

## Association of Proton Pump Inhibitor Use With All-cause and Cause-specific Mortality

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### Table of Contents

Supplementary Table 1. Age-standardized characteristics of study participants according to histamine-2 receptor antagonist use over follow-up .....	2
Supplementary Table 2. Hazard ratios (95% confidence intervals) for all-cause and cause-specific mortality according to proton pump inhibitor use and histamine-2 receptor antagonist use .....	4
Supplementary Table 3. Hazard ratios (95% confidence intervals) for all-cause and cause-specific mortality according to proton pump inhibitor use in an active-comparator analysis.....	5

**Supplementary Table 1. Age-standardized characteristics of study participants according to histamine-2 receptor antagonist use over follow-up<sup>a</sup>**

	Women (N=50,156)			Men (N=21,731)		
	All	H2RA non-users	H2RA users	All	H2RA non-users	H2RA users
Age at baseline, years, mean (SD)	68.8 (6.9)	68.8 (6.9)	68.2 (6.8)	68.0 (8.0)	68.0 (8.0)	67.0 (7.6)
White, %	91.4	91.4	90.5	95.0	95.0	96.4
Smoking status, %						
Never smokers	49.5	49.6	45.4	54.6	54.7	48.1
Past smokers	47.2	47.0	52.0	42.5	42.4	49.7
Current smokers	3.3	3.4	2.6	2.9	2.9	2.2
Body mass index, kg/m <sup>2</sup> , mean (SD)	25.8 (5.2)	25.7 (5.2)	26.6 (5.3)	25.9 (3.9)	25.9 (3.9)	26.3 (4.4)
Physical activity, MET-hrs/wk, mean (SD)	18.7 (14.9)	18.8 (14.9)	17.4 (14)	34.6 (23.3)	34.7 (23.4)	31.5 (20.5)
Alternate Healthy Eating Index-2010, mean (SD)	49.7 (8.9)	49.7 (8.9)	49.2 (8.8)	50.4 (9.4)	50.4 (9.4)	49.9 (9.3)
Alcohol intake, g/d, mean (SD)	5.8 (8.6)	5.8 (8.6)	5.5 (8.2)	11.3 (12.6)	11.3 (12.6)	12.4 (13.3)
Regular NSAID use, %	67.1	66.9	73.7	55.6	55.4	63.1
Physical examination in the past two years, %	76.8	76.8	75.6	69.2	69.2	69.9
Medical condition						
Cancer	23.0	22.9	24.9	24.9	24.9	30.1
Myocardial infarction	5.2	5.2	7.9	9.9	9.8	14.7
Stroke	3.5	3.5	5.5	4.1	4.1	6.3
Hypertension	63.7	63.3	76.6	56.6	56.3	70.6
Diabetes mellitus	12.4	12.3	15.3	12.9	12.8	18.2
Hypercholesterolemia	71.7	71.4	80.1	64.5	64.4	74.5
Chronic obstructive pulmonary disease	8.9	8.8	12.4	3.8	3.7	5.5

Abbreviations: H2RA, histamine-2 receptor antagonist; MET, metabolic equivalent of task; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

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<sup>a</sup> Characteristics of study participants are presented by H2RA use. All variables are standardized to the age distribution of the study population except for age. Mean (SD) is presented for continuous variables and percentage of participants for categorical variables. Values for all variables but age were calculated over follow-up.

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**Supplementary Table 2. Hazard ratios (95% confidence intervals) for all-cause and cause-specific mortality according to proton pump inhibitor use and histamine-2 receptor antagonist use**

Cause of death	Non-users of PPIs and H2RAs		PPI users		H2RA users	
	No. of events	HR (95% CI) <sup>a</sup>	No. of events	HR (95% CI) <sup>a</sup>	No. of events	HR (95% CI) <sup>a</sup>
<b>All causes</b>	18440	1 (reference)	1657	1.25 (1.19-1.32)	473	1.09 (0.99-1.20)
<b>Cancer</b>	3842	1 (reference)	386	1.40 (1.25-1.56)	105	1.29 (1.05-1.57)
<b>Cardiovascular diseases</b>	4508	1 (reference)	365	1.18 (1.06-1.33)	120	1.11 (0.91-1.34)
<b>Others<sup>b</sup></b>	10090	1 (reference)	906	1.23 (1.15-1.33)	248	1.02 (0.90-1.16)

Abbreviations: CI, confidence interval; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

<sup>a</sup> Cox proportional hazards models stratified by age, cohort, and questionnaire cycle and adjusted for race, smoking status, body mass index, physical activity, Alternate Healthy Eating Index-2010, alcohol intake, regular NSAID use, history of cancer, myocardial infarction, stroke, hypertension, diabetes mellitus, hypercholesterolemia, gastroesophageal reflux disease, Barrett's esophagus, peptic ulcer disease, gastrointestinal bleeding, and chronic obstructive pulmonary disease.

<sup>b</sup> Others include respiratory diseases, digestive diseases, renal diseases, neurological diseases, infectious diseases, and other less common medical conditions.

**Supplementary Table 3. Hazard ratios (95% confidence intervals) for all-cause and cause-specific mortality according to proton pump inhibitor use in an active-comparator analysis**

Cause of death	Lag-time <sup>a</sup>					
	No lag		2 years		4 years	
	No. of events	HR (95% CI) <sup>b</sup>	No. of events	HR (95% CI) <sup>b</sup>	No. of events	HR (95% CI) <sup>b</sup>
<b>All causes</b>						
H2RA users	473	1 (reference)	411	1 (reference)	364	1 (reference)
PPI users	1747	1.14 (1.03-1.27)	1475	1.10 (0.99-1.23)	1172	0.97 (0.86-1.10)
<b>Cancer</b>						
H2RA users	105	1 (reference)	76	1 (reference)	55	1 (reference)
PPI users	404	1.08 (0.86-1.34)	285	1.08 (0.83-1.39)	188	0.96 (0.71-1.31)
<b>Cardiovascular diseases</b>						
H2RA users	120	1 (reference)	105	1 (reference)	95	1 (reference)
PPI users	384	1.06 (0.86-1.32)	323	0.99 (0.78-1.24)	259	0.87 (0.68-1.11)
<b>Others<sup>c</sup></b>						
H2RA users	248	1 (reference)	230	1 (reference)	214	1 (reference)
PPI users	959	1.21 (1.05-1.40)	867	1.16 (1.00-1.34)	725	1.02 (0.88-1.20)

Abbreviations: CI, confidence interval; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

<sup>a</sup> For a modified lag-time approach, we considered a two-year, a four-year, and a six-year lag-time based on the structure of our data. For example, in a two-year lag-time analysis, we used the exposure status in 2004 to model mortality risk starting in 2006; in a four-year lag-time analysis, we used the exposure status in 2004 to model mortality risk starting in 2008, and so on.

<sup>b</sup> Cox proportional hazards models stratified by age, cohort, and questionnaire cycle and adjusted for race, smoking status, body mass index, physical activity, Alternate Healthy Eating Index-2010, alcohol intake, regular NSAID use, history of cancer, myocardial infarction, stroke, hypertension, diabetes mellitus, hypercholesterolemia,

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gastroesophageal reflux disease, Barrett's esophagus, peptic ulcer disease, gastrointestinal bleeding, and chronic obstructive pulmonary disease.

° Others include respiratory diseases, digestive diseases, renal diseases, neurological diseases, infectious diseases, and other less common medical conditions.

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