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**Supplementary Table 1. List of British National Formulary Codes for Proton Pump Inhibitors**

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<b>British National Formulary Code</b>	<b>British National Formulary Header</b>
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

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

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<b>British National Formulary Code</b>	<b>British National Formulary Header</b>
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

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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 (%) <sup>§</sup>	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 (%) <sup>§</sup>	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 (%) <sup>§</sup>	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 (%) <sup>§</sup>	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)

<sup>§</sup> 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**

<b>Interval</b>	<b>Proton Pump Inhibitor IRR (95% CI)</b>	<b>Histamine-2 Receptor Antagonists IRR (95% CI)</b>
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.

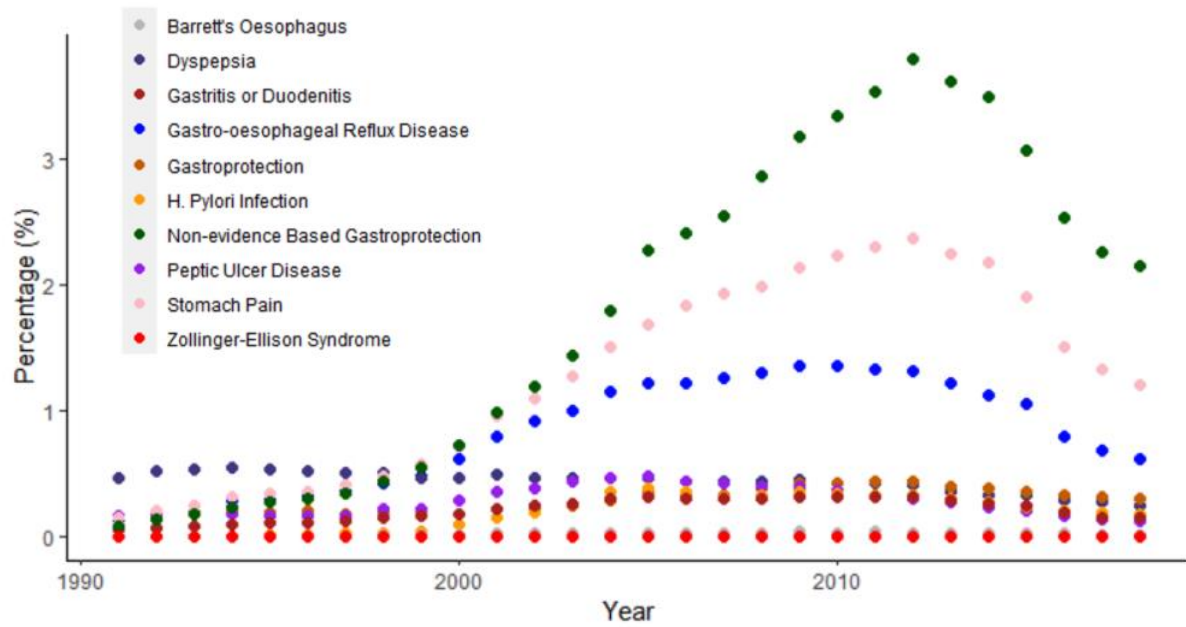
**Supplementary Table 5. Reason for Discontinuation of Initial Acid Suppressant Treatment Course Under Alternate Grace Periods**

<b>Reason for Discontinuation</b>	<b>Proton Pump Inhibitors (n=1,699,837)</b>	<b>Histamine-2 Receptor Antagonists (n=385,988)</b>
<b>7 Day Grace Period †</b>		
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)
<b>60 Day Grace Period ‡</b>		
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)

