected. Additionally, patients over the age of 60 who are prescribed NSAIDs or dual antiplatelet therapy may be prescribed an acid suppressant drug for gastroprotection,[2] which may contribute to the increased prescribing trends among older adults.

In recent years, there have been concerns about the increasing inappropriate use of PPIs.[4] [5] Indeed, between 40% and 55% of primary care patients in the United States and the UK do not have an evidence-based indication for long-term PPI use.[27] [28] This is particularly relevant as evidence continues to emerge that PPIs are associated with a number of serious adverse events.[10-16] Our study adds to the growing literature surrounding inappropriate use, as we illustrated that these issues extend to H2RA users as well. Indeed, close to 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 one year of follow-up, despite recommendations to limit use to 4-8 weeks at a time for symptomatic treatment of GERD and PUD.[17] While some of this high persistence may be explained by ongoing use for gastroprotection, a significant portion likely represents overtreatment and failure to re-evaluate for ongoing necessity.

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 30-year period, which is 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,[21 22] and shown to be representative of the UK general population.[18 19] 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. While this may slightly affect the estimate of cumulative incidence of discontinuation, the rest of our analyses focus on physician prescribing trends, which would not be influenced by adherence. 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.[29] 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 pertaining to over the counter use of PPIs and H2RAs. Thus, the relatively high prevalence of patients exposed to acid suppressant drugs (21.3%) would be even higher if over the counter usage was considered.

This study demonstrates that while prevalence of PPI use has increased with time, its prescribing intensity has plateaued in recent years. In contrast, while prevalence of H2RAs was consistently low, its prescribing intensity has increased over the last decade. Given that PPIs are associated with a number of adverse effects, most of which are not attributed to H2RAs, H2RAs remain a valuable treatment option for individuals with gastric conditions.

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Table 1. Characteristics of Individuals Newly Prescribed Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Characteristic	Proton Pump Inhibitors †	Histamine-2 Receptor Antagonists ‡
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 (%)§		
Dyspepsia	400,900 (48.7)	134,841 (64.6)
Gastroprotection	292,781 (35.6)	45,776 (21.9)
Gastroesophageal reflux disease	185,557 (22.5)	57,604 (27.6)
Peptic ulcer disease	71,945 (8.7)	20,150 (9.7)
Helicobacter pylori infection	48,976 (5.9)	13,050 (6.3)
Barrett's oesophagus	4,709 (0.57)	1,962 (0.94)
Zollinger-Ellison syndrome	27 (0.0033)	15 (0.0072)
Off-label indication, n (%)§		
Stomach pain	214,814 (69.2)	51,050 (73.2)
Gastritis or duodenitis	36,138 (11.6)	11,726 (16.8)
Non-evidence based gastroprotection	330,273 (19.4)	49,501 (12.8)
No recorded indication, n (%)	310,592 (18.3)	69,741 (18.1)
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)

† 823,393 (48.4%) evidence-based indication, 235,579 (13.9%) off-label indication.
‡ 208,789 (54.1%) evidence-based indication, 57,957 (15.0%) off-label indication.
§ Indication categories are not mutually exclusive.
¶ Median duration of first treatment course for PPI users and H2RA users was 144 and 279 days, respectively.

FIGURE LEGENDS

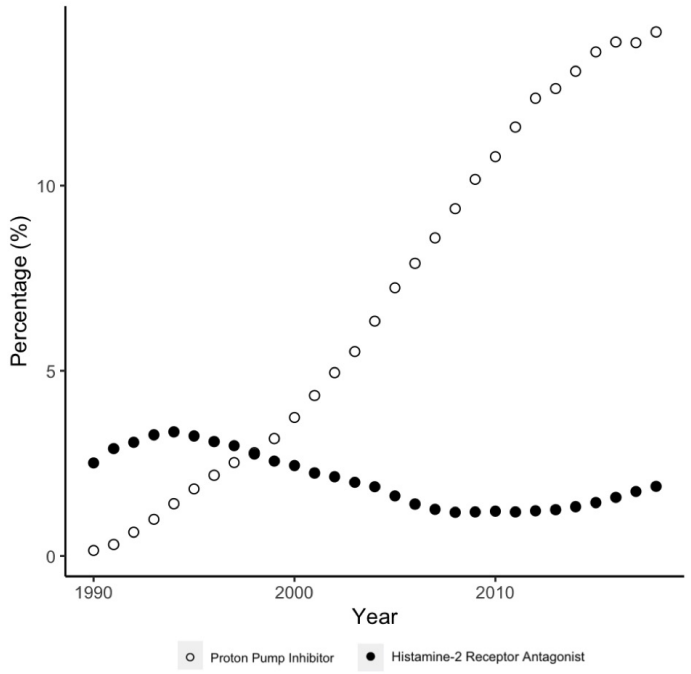
Figure 1 Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

Figure 2 Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

Figure 3 Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use

Figure 4 Persistence to Original Treatment Course for A) Proton Pump Inhibitor Initiators and B) Histamine-2 Receptor Antagonist Initiators

Figure 1



Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

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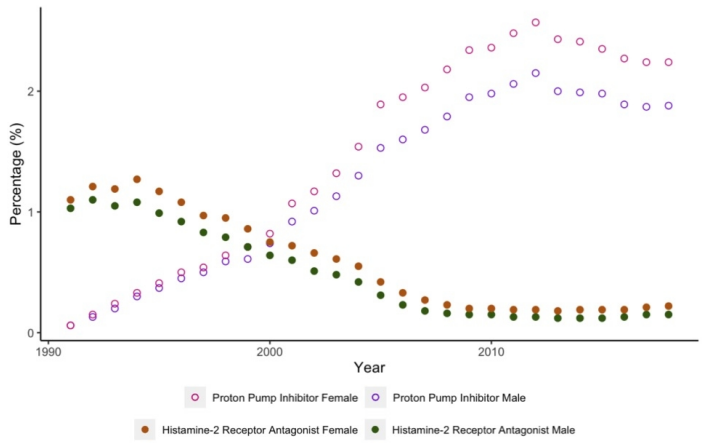
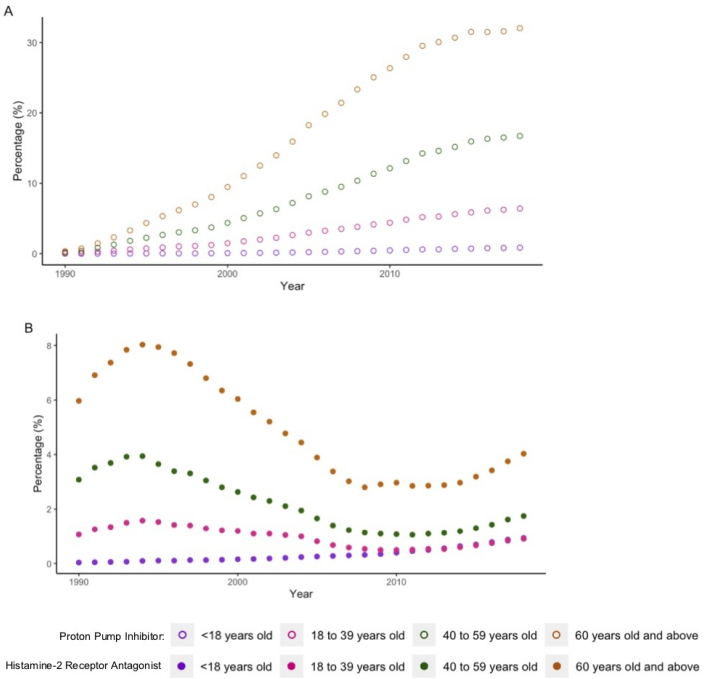
Figure 2



Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

215x279mm (150 x 150 DPI)

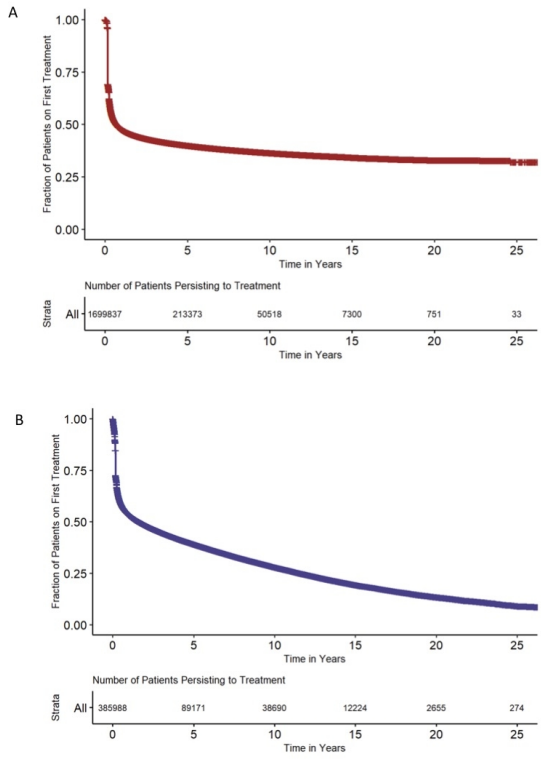
Figure 3



Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use

215x279mm (150 x 150 DPI)

Figure 4



Persistence to Original Treatment Course for A) Proton Pump Inhibitor Initiators and B) Histamine-2 Receptor Antagonist Initiators

215x279mm (150 x 150 DPI)

Table of Contents

Supplementary Table 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
01030800/05011100/05040200/ 05040300/05040400/07020251	Helicobacter Pylori Eradication/Metronidazole And Tinidazole/Amoebicides/Trichomonacides/ Antigiardial Drugs/Preparations For Other Vaginal Infections
1030500	Proton Pump Inhibitors

Supplementary Table 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

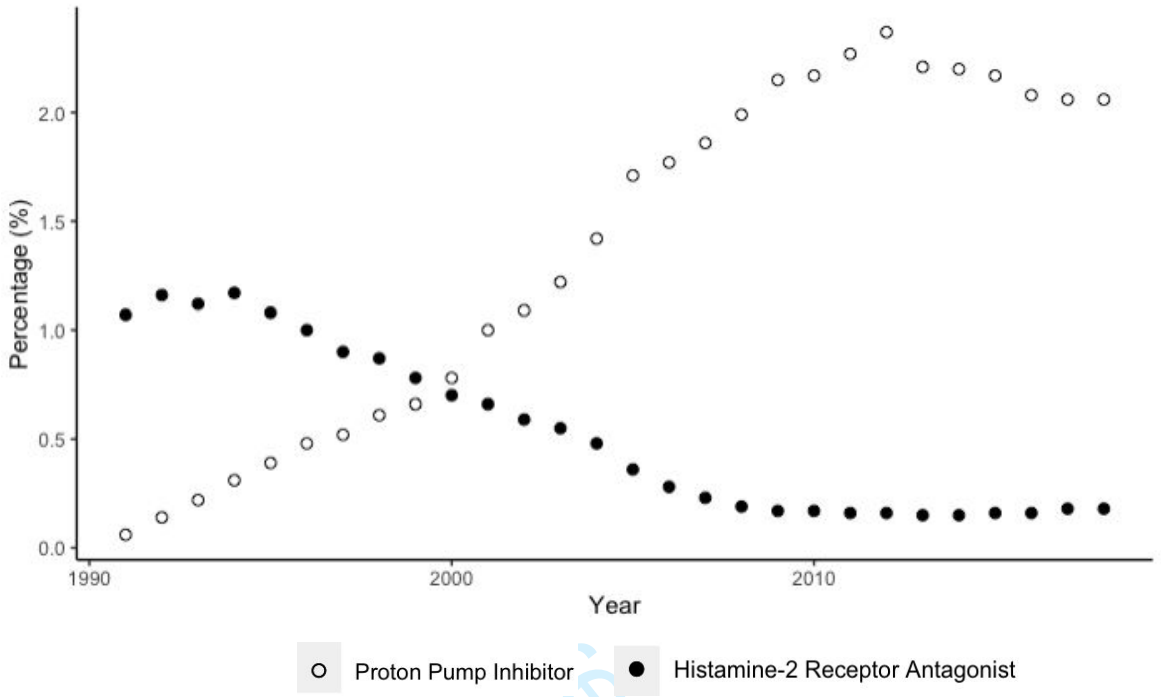
Abbreviations: H2, Histamine-2.

Supplementary Table 3. Reason for Discontinuation of Initial Acid Suppressant Treatment Course Under Alternate Grace Periods

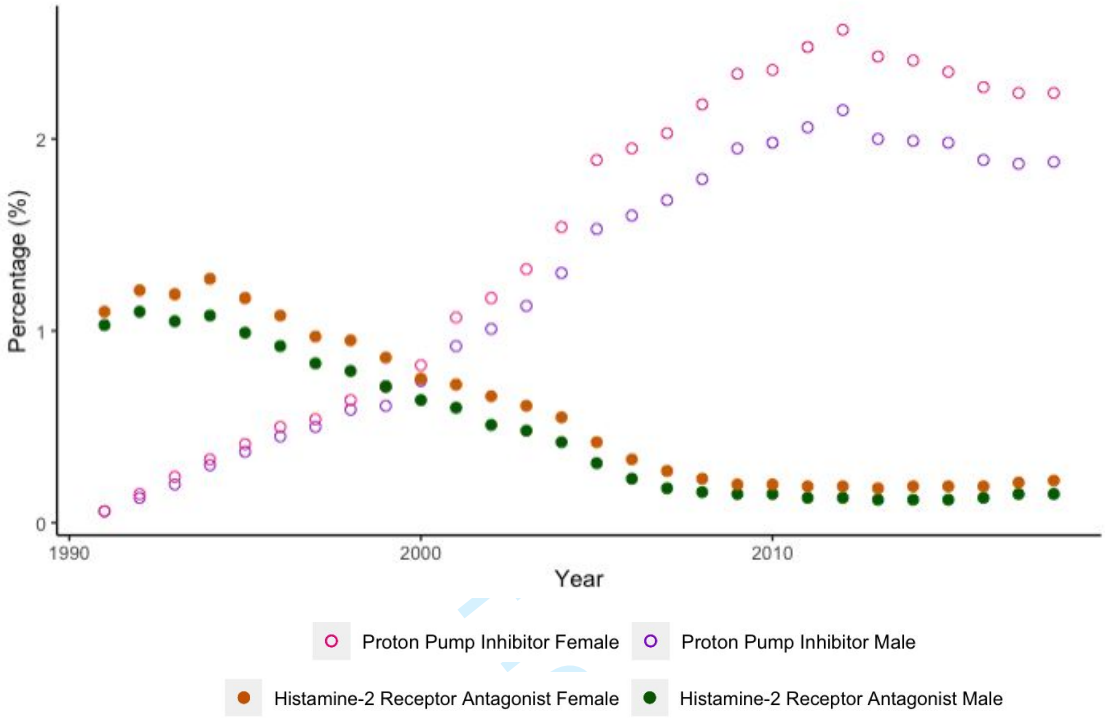
Reason for Discontinuation	Proton Pump Inhibitors (n=1,699,837)	Histamine-2 Receptor Antagonists (n=385,988)
60 Day Grace Period †		
Switch to other class	54,783 (3.2)	135,039 (35.0)
Treatment gap > 60 days	778,676 (45.8)	103,837 (26.9)
Administrative Censoring	866,378 (51.0)	147,112 (38.1)
7 Day Grace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

