**Supplemental Digital Content 3**

**Table S1.** Head-to-head comparison of PPIs versus H2RAs on risk of all-cause and cause-specific mortality

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cause of death** | **Cases** | **Person-years** | **Incidence rate \*** | **Hazard Ratio [95% Confidence Interval]** |
| Age, gender and indication-stratified model | Multivariable adjusted model † |
| **All**  |  |  |  |  |  |
| Regular H2RA user | 230 | 39935 | 575.9 | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPIs user | 1,614 | 212775 | 758.5 | 1.17 [1.02,1.35] | 1.09 [0.95,1.26] |
| **Neoplasms (C00-D49)** |  |  |  |  |  |
| Regular H2RA user | 126 | 39935 | 315.5 | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPIs user | 787 | 212775 | 369.9 | 1.02 [0.84,1.23] | 1.03 [0.85,1.25] |
| **Circulatory system diseases (I00-I99)** |  |  |  |  |  |
| Regular H2RA user | 37 | 39935 | 92.7 | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPIs user | 315 | 212775 | 148 | 1.41 [1.00,1.99] | 1.26 [0.89,1.79] |
| **Respiratory system diseases (J00-J99)** |  |  |  |  |  |
| Regular H2RA user | 22 | 39935 | 55.1 | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPIs user | 160 | 212775 | 75.2 | 1.15 [0.73,1.80] | 0.92 [0.59,1.46] |
| **Digestive system diseases (K00-K99)** |  |  |  |  |  |
| Regular H2RA user | 12 | 39935 | 30 | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPIs user | 101 | 212775 | 47.5 | 1.15 [0.88,2.97] | 1.22 [0.66,2.27] |
| **External causes (V00-Y99)** |  |  |  |  |  |
| Regular H2RA user | 9 | 39935 | 22.5 | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPIs user | 49 | 212775 | 23 | 1.10 [0.53,2.28] | 0.99 [0.47,2.06] |
| **Other causes (A00-B99, D55-H99,L00-R99, U00-U49)** |  |  |  |  |  |
| Regular H2RA user | 24 | 39935 | 60.1 | 1.00 [Reference] | 1.00 [Reference] |
| Regular PPIs user | 202 | 212775 | 94.9 | 1.48 [0.97,2.28] | 1.28 [0.83,1.97] |

\* Per 100 000 person years.

† Multivariable adjusted model: additionally adjusted for ethnicity (*white*, or *other*), socioeconomic status (*index of multiple deprivation*, fifth), education level (*college or university degree*, *other*),smoking status (*never smoker*, *previous smoker*, *current smoker*), alcohol consumption (*daily or almost daily*, *one to four times a week*, *one to three times a month*, *special occasions only or never*), physical activity (*low*, *moderate*, *high*), fruit and vegetable intake (*≥5 portions*, *<5 portions*), salt added to food (*never or rarely*, *sometimes*, *usually*, *always*), BMI, sleep time (*<8 hours*, *8 hours*, *8 to 9 hours*, *>9 hours*), hypercholesterolemia (*yes* or *no*), hypertension (*yes* or *no*), diabetes (*yes* or *no*), mental health disorders (*yes* or *no*), COPD (*yes* or *no*), asthma (*yes* or *no*), atrial fibrillation (*yes* or *no*), inflammatory bowel disease (*yes* or *no*), cholelithiasis (*yes* or *no*), rheumatoid arthritis (*yes* or *no*), renal failure (*yes* or *no*), gastritis (*yes* or *no*), liver problem (*yes* or *no*), anaemia (*yes* or *no*), multivitamin use (*yes* or *no*), mineral supplements intake (*yes* or *no*), aspirin (*yes* or *no*), non-aspirin NSAIDs (*yes* or *no*), acetaminophen (*yes* or *no*), angiotensin-converting enzyme inhibitor (*yes* or *no*), angiotensin receptor blocker (*yes* or *no*), beta-blockers (*yes* or *no*), calcium channel blockers (*yes* or *no*), thiazide diuretics (*yes* or *no*), statin (*yes* or *no*), metformin (*yes* or *no*), insulin treatment (*yes* or *no*), overall health rating (*poor*, *fair*, *good*, *excellent*) and longstanding illness (*yes* or *no*).

Abbreviation: PPI, proton pump inhibitor; H2RAs, histamine-2 receptor antagonists.