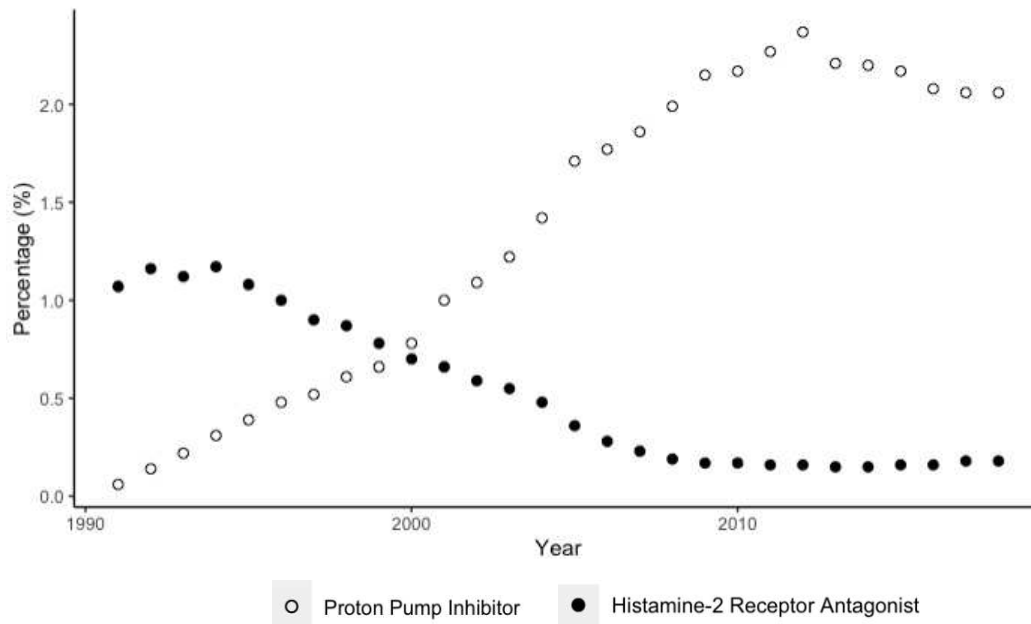
† median (interquartile range) duration of first treatment course for PPI users and H2RA users was 66 (36 to 560) and 149 (38 to 1,479) days, respectively.