† median duration of first treatment course for PPI users and H2RA users was 231 and 381 days, respectively
‡ median duration of first treatment course for PPI users and H2RA users was 66 and 149 days, respectively

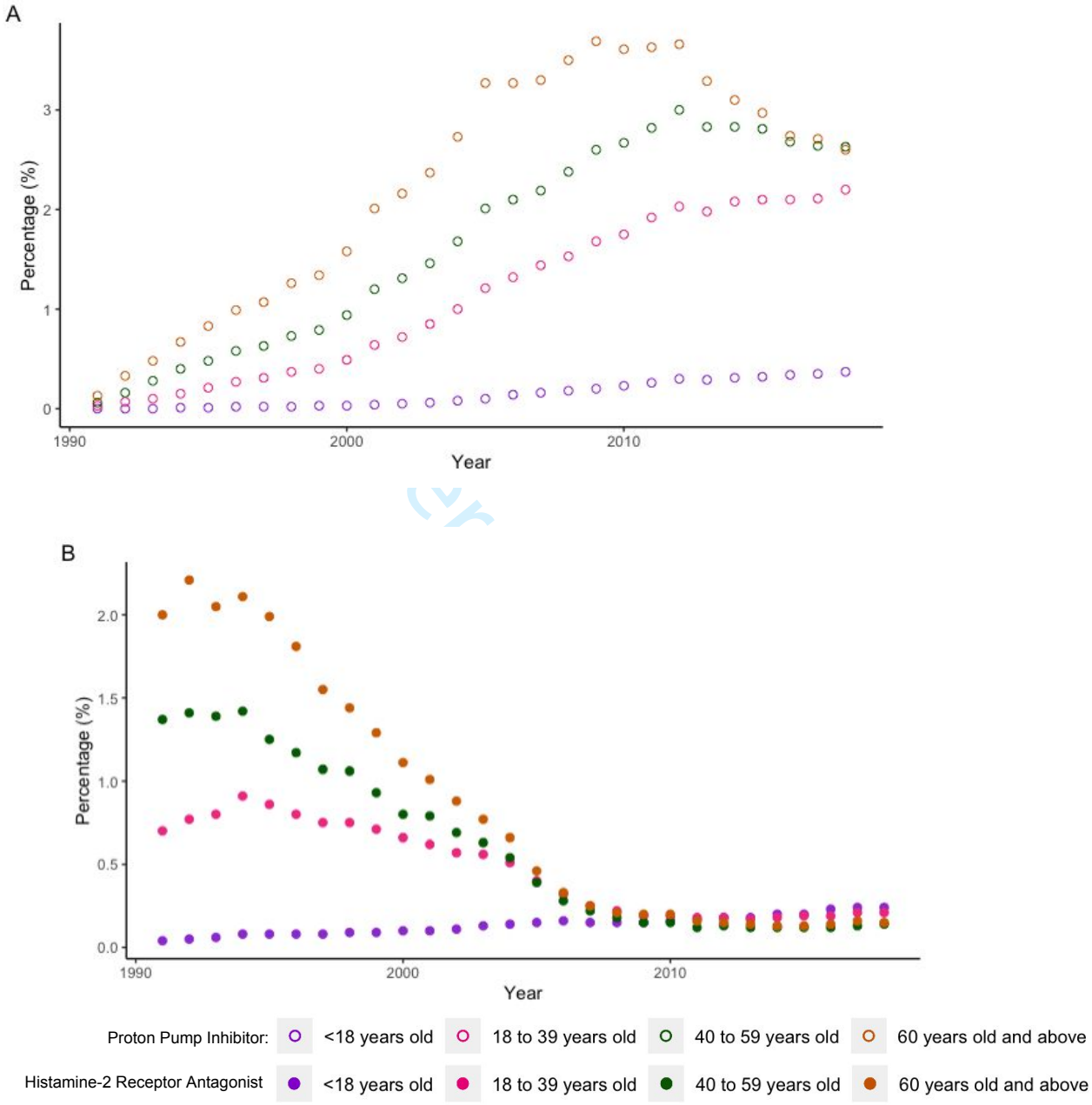
Supplementary Figure 1. Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users



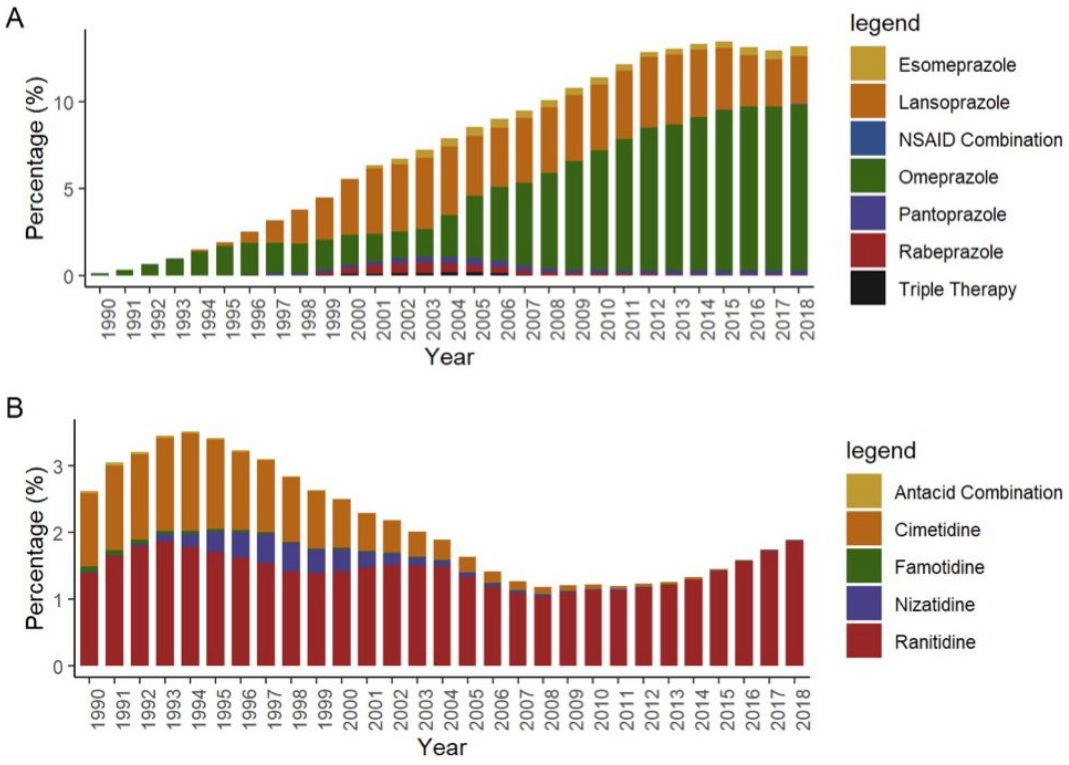
Supplementary Figure 2. Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users



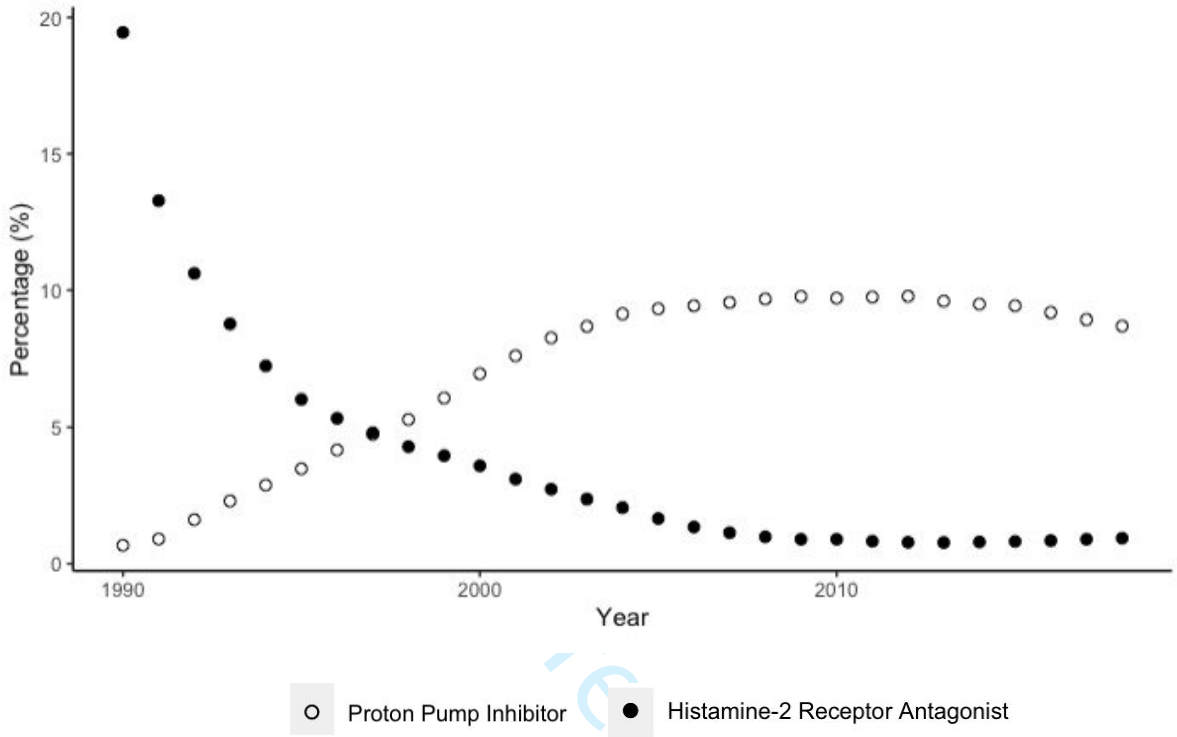
Supplementary Figure 3. Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use in New Users



Supplementary Figure 4. Prevalence of A) Proton Pump Inhibitor Prescriptions and B) Histamine-2 Receptor Antagonist Prescriptions Stratified by Individual Drug Type



Supplementary Figure 5. Prescribing Intensity of Proton Pump Inhibitors and Histamine-2 Receptor Antagonists



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9, 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9, 10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9, 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8, 9, 10
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9, 10
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	12, 13, 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, 13, 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Trends in Acid Suppressant Drug Prescriptions in Primary Care in the United Kingdom: A Population Based Cross Sectional Study

Devin Abrahami[1,2], Emily G. McDonald[3,4], Mireille Schnitzer[5], Laurent Azoulay[1,2,6]

[1] Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Canada

[2] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada

[3] Division of General Internal Medicine, Department of Medicine, McGill University Health Centre

[4] Division of Experimental Medicine, McGill University, Montreal Canada

[5] Faculty of Pharmacy, Université de Montréal, Montréal, Québec, Canada

[6] Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada

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Address for correspondence:

Dr Laurent Azoulay

Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital

3755 Cote Sainte-Catherine Road, H425.1

Montreal, Quebec, Canada H3T 1E2

Telephone: (514) 340-8222 Ext. 28396

Fax: (514) 340-7564

Email: laurent.azoulay@mcgill.ca

August 13, 2020

ABSTRACT

Objective: To examine proton pump inhibitors (PPI) and histamine-2 receptor antagonists (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 United Kingdom Clinical Practice Research Datalink.

Participants: Within a cohort of 14,242,329 patients registered in the Clinical Practice Research Datalink, 3,027,383 patients were prescribed at least one PPI or H2RA from January 1, 1990 to December 31, 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 Clinical Practice Research Datalink 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 0.2-14.2%, 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 five 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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Largest and most comprehensive study to date describing trends of acid suppressant drugs 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

Funding Statement: This study was funded by a Foundation Scheme Grant from the Canadian Institutes of Health Research (FDN-143328). The sponsor had no influence on design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. DA is the recipient of a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research. EGM receives Salary support from the Fonds de Recherche du Québec – Santé. MS holds a New Investigator Salary Award from the Canadian Institutes of Health Research and is the recipient of the Canadian Institutes of Health Research Canada Research Chair, tier 2. LA holds a Chercheur-Boursier Senior award from the Fonds de Recherche du Québec – Santé and is the recipient of a William Dawson Scholar Award from McGill University.

Competing Interests Statement: The authors have no conflicts of interest to disclose.

Author Contributions: 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 all 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.

Data Sharing: No additional data available.

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 United Kingdom (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 to 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 1988.[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 regards 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 week duration for most conditions, may be associated with certain adverse health outcomes. These include enteric infections such as *Clostridium difficile,* acute interstitial nephritis, hypomagnesemia and increased intestinal colonization 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 emphasize 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 utilization study was to determine the prescribing patterns of PPIs and H2RAs in UK primary care over a 29-year period.

METHODS

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]

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 19_119RA) and by the Research Ethics Board of the Jewish General Hospital. All authors had access to the study data and reviewed and approved the final manuscript.

Study Population

Using the CPRD, we identified a cohort of patients who were registered with a general practitioner from January 1, 1990 to December 31, 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 (January 1, 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 (December 31, 2018).

Exposure Definition

We identified all PPIs and H2RAs prescriptions within the study period using the British National Formulary (**Supplementary 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.

Statistical Analysis

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 either 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, 19-39, 40-59, ≥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 (i.e. PPI or H2RA) within the study period. To determine new use, individuals prescribed acid suppressants were required to have at least one year of medical history in the CPRD prior to their first prescription. Similarly, patients

in the CPRD were required to have at least one year of follow-up to contribute to the denominator. Individuals co-prescribed 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.

Indications for use

Indications for use among new users (i.e. 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 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 co-prescription 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 one year of follow-up.

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 [e.g. 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 based 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 five-year intervals and estimated incident rate ratios (IRRs) with 95% CIs using negative binomial regression, with log of follow-up time included as an offset variable.

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 (i.e. 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 version 9.4 (SAS institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

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.

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 to males (**Supplementary 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 (**Supplementary Figure 1**).

Figures 1 to **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 to 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 (**Supplementary Figures 2** and **3**), though the prevalence of H2RA use among new users was consistent across all age categories over the past decade (**Supplementary Figure 4**). Omeprazole was the most commonly prescribed PPI during the study period, followed by lansoprazole (**Supplementary 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 (**Supplementary 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 (**Supplementary 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 (**Supplementary Table 4**). In contrast, H2RA yearly prescribing intensity decreased from 1990 to 2009, and has begun to increase slightly over the past five years.

Within new users of PPIs (n=1,699,837) the median duration of the first treatment course was 144 (interquartile range [IQR]: 59 to 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 (2.1%) 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=385,988) was 279 (IQR: 61 to 1,645) 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. **Supplementary 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 to 560) and 149 (38 to 1,479) days, respectively. When a grace period of 60 days was used, the median (IQR) duration of PPI use was 231 (89 to 1,097) days, and H2RA use was 381 (91 to 1,785) 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 one-year recommended duration,[16] and12.6% 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 (**Supplementary Figures 7** to **10**).

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%, 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 five years.

The overall high prevalence of PPI use in the UK is consistent with a utilization study of PPIs using CPRD data, but whose follow-up period ended at the end of 2014.[11]. Importantly, our study further contextualizes 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 United States 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 hypomagnesemia.[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 one 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 hospitalization 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 five years. Given that PPIs are associated certain adverse effects not attributed to H2RAs, H2RAs remain a valuable treatment option for individuals with gastric conditions.

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Table 1. Characteristics of Individuals Newly Prescribed Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Characteristic	Proton Pump Inhibitors †	Histamine-2 Receptor Antagonists ‡
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 (interquartile range) duration of first treatment course for PPI users and H2RA users was 144 (59 to 870) days and 279 (61 to 1,645) days, respectively.

FIGURE LEGENDS

Figure 1 Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

Figure 2 Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

Figure 3 Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use

Figure 4 Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators

Figure 1

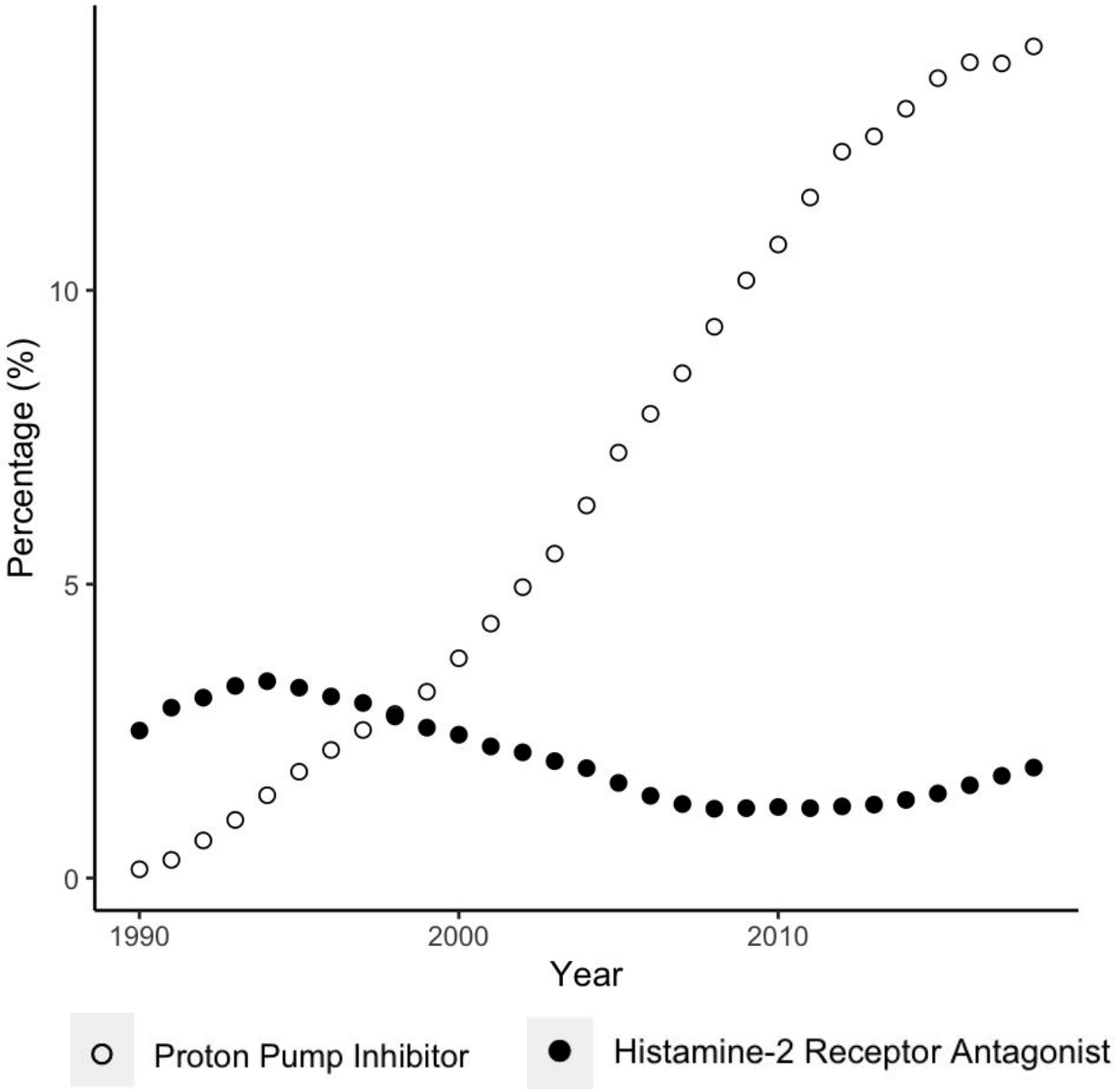

Percentage (%)
10
5
0
1990
2000
2010
Year
Proton Pump Inhibitor
Histamine-2 Receptor Antagonist

Figure 2

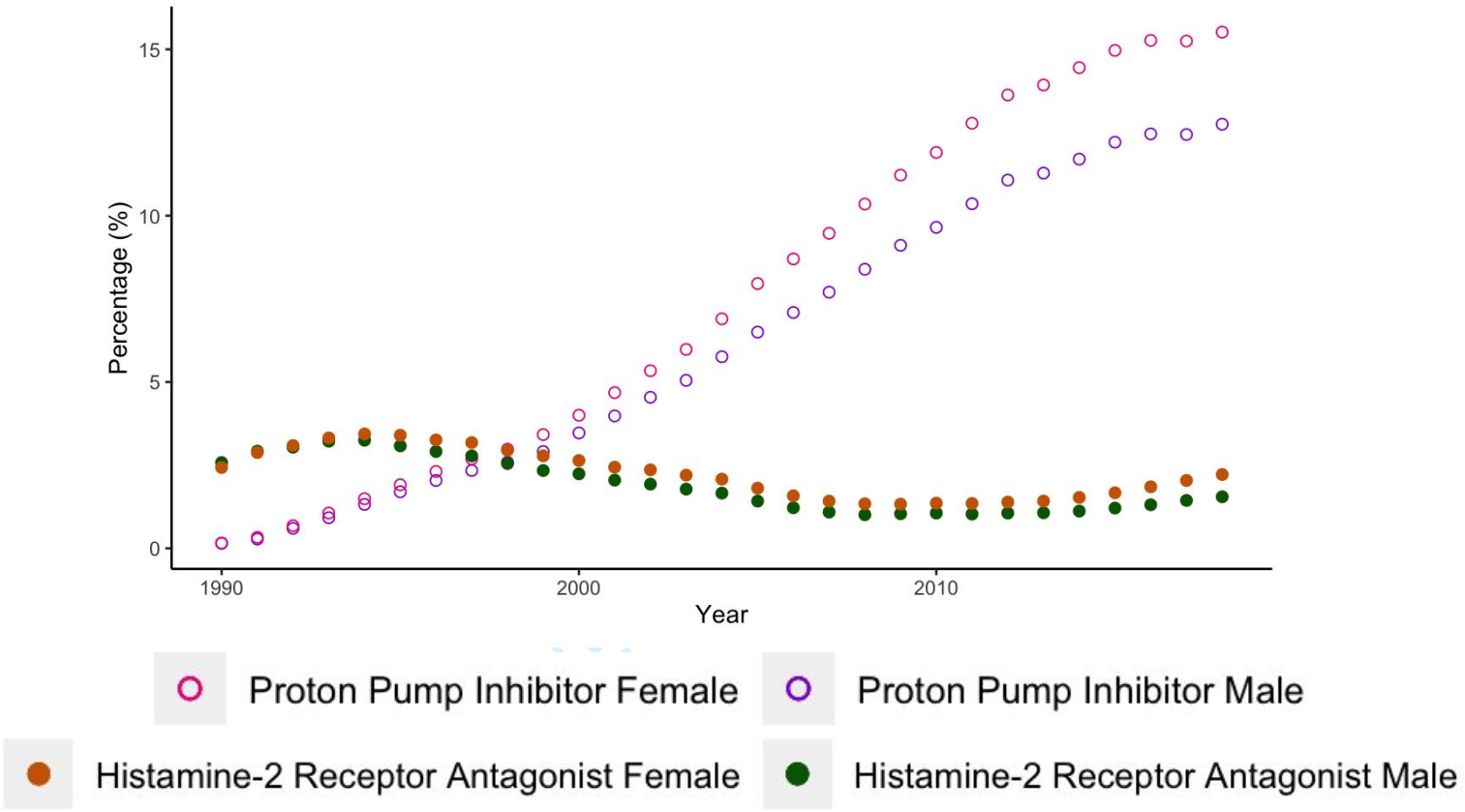


Figure 3

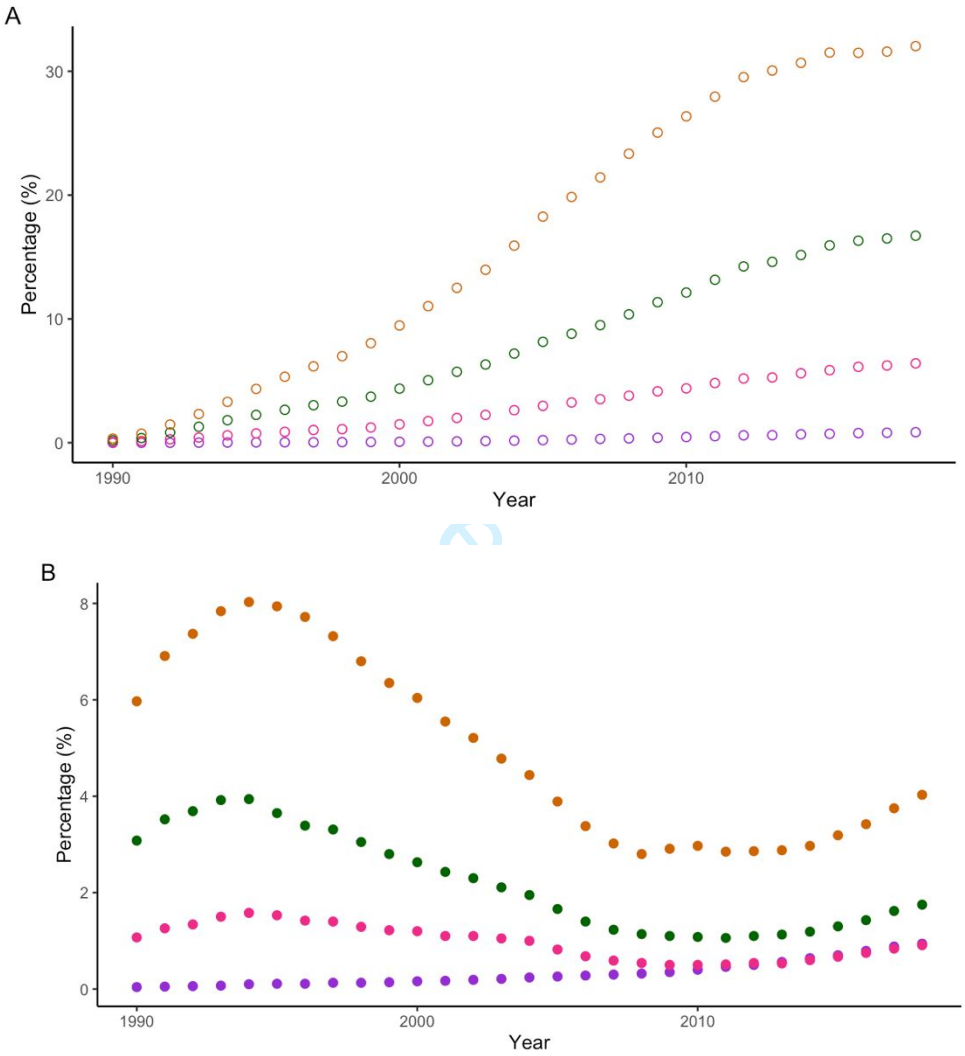

A
Percentage (%)
0
10
20
30
1990
2000
2010
Year
B
Percentage (%)
0
2
4
6
8
1990
2000
2010
Year
Proton Pump Inhibitor:
<18 years old
18 to 39 years old
40 to 59 years old
60 years old and above
Histamine-2 Receptor Antagonist:
<18 years old
18 to 39 years old
40 to 59 years old
60 years old and above

Figure 4

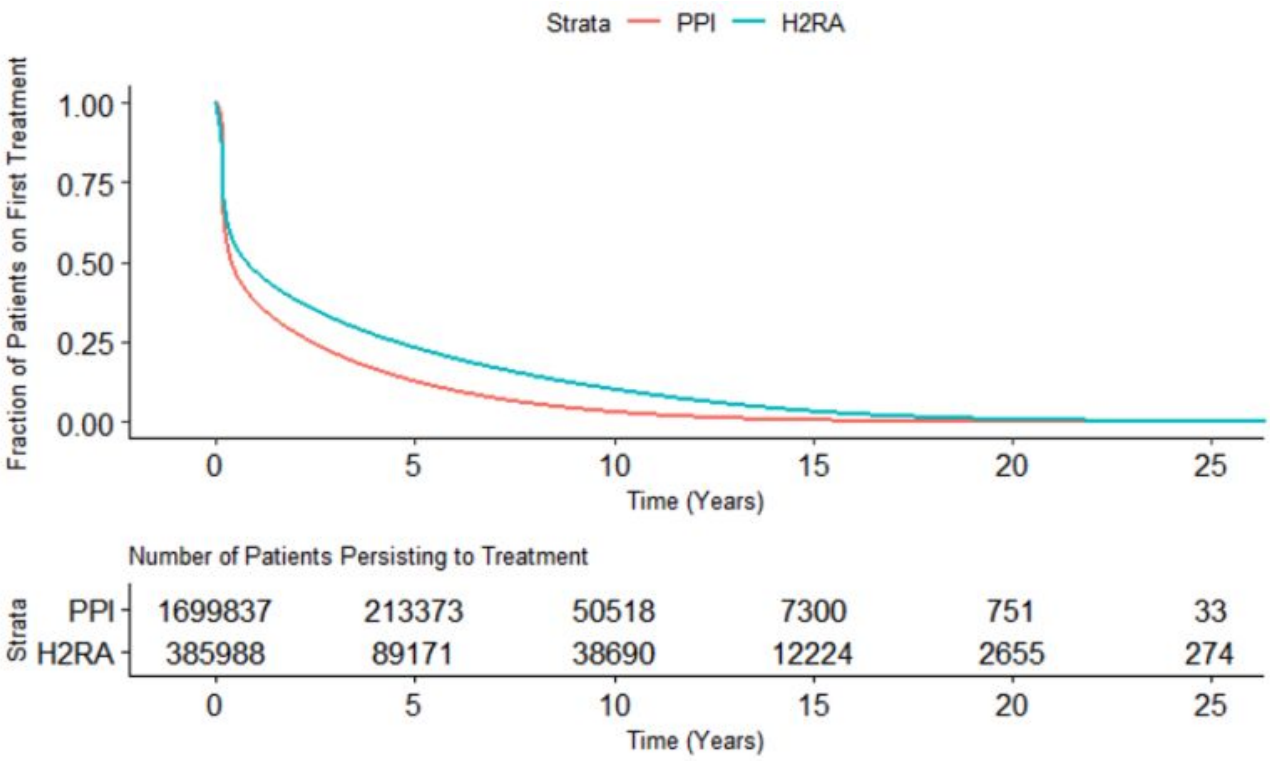


Table of Contents

Supplementary Table 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
01030800/05011100/05040200/ 05040300/05040400/07020251	Helicobacter Pylori Eradication/Metronidazole And Tinidazole/Amoebicides/Trichomonacides/ Antigiardial Drugs/Preparations For Other Vaginal Infections
1030500	Proton Pump Inhibitors

Supplementary Table 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 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. 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.