‡ 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

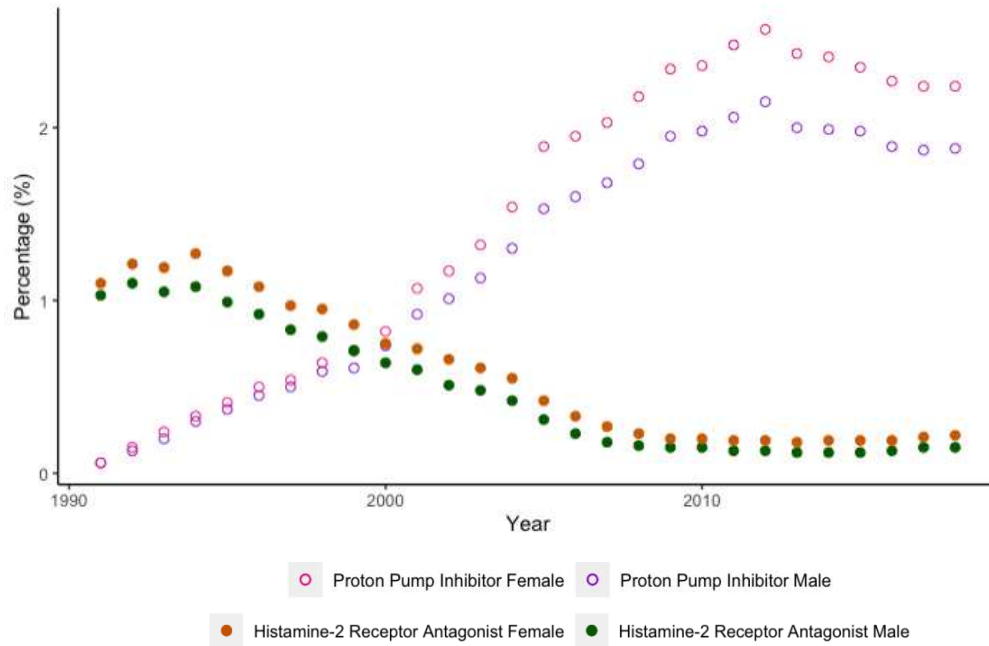


### Supplementary Figure 2. Overall Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users