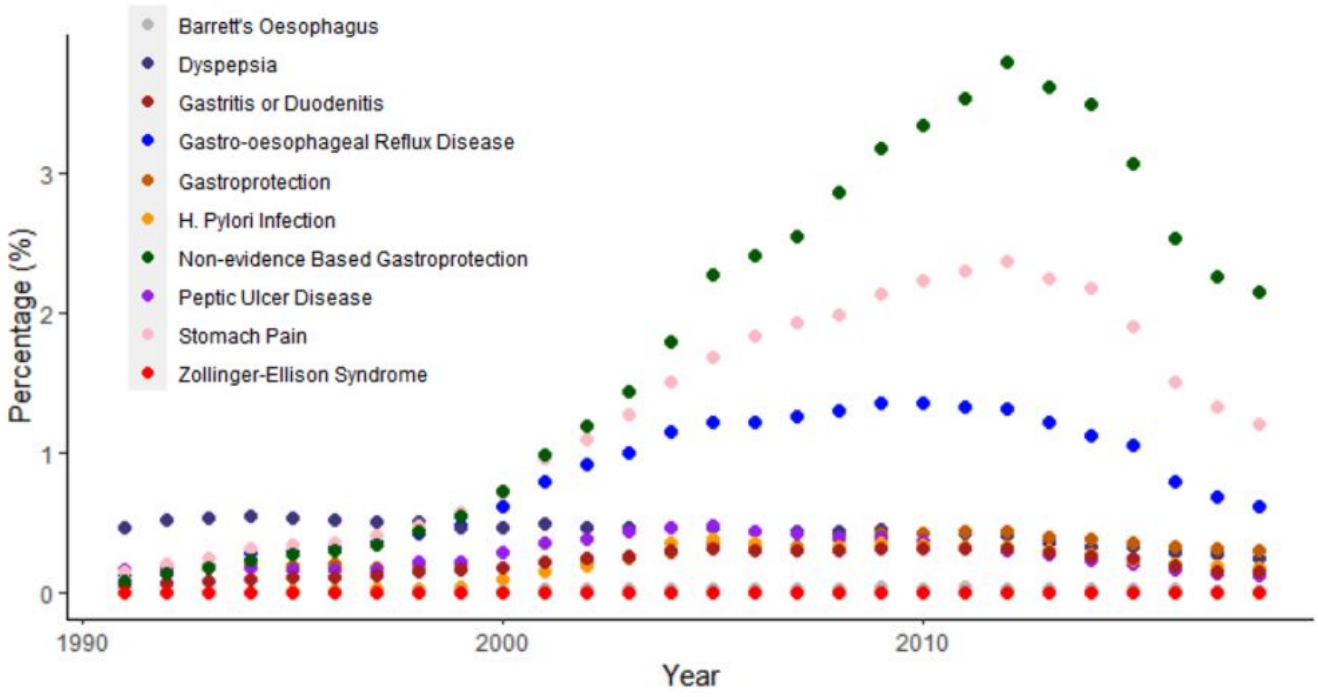
Supplementary Table 5. Reason for Discontinuation of Initial Acid Suppressant Treatment Course Under Alternate Grace Periods

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)

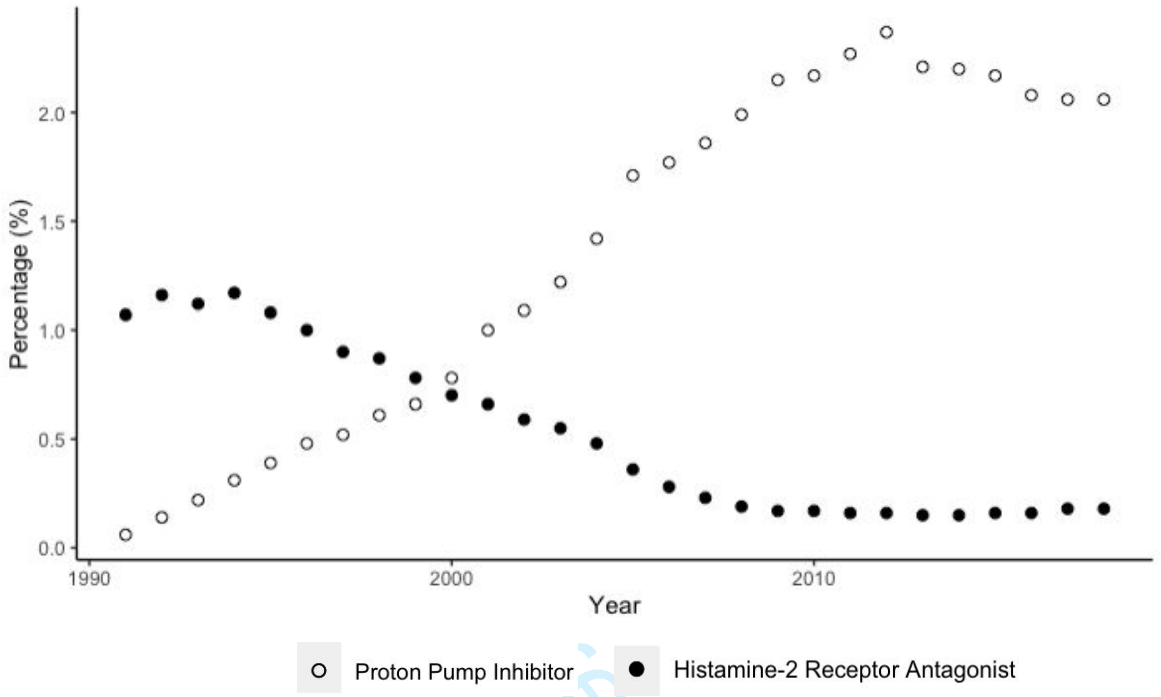
† median (interquartile range) duration of first treatment course for PPI users and H2RA users was 66 (36 to 560) and 149 (38 to 1,479) days, respectively.

‡ 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.

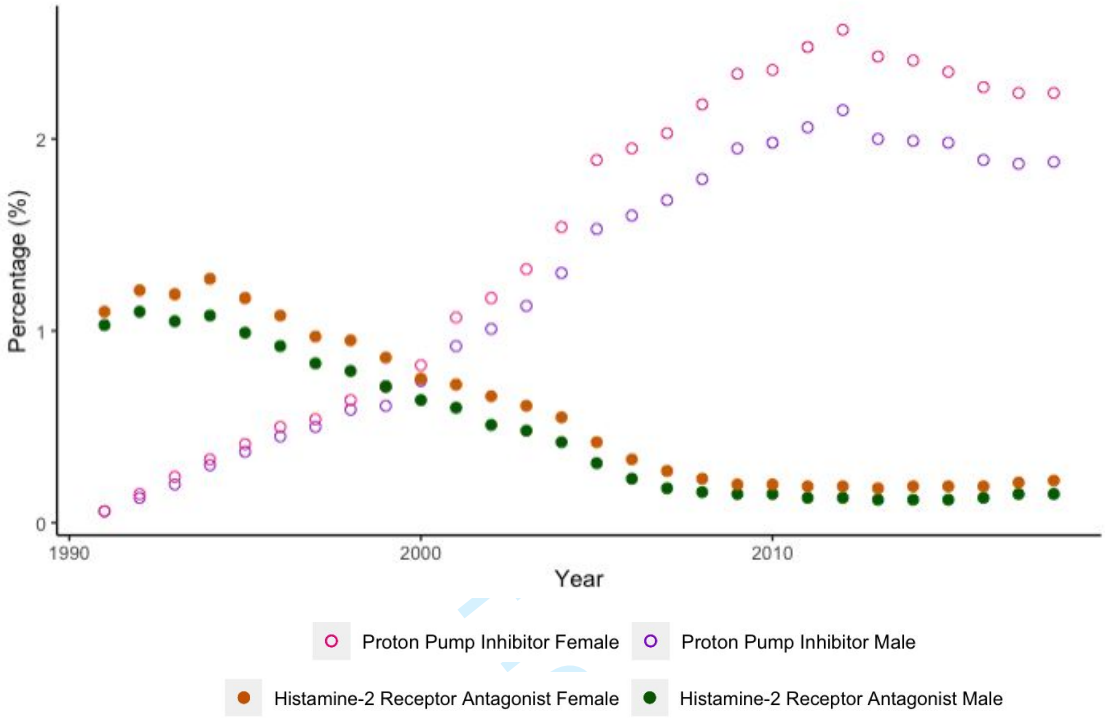
Supplementary Figure 1. Incidence of Indications for Proton Pump Inhibitors and Histamine-2 Receptor Antagonists Over Time



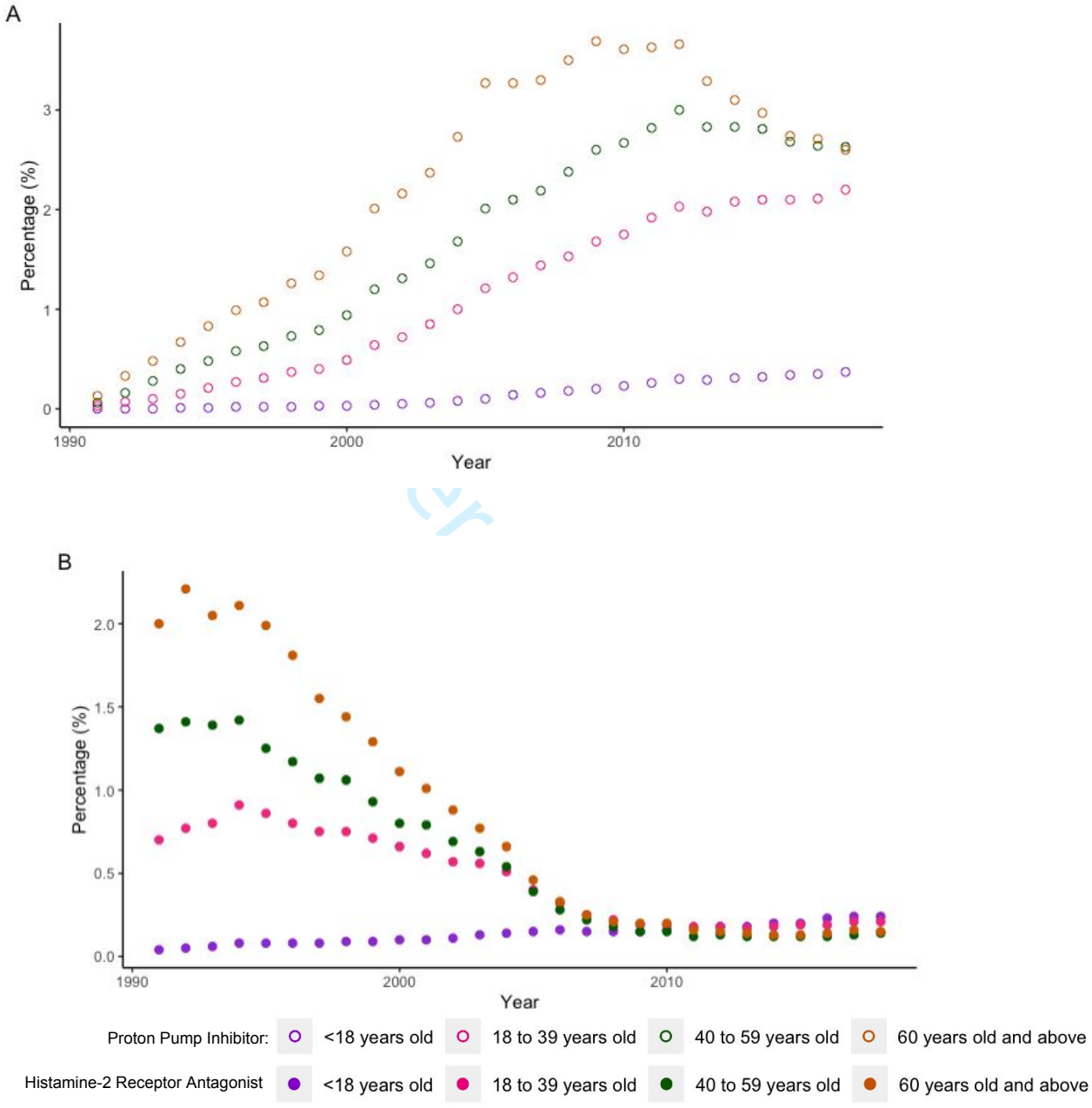
Supplementary Figure 2. Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users



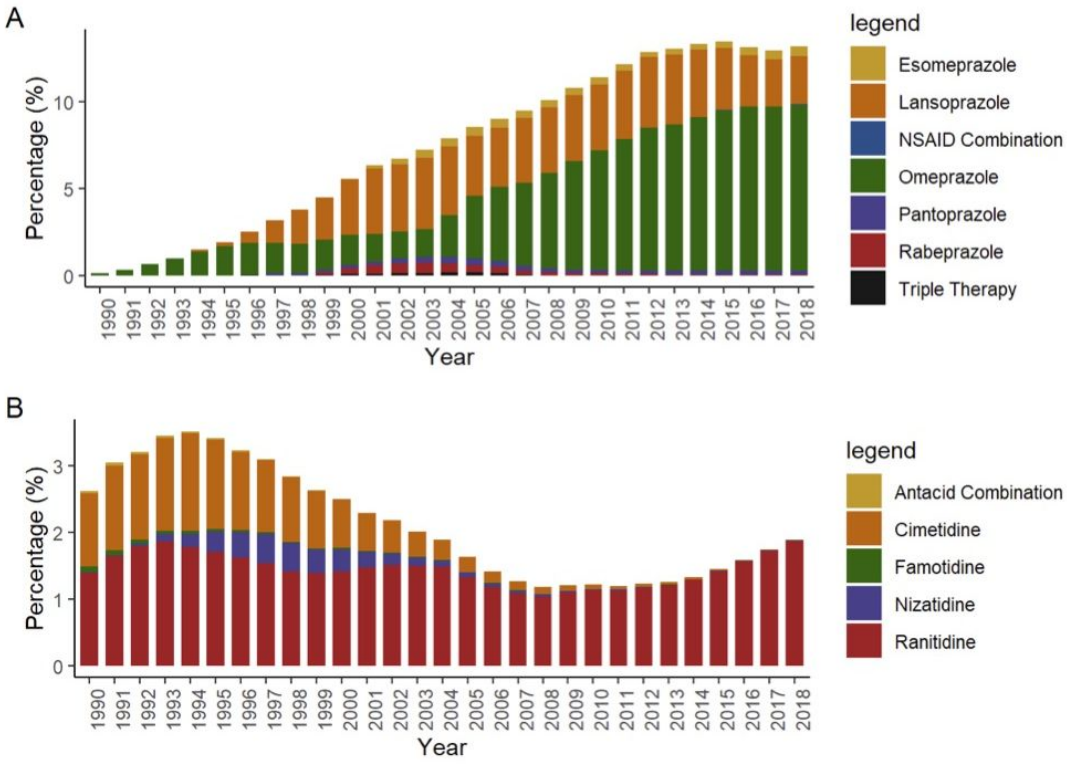
Supplementary Figure 3. Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users



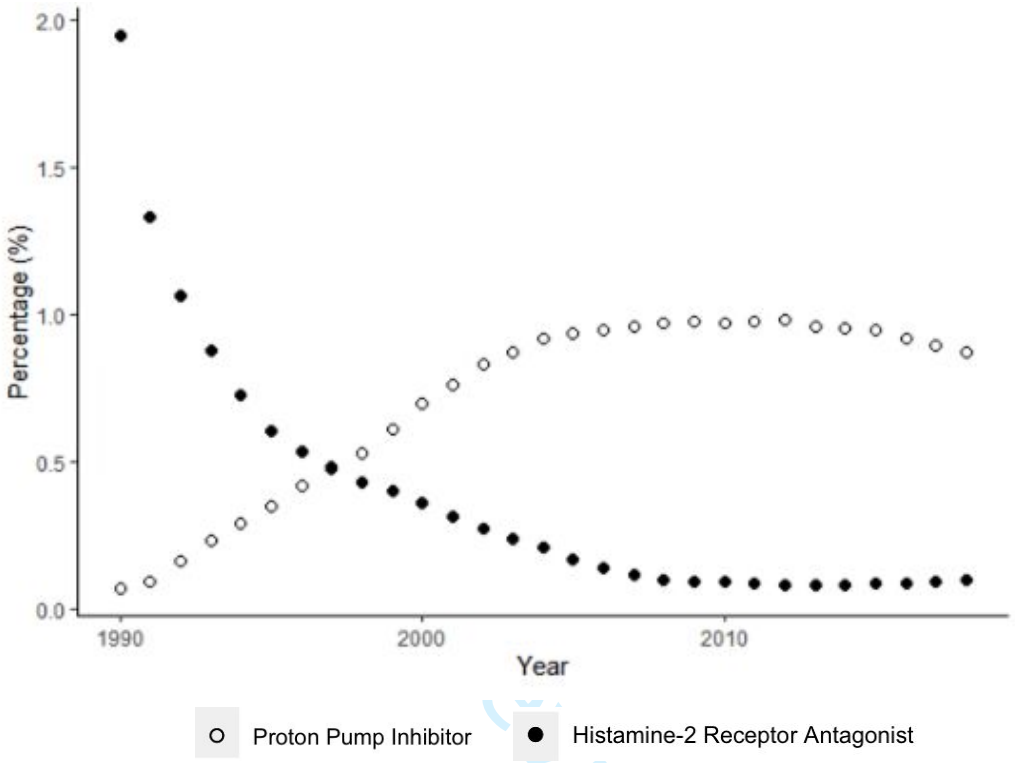
Supplementary Figure 4. Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use in New Users



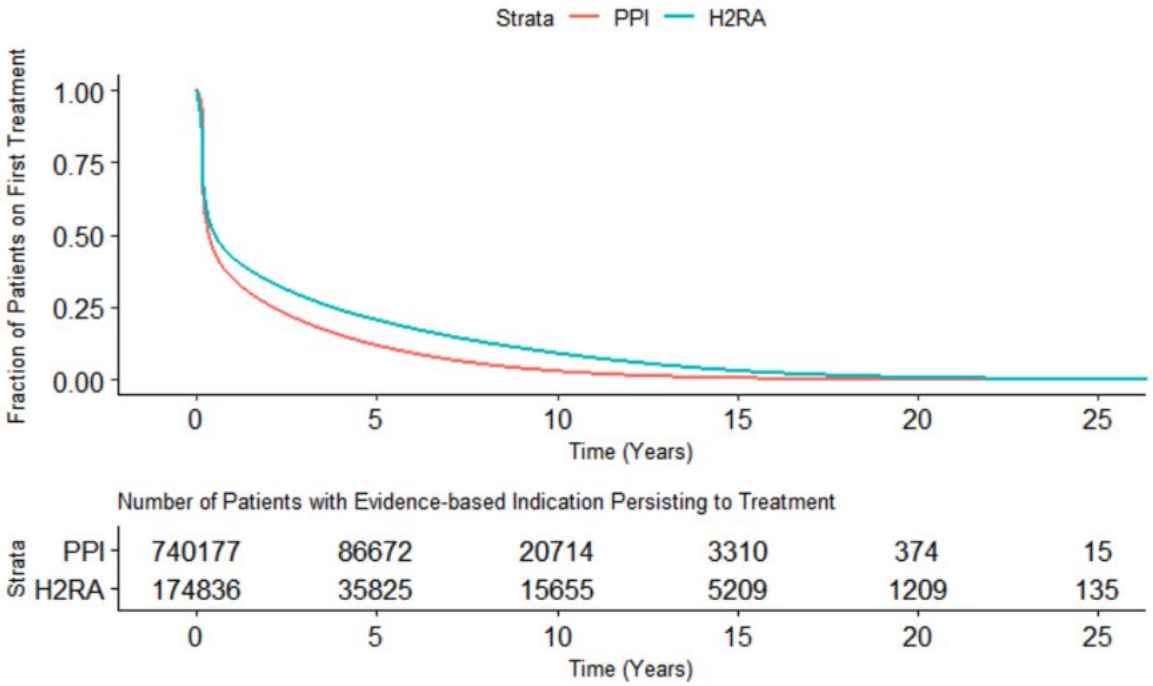
Supplementary Figure 5. Prevalence of A) Proton Pump Inhibitor Prescriptions and B) Histamine-2 Receptor Antagonist Prescriptions Stratified by Individual Drug Type



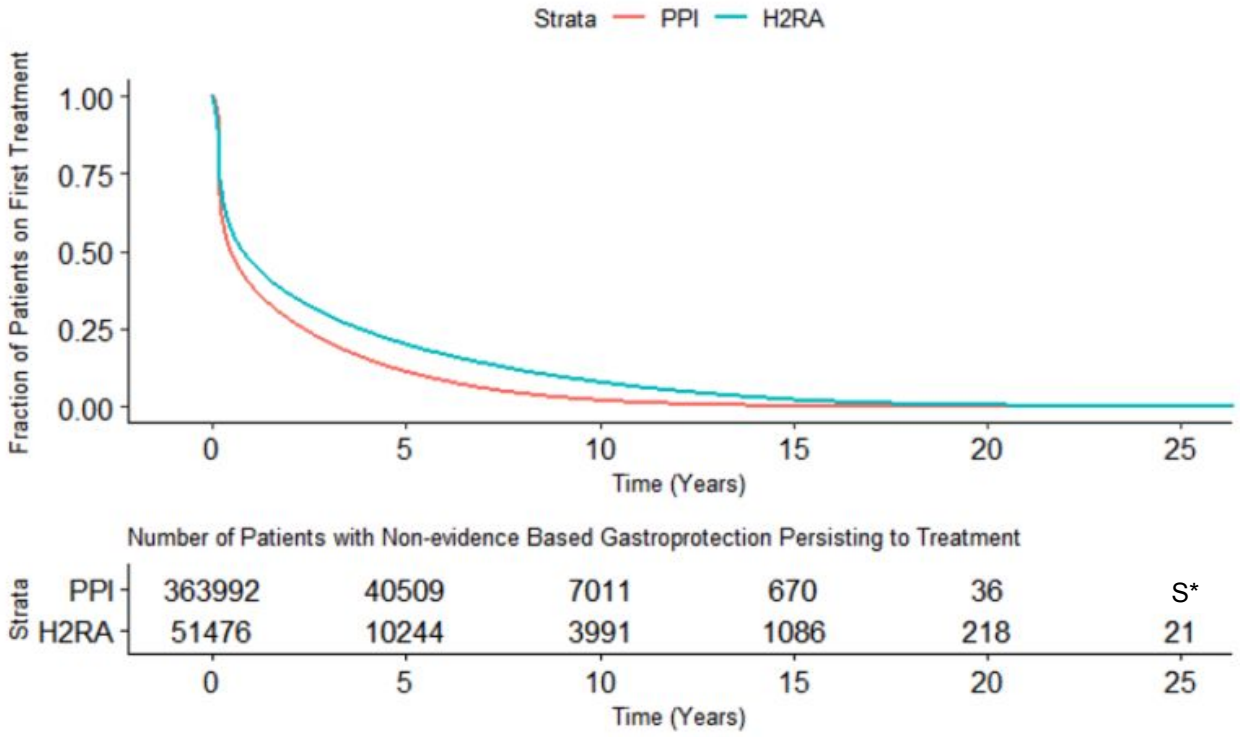
Supplementary Figure 6. Prescribing Intensity of Proton Pump Inhibitors and Histamine-2 Receptor Antagonists



Supplementary Figure 7. Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Evidence-based Indications for Use

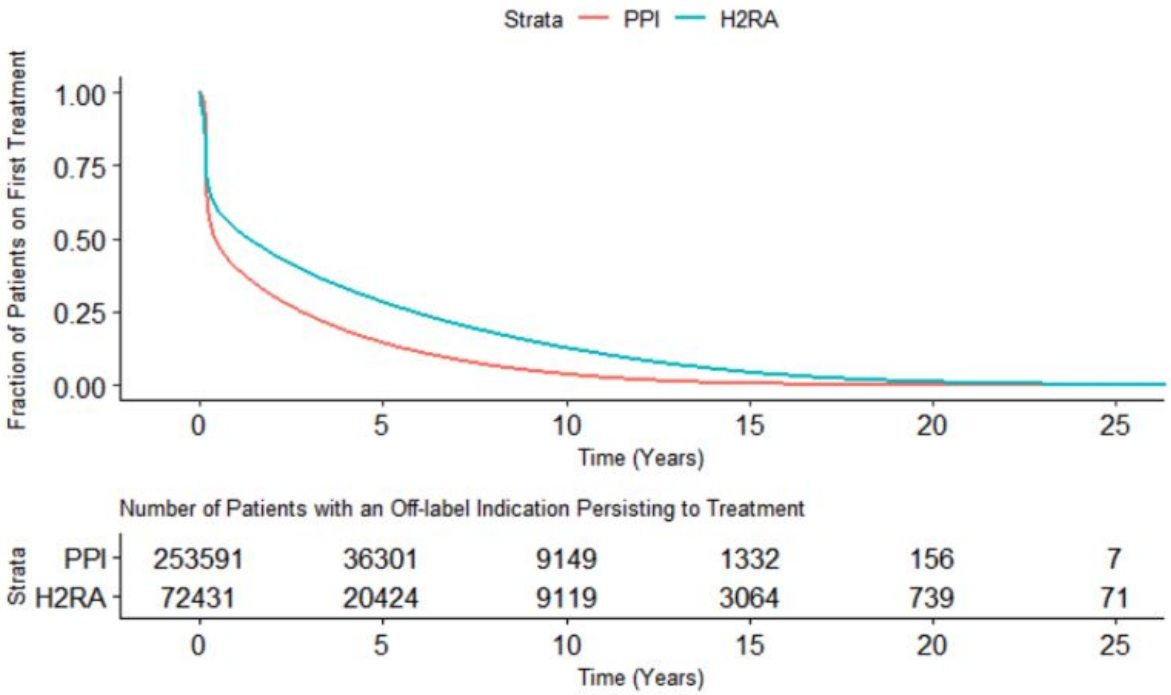


Supplementary Figure 8. Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Non-evidence Based Gastroprotection

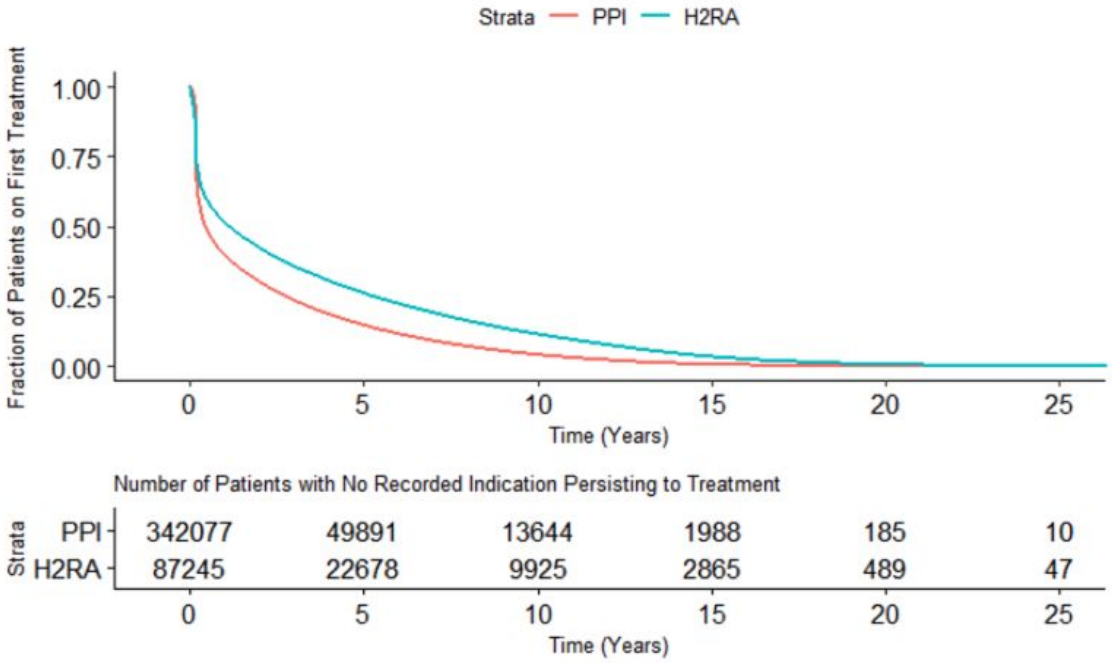


S* Numbers <5 are not displayed, as per the confidentially practices of the Clinical Practice Research Datalink.