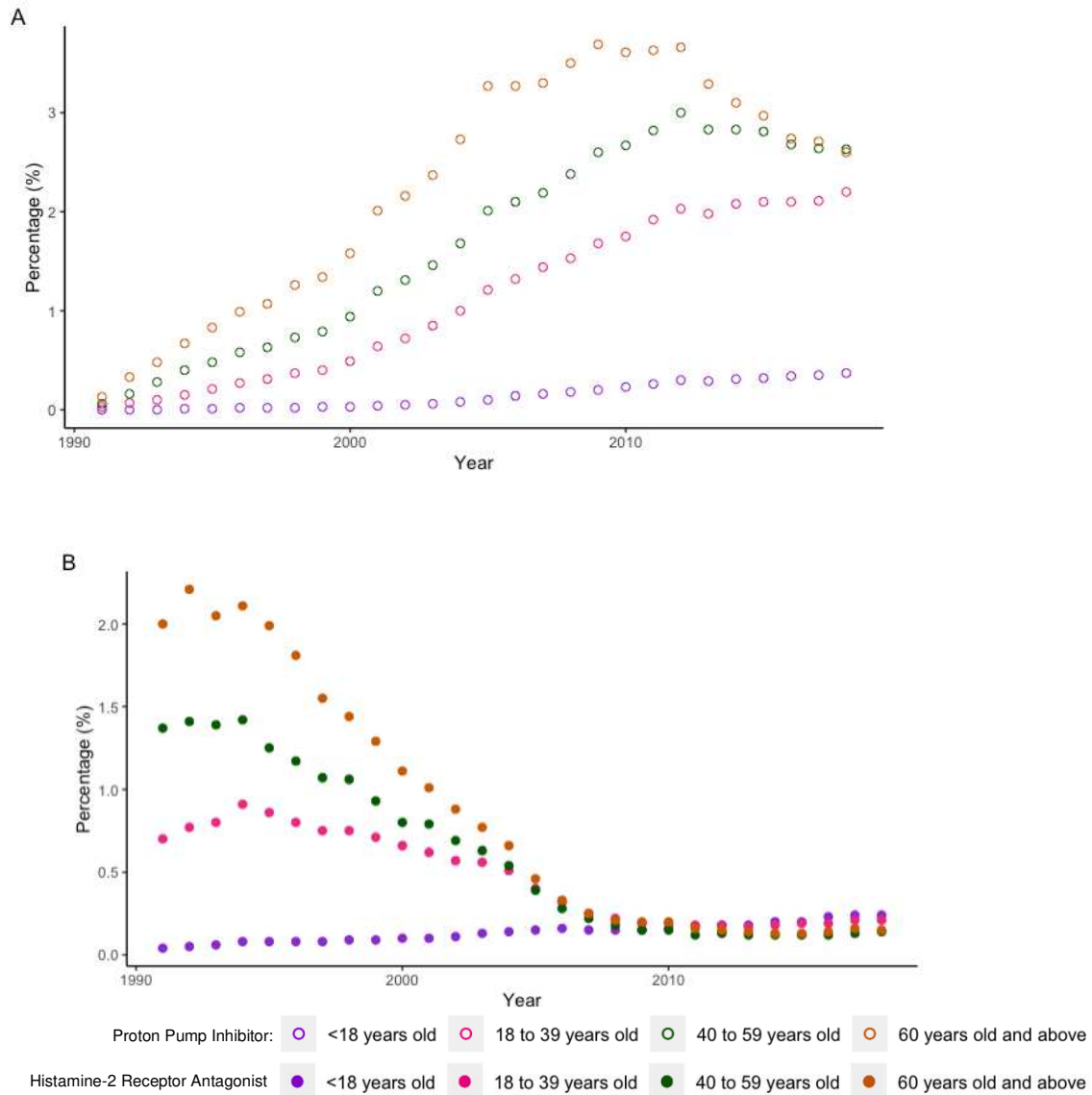


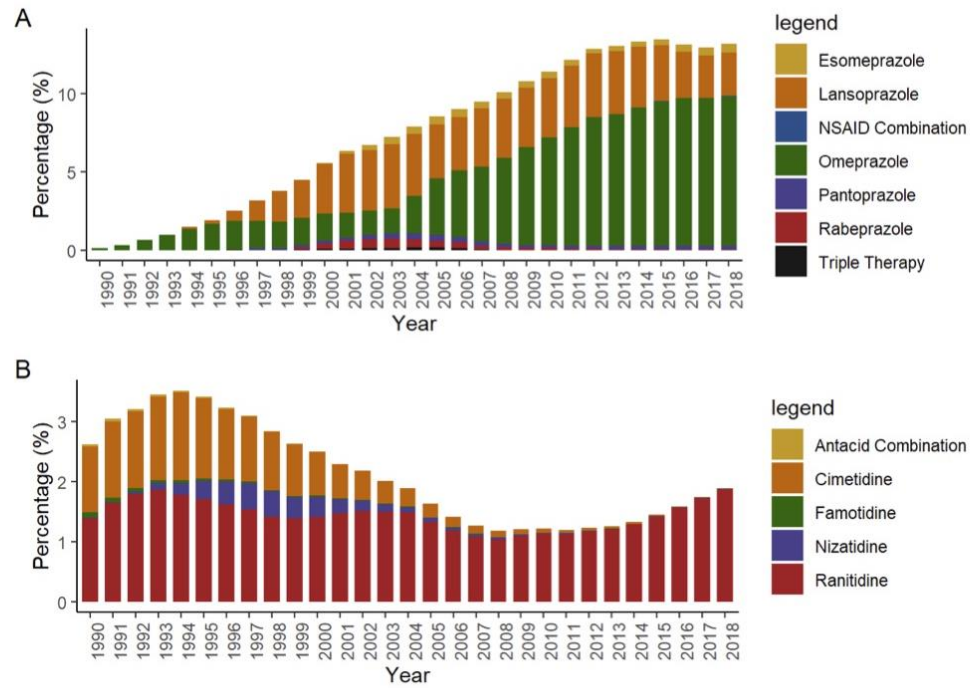


### Supplementary Figure 3. Sex-stratified Prevalence of Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use in New Users