Supplementary Figure 9. Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Off-label Indications for Use



Supplementary Figure 10. Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with No Recorded Indication for Use



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Trends in Acid Suppressant Drug Prescriptions in Primary Care in the United Kingdom: A Population Based Cross Sectional Study

Devin Abrahami[1,2], Emily G. McDonald[3,4], Mireille Schnitzer[5], Laurent Azoulay[1,2,6]

[1] Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Canada

[2] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada

[3] Division of General Internal Medicine, Department of Medicine, McGill University Health Centre

[4] Division of Experimental Medicine, McGill University, Montreal Canada

[5] Faculty of Pharmacy, Université de Montréal, Montréal, Québec, Canada

[6] Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada

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Address for correspondence:

Dr Laurent Azoulay

Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital

3755 Cote Sainte-Catherine Road, H425.1

Montreal, Quebec, Canada H3T 1E2

Telephone: (514) 340-8222 Ext. 28396

Fax: (514) 340-7564

Email: laurent.azoulay@mcgill.ca

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ABSTRACT

Objective: To examine proton pump inhibitors (PPI) and histamine-2 receptor antagonists (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 United Kingdom Clinical Practice Research Datalink.

Participants: Within a cohort of 14,242,329 patients registered in the Clinical Practice Research Datalink, 3,027,383 patients were prescribed at least one PPI or H2RA from January 1, 1990 to December 31, 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 Clinical Practice Research Datalink 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 0.2-14.2%, 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 five 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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Largest and most comprehensive study to date describing trends of acid suppressant drugs 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

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Competing Interests Statement: The authors have no conflicts of interest to disclose.

Author Contributions: 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 all 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.

Data Sharing: No data are available.

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 United Kingdom (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 to 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 1988.[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 regards 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 week duration for most conditions, may be associated with certain adverse health outcomes. These include enteric infections such as *Clostridium difficile,* acute interstitial nephritis, hypomagnesemia and increased intestinal colonization 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 emphasize 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 utilization study was to determine the prescribing patterns of PPIs and H2RAs in UK primary care over a 29-year period.

METHODS

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]

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 19_119RA) and by the Research Ethics Board of the Jewish General Hospital. All authors had access to the study data and reviewed and approved the final manuscript.

Study Population

Using the CPRD, we identified a cohort of patients who were registered with a general practitioner from January 1, 1990 to December 31, 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 (January 1, 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 (December 31, 2018).

Exposure Definition

We identified all PPIs and H2RAs prescriptions within the study period using the British National Formulary (**Supplementary 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.

Statistical Analysis

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 either 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, 19-39, 40-59, ≥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 (i.e. PPI or H2RA) within the study period. To determine new use, individuals prescribed acid suppressants were required to have at least one year of medical history in the CPRD prior to their first prescription. Similarly, patients

in the CPRD were required to have at least one year of follow-up to contribute to the denominator. Individuals co-prescribed 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.

Indications for use

Indications for use among new users (i.e. 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 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 co-prescription 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 one year of follow-up.

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 [e.g. 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 based 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 five-year intervals and estimated incident rate ratios (IRRs) with 95% CIs using negative binomial regression, with log of follow-up time included as an offset variable.

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 (i.e. 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 version 9.4 (SAS institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

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.

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 to males (**Supplementary 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 (**Supplementary Figure 1**).

Figures 1 to **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 to 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 (**Supplementary Figures 2** and **3**), though the prevalence of H2RA use among new users was consistent across all age categories over the past decade (**Supplementary Figure 4**). Omeprazole was the most commonly prescribed PPI during the study period, followed by lansoprazole (**Supplementary 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 (**Supplementary 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 (**Supplementary 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 (**Supplementary Table 4**). In contrast, H2RA yearly prescribing intensity decreased from 1990 to 2009, and has begun to increase slightly over the past five years.

Within new users of PPIs (n=1,699,837) the median duration of the first treatment course was 144 (interquartile range [IQR]: 59 to 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 (2.1%) 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=385,988) was 279 (IQR: 61 to 1,645) 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. **Supplementary 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 to 560) and 149 (38 to 1,479) days, respectively. When a grace period of 60 days was used, the median (IQR) duration of PPI use was 231 (89 to 1,097) days, and H2RA use was 381 (91 to 1,785) 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 one-year recommended duration,[16] and12.6% 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 (**Supplementary Figures 7** to **10**).

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%, 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 five years.

The overall high prevalence of PPI use in the UK is consistent with a utilization study of PPIs using CPRD data, but whose follow-up period ended at the end of 2014.[11]. Importantly, our study further contextualizes 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 United States 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 hypomagnesemia.[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 one 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 hospitalization 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 five years. Given that PPIs are associated certain adverse effects not attributed to H2RAs, H2RAs remain a valuable treatment option for individuals with gastric conditions.

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Table 1. Characteristics of Individuals Newly Prescribed Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Characteristic	Proton Pump Inhibitors †	Histamine-2 Receptor Antagonists ‡
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 (interquartile range) duration of first treatment course for PPI users and H2RA users was 144 (59 to 870) days and 279 (61 to 1,645) days, respectively.

FIGURE LEGENDS

Figure 1 Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

Figure 2 Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

Figure 3 Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use

Figure 4 Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators

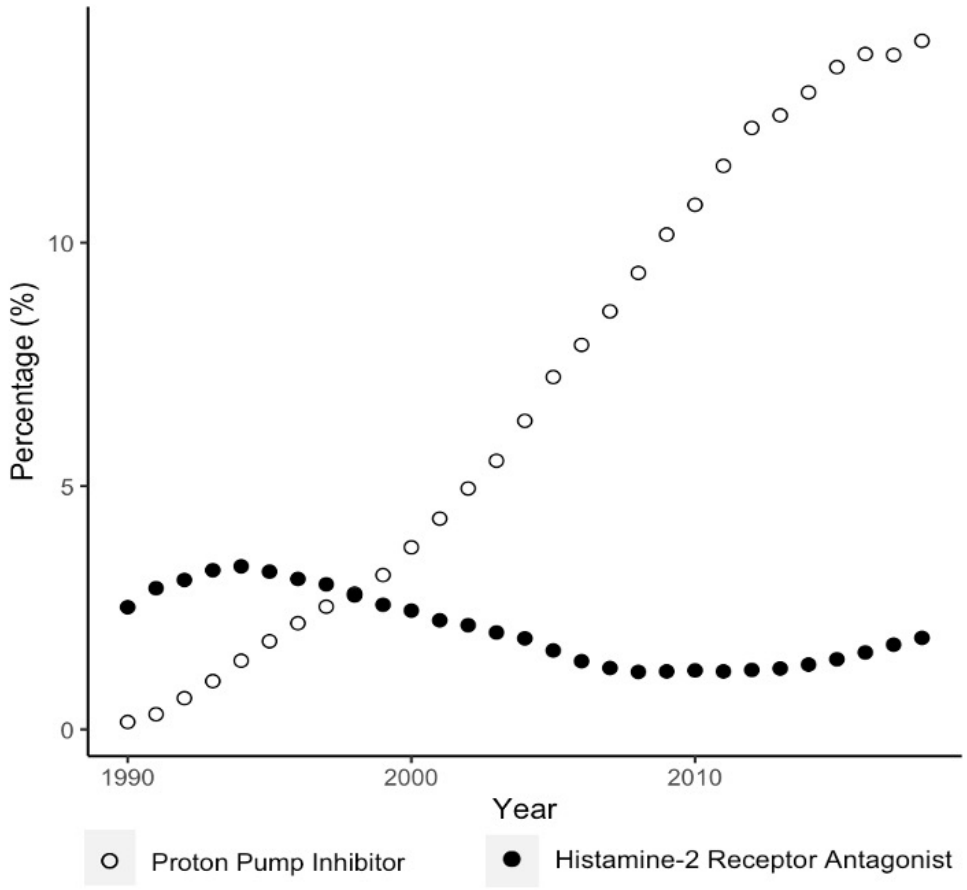


Figure 1
Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

128x116mm (144 x 144 DPI)

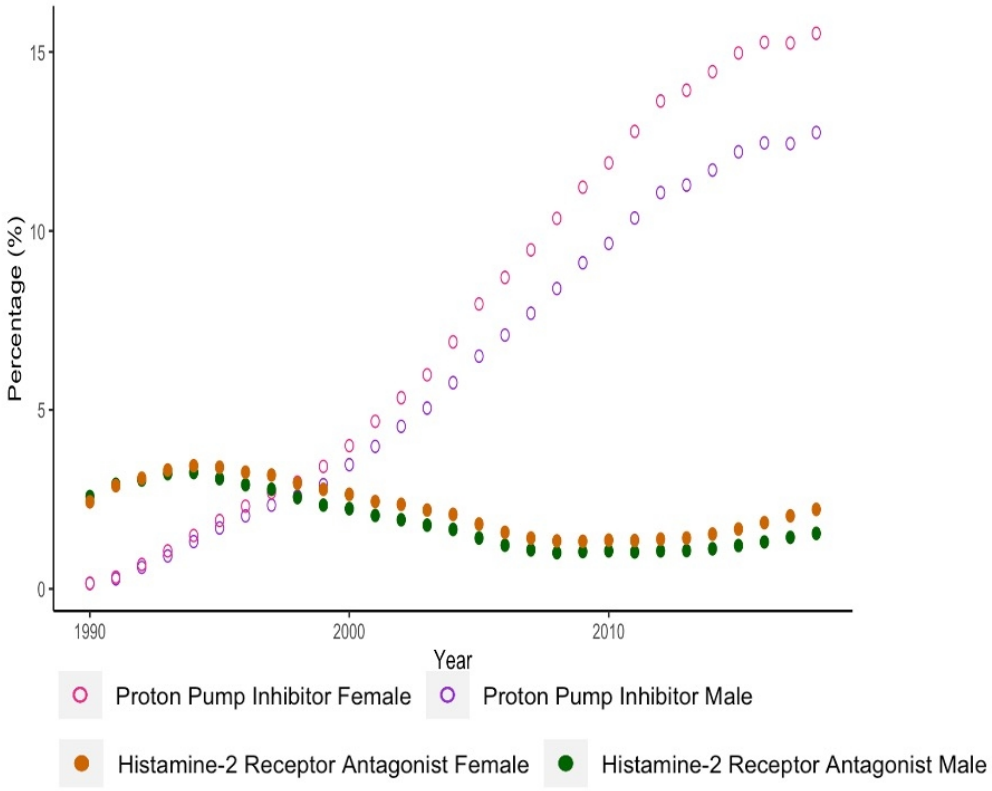


Figure 2
Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use

158x129mm (144 x 144 DPI)

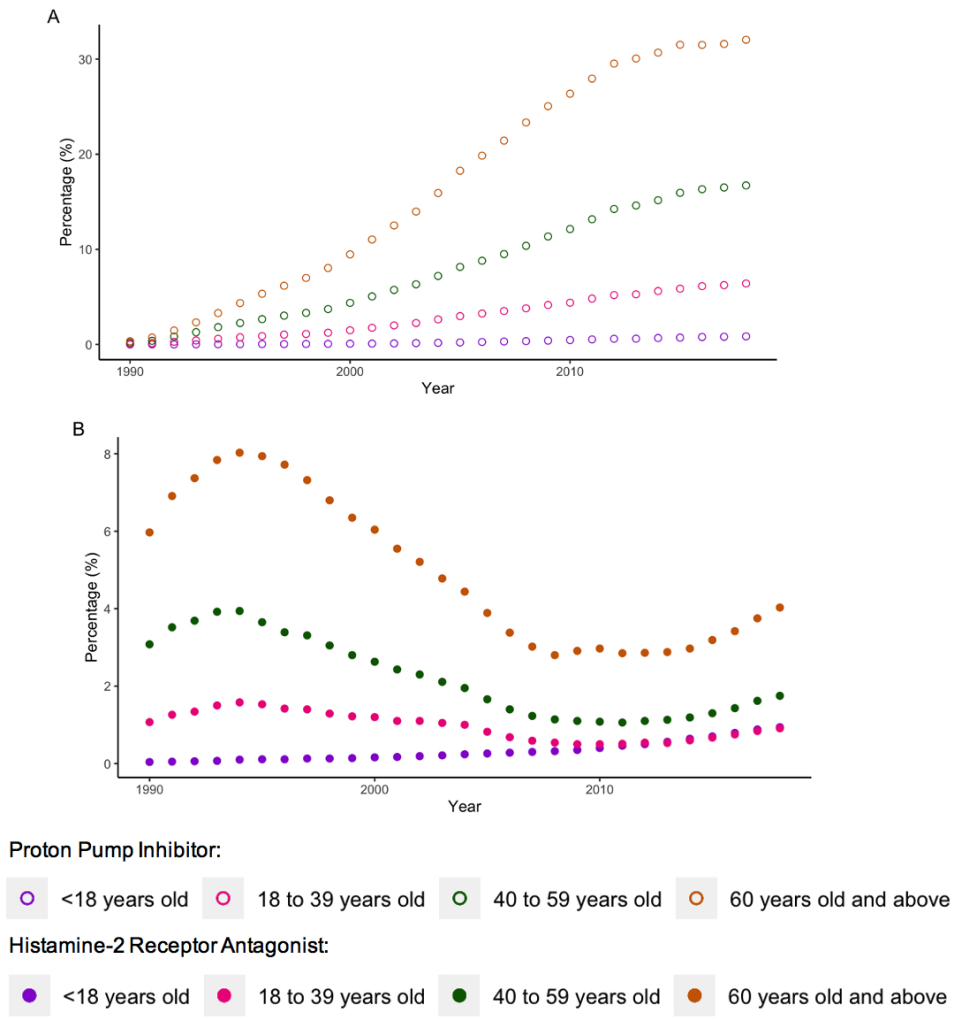


Figure 3
Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use

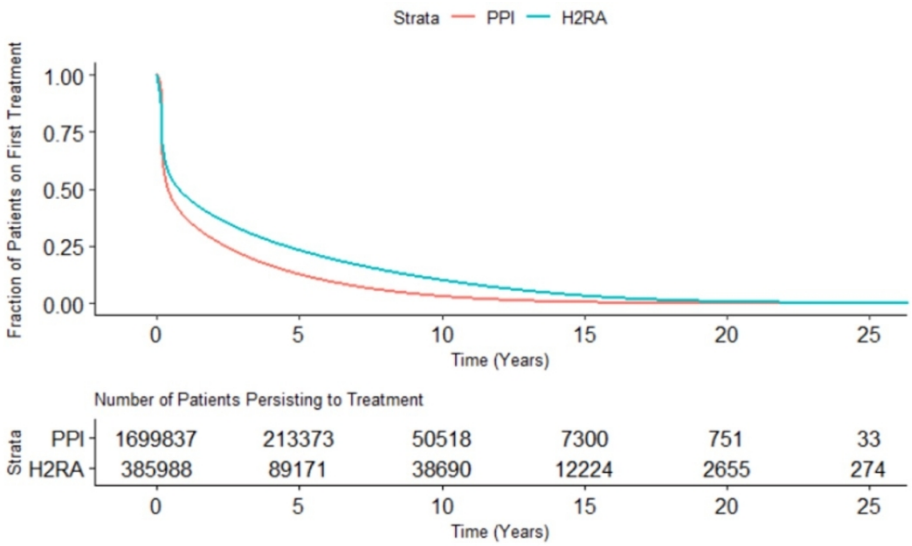


Figure 4
Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators

245x136mm (144 x 144 DPI)

Table of Contents

Supplementary Table 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 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 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. 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.

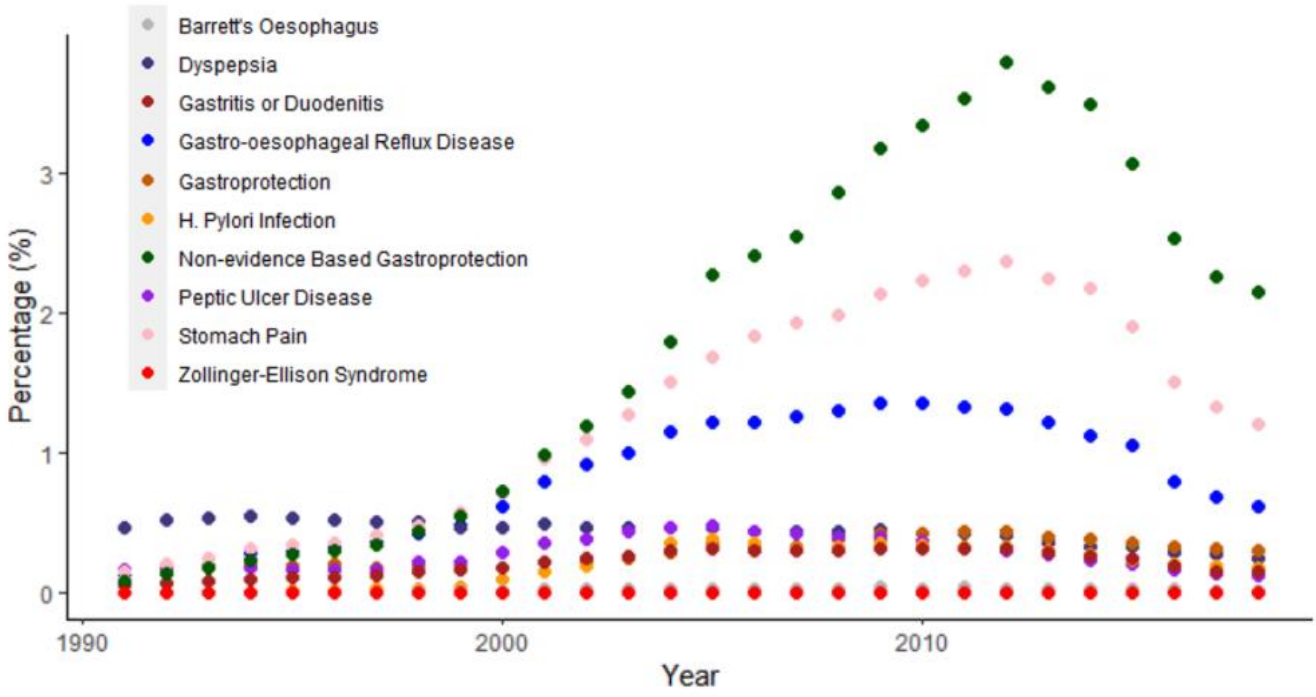
Supplementary Table 5. Reason for Discontinuation of Initial Acid Suppressant Treatment Course Under Alternate Grace Periods

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)

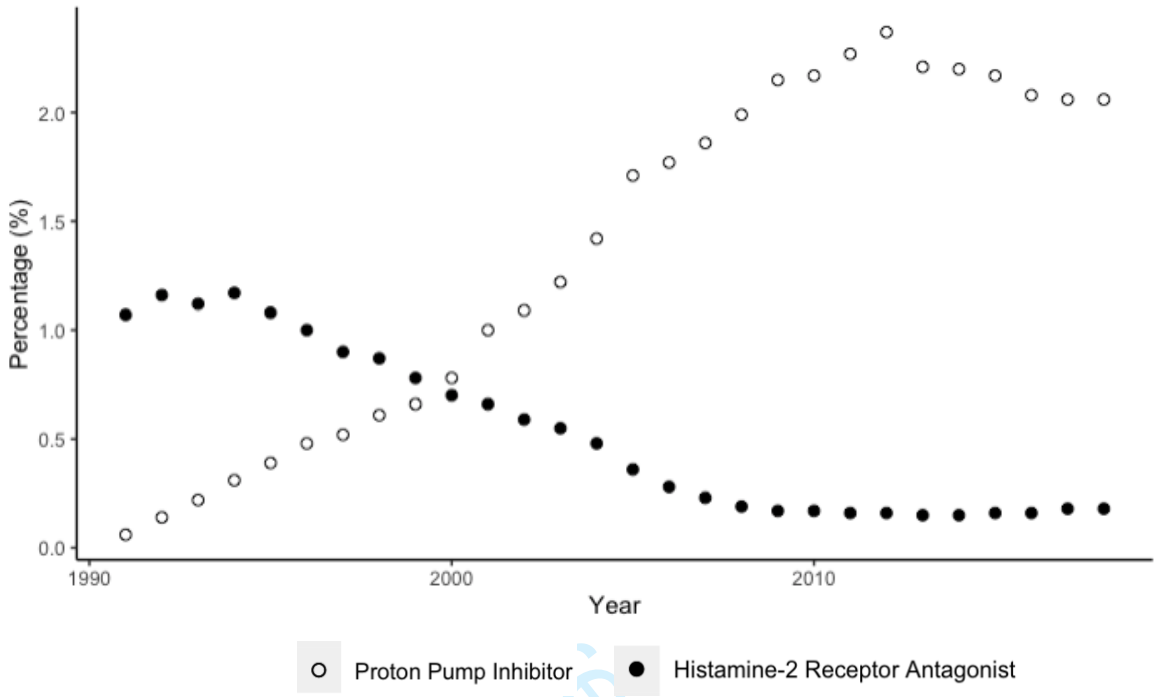
† median (interquartile range) duration of first treatment course for PPI users and H2RA users was 66 (36 to 560) and 149 (38 to 1,479) days, respectively.

‡ 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.

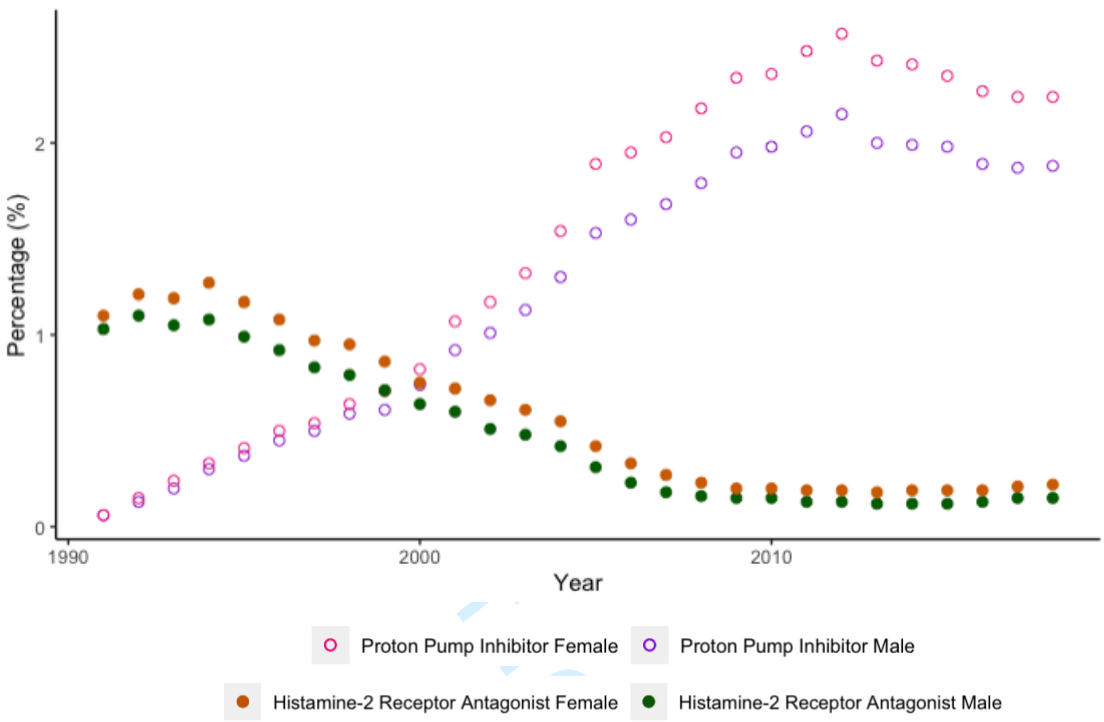
Supplementary Figure 1. Incidence of Indications for Proton Pump Inhibitors and Histamine-2 Receptor Antagonists Over Time



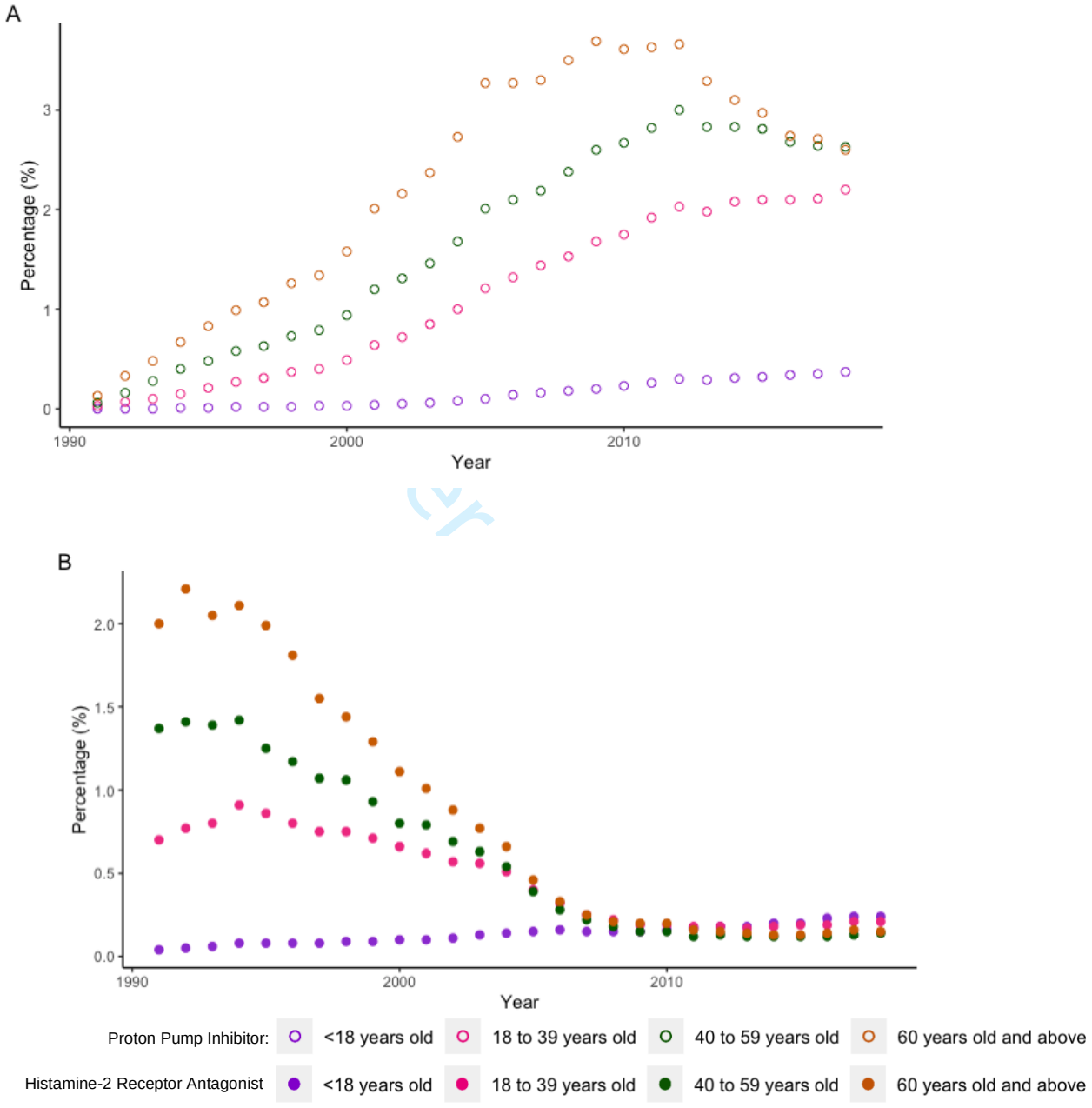
Supplementary Figure 2. Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users



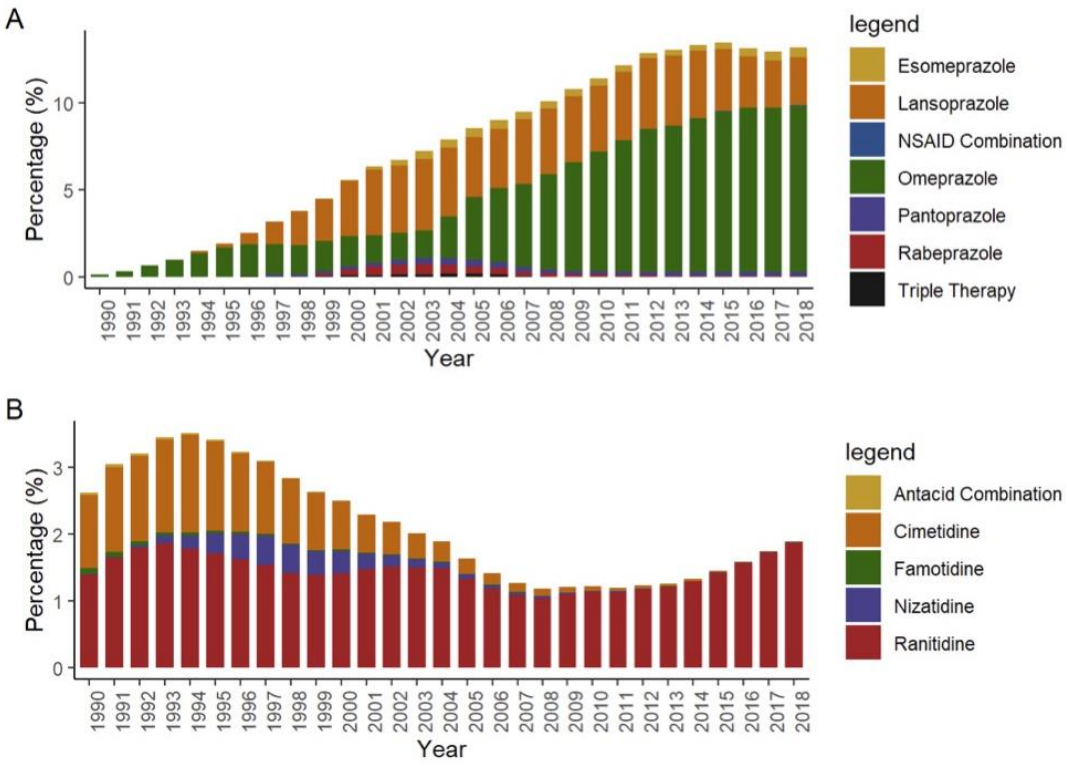
Supplementary Figure 3. Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users