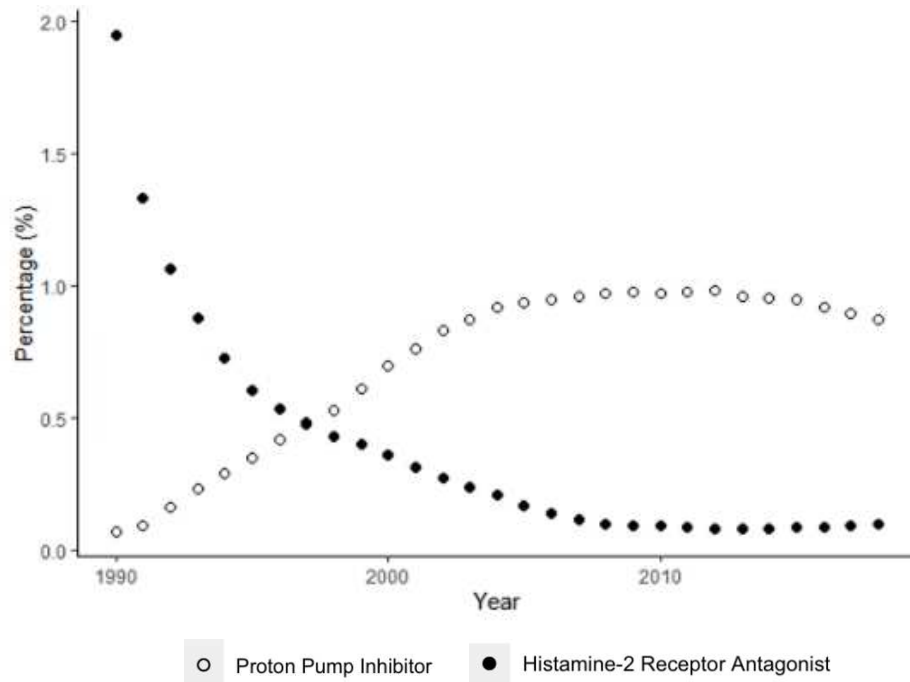


**Supplementary Figure 4. Age-stratified Prevalence of A) Proton Pump Inhibitor Use and b) Histamine-2 Receptor Antagonist Use in New Users**

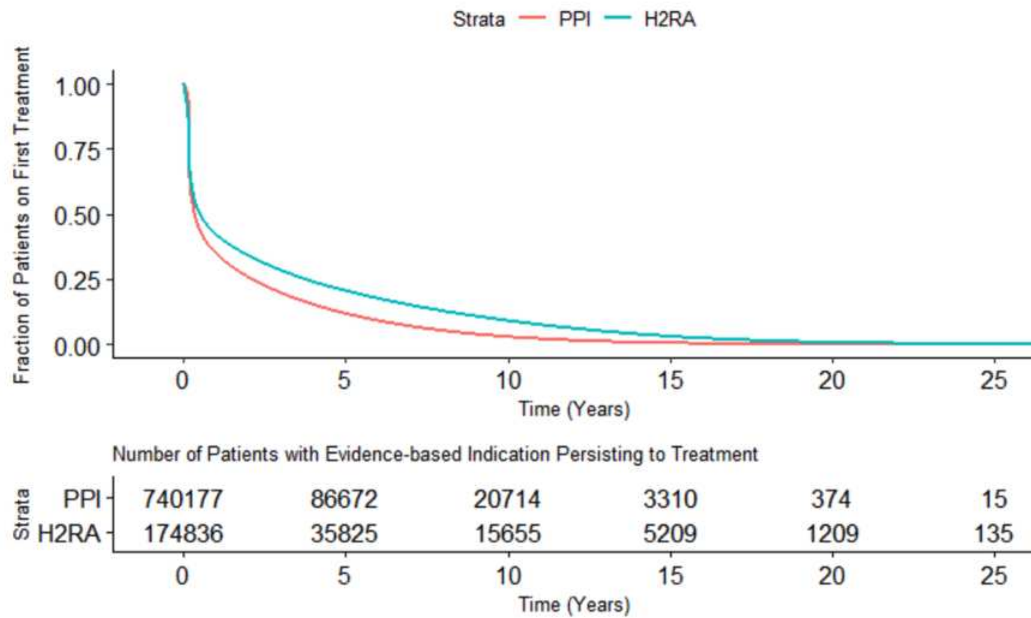


**Supplementary Figure 5. Prevalence of A) Proton Pump Inhibitor Prescriptions and B) Histamine-2 Receptor Antagonist Prescriptions Stratified by Individual Drug Type**