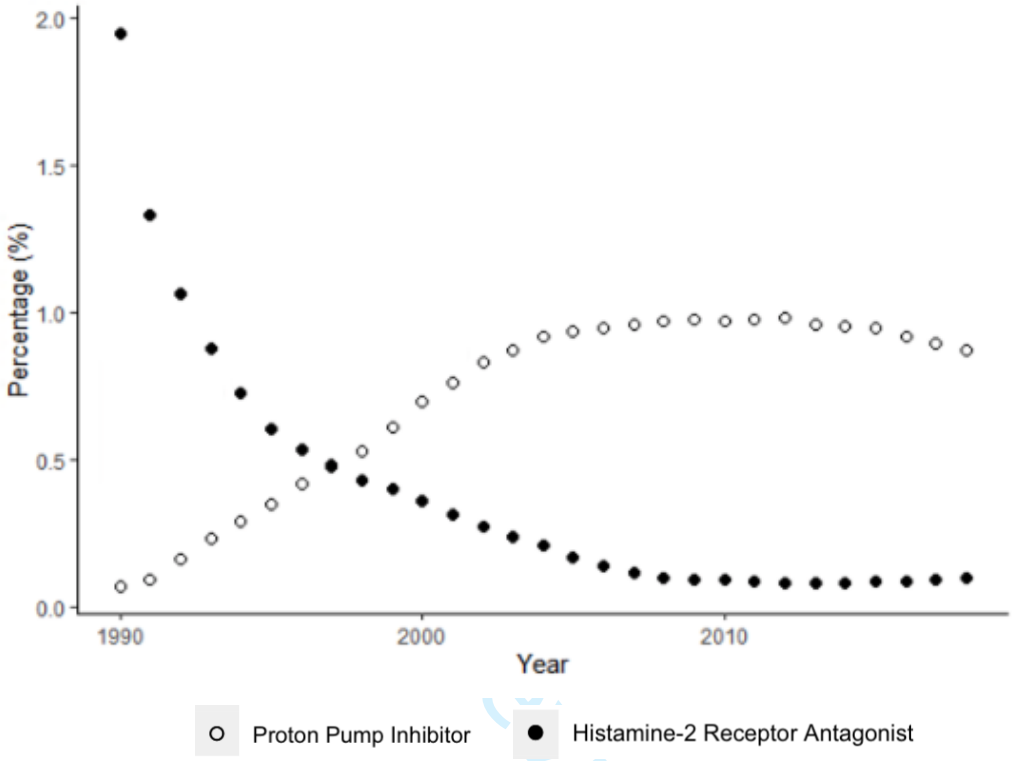
Supplementary Figure 4. Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use in New Users



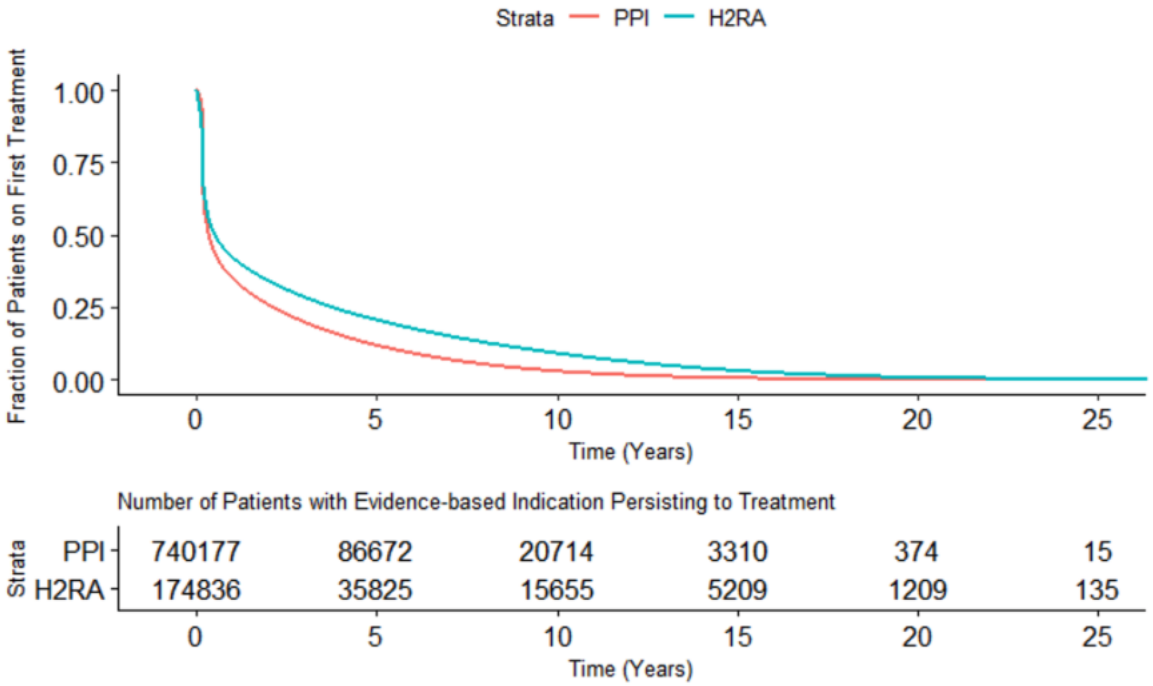
Supplementary Figure 5. Prevalence of A) Proton Pump Inhibitor Prescriptions and B) Histamine-2 Receptor Antagonist Prescriptions Stratified by Individual Drug Type



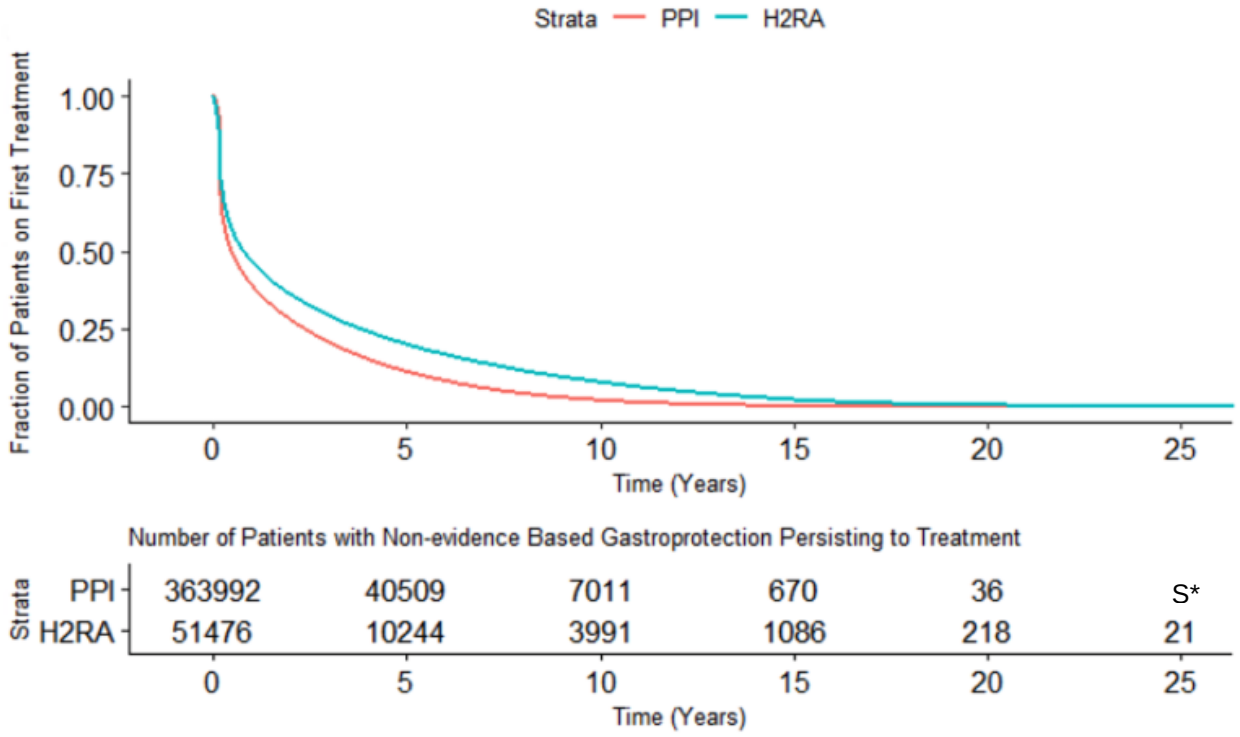
Supplementary Figure 6. Prescribing Intensity of Proton Pump Inhibitors and Histamine-2 Receptor Antagonists



Supplementary Figure 7. Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Evidence-based Indications for Use

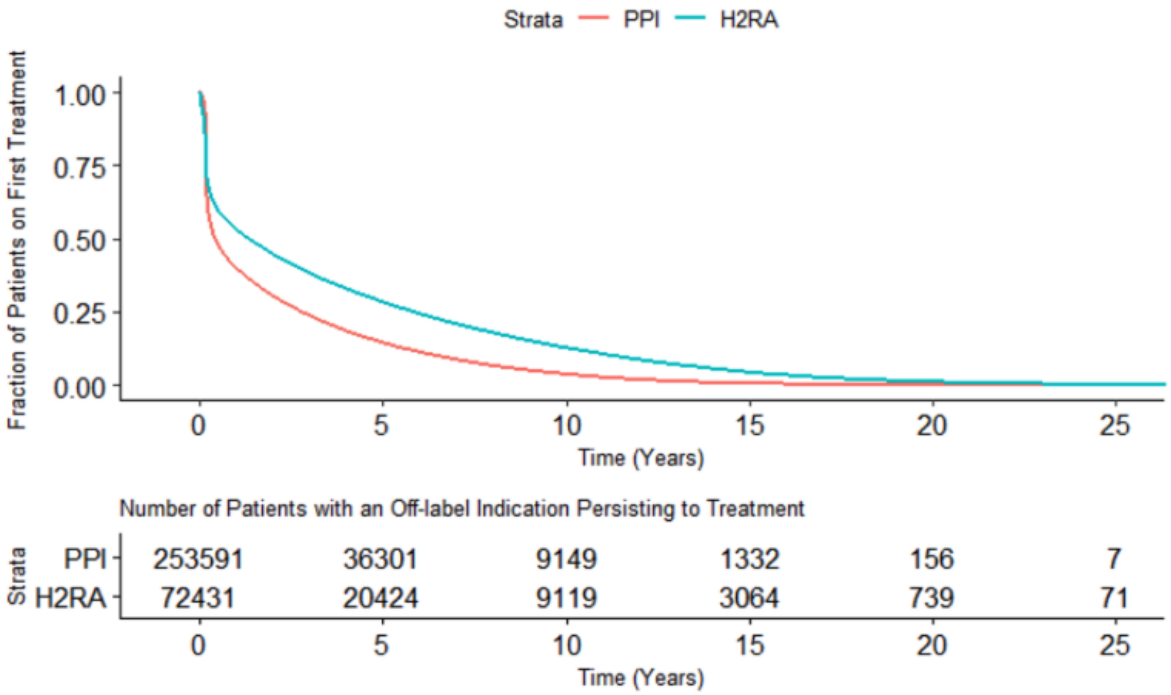


Supplementary Figure 8. Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Non-evidence Based Gastroprotection

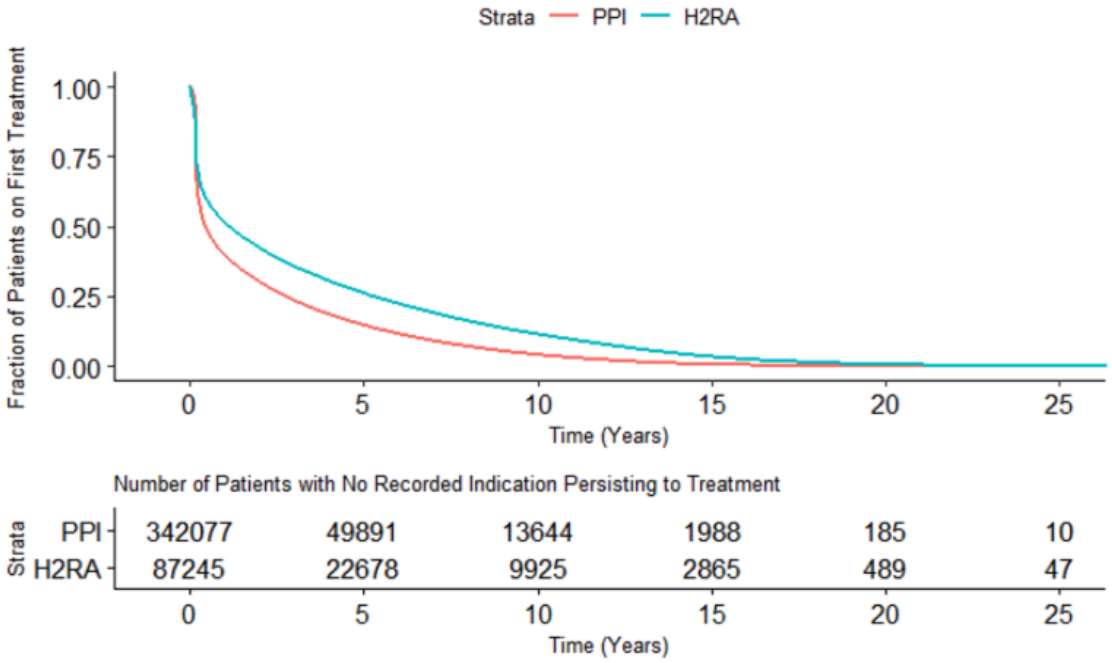


S* Numbers <5 are not displayed, as per the confidentially practices of the Clinical Practice Research Datalink.

Supplementary Figure 9. Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Off-label Indications for Use



Supplementary Figure 10. Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with No Recorded Indication for Use



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9, 10, 11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9, 10, 11
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	7, 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9, 10, 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8, 9, 10, 11
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9, 10, 11
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	12, 13, 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, 13, 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17, 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15, 16, 17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.