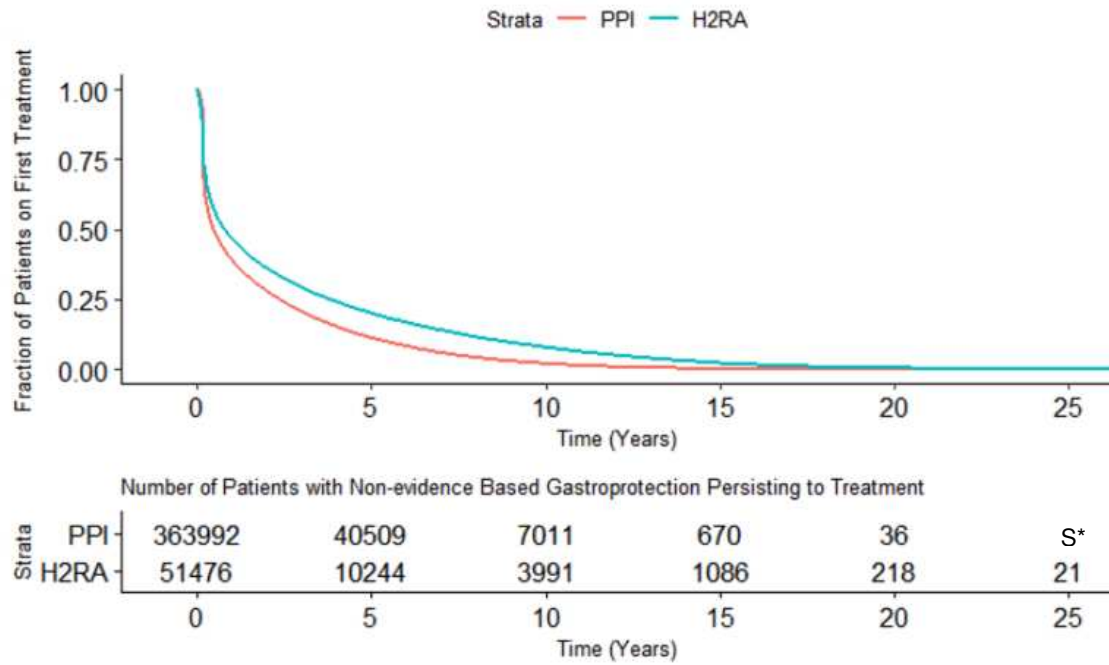
### Supplementary Figure 6. Prescribing Intensity of Proton Pump Inhibitors and Histamine-2 Receptor Antagonists



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

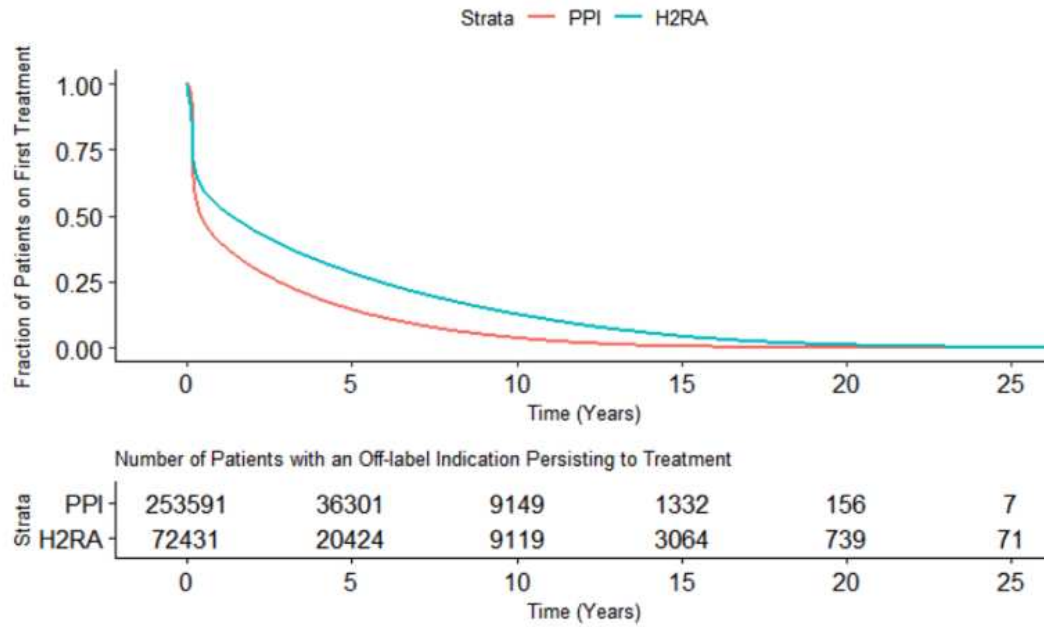


**Supplementary Figure 8. Persistence to Original Treatment Course for Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Initiators with Non-evidence Based Gastroprotection**



S\* Numbers <5 are not displayed, as per the confidentiality 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**

