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GASTRODUODENAL

Association of Proton Pump Inhibitor Use With All-Cause and Cause-Specific Mortality

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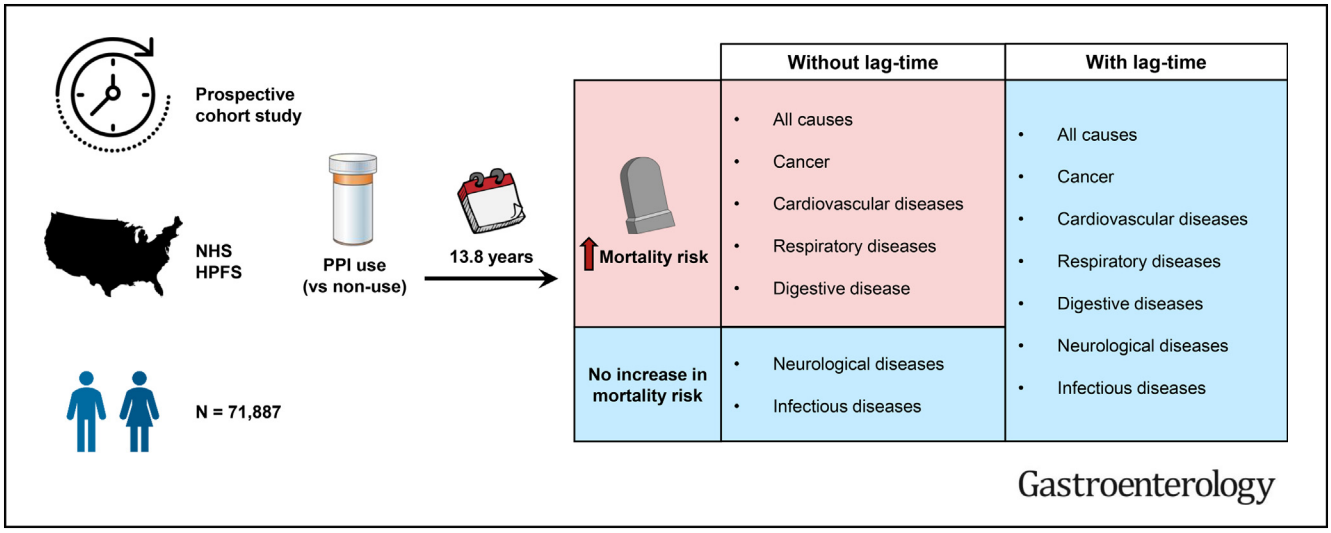

BACKGROUND & AIMS: The use of proton pump inhibitors (PPIs) has increased rapidly in the past 2 decades. Concerns about the regular use of PPIs contributing to mortality have been raised. **METHODS:** We conducted a prospective cohort study using data collected from the Nurses' Health Study (2004–2018) and the Health Professionals Follow-up Study (2004–2018). Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs for mortality according to PPI use. We used a modified lag-time approach to minimize reverse causation (ie, protopathic bias). **RESULTS:** Among 50,156 women and 21,731 men followed for 831,407 person-years and a median of 13.8 years, we documented 22,125 deaths, including 4592 deaths from cancer, 5404 from cardiovascular diseases, and 12,129 deaths from other causes. Compared with nonusers of PPIs, PPI users had significantly higher risks of all-cause mortality (HR, 1.19; 95% CI, 1.13–1.24) and mortality due to cancer (HR, 1.30; 95% CI, 1.17–1.44), cardiovascular diseases (HR, 1.13; 95% CI, 1.02–1.26), respiratory diseases (HR, 1.32; 95% CI, 1.12–1.56), and digestive diseases (HR, 1.50; 95% CI, 1.10–2.05). Upon applying lag times of up to 6 years, the associations were attenuated and no longer statistically significant (all-cause: HR, 1.04; 95% CI, 0.97–1.11; cancer: HR, 1.07; 95% CI, 0.89–1.28; cardiovascular diseases: HR, 0.94; 95% CI, 0.81–1.10; respiratory diseases: HR, 1.20; 95% CI, 0.95–1.50; digestive diseases: HR, 1.38; 95% CI, 0.88–2.18). Longer duration of PPI use did not confer higher risks for all-cause and cause-specific mortality. **CONCLUSIONS:** After accounting for protopathic

bias, PPI use was not associated with higher risks of all-cause mortality and mortality due to major causes.

Keywords: Antacid; Death; Epidemiology; GERD; Medication.

Proton pump inhibitors (PPIs) are commonly used medications, available either by prescription or over the counter in the United States. These agents inhibit gastric acid secretion and are often used to treat acid-mediated upper gastrointestinal disorders and for prophylaxis against stress ulcers.[1] There has been a constant increase in the use of PPIs over the past few decades. For instance, the use of prescription PPIs alone doubled from 1999 to 2012 in the United States.[2] Such growth is related to both the medication's proven efficacy for approved indications and the overuse of potentially inappropriate prescriptions.[3] Along with the increase in PPI use, there is growing concern about possible long-term adverse outcomes.

Accumulating evidence from numerous studies examining PPI-related adverse events has gained attention over the past 2 decades.[4] Some studies have suggested an association with mortality,[5–18] although most have been restricted to populations with certain medical conditions.[9–11,13–18] It is unclear whether PPI use is associated with higher mortality risks in an unselected population. Furthermore, a major challenge that pharmacoepidemiologic studies often face is the susceptibility to protopathic bias. Protopathic bias occurs when a pharmaceutical agent is prescribed for an early manifestation of a disease and then appears to cause the disease when it is eventually diagnosed.[19] In the case of PPIs and mortality, individuals who use PPIs in response to upper gastrointestinal symptoms are more likely to have comorbidities and, as a result, die from these medical conditions. Although randomized controlled trials may address this type of bias, they are often restricted by ethical concerns, sample size, cost, and length of follow-up. One approach to account for this bias in nonexperimental studies is to incorporate lag times into the exposure definition.[19,20] Using this approach, any increased PPI use during the excluded period, which could be due to comorbid conditions before death, will not be considered in the quantification of the exposure and, thus, protopathic bias would be avoided.

Here, we used a modified lag-time approach to investigate the association between PPI use and all-cause and cause-specific mortality. Data were collected from 2 large prospective cohorts in which detailed information about medication use, lifestyle, and medical conditions has been periodically updated over long-term follow-up. These cohorts also provide a unique opportunity to examine PPI use over a range of durations in relation to mortality risks.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Proton pump inhibitor (PPI) use has been associated with a possible increased risk of death. However, prior studies vary widely with regard to study population, methodology, and end points.

NEW FINDINGS

PPI use was associated with higher risks of all-cause mortality and mortality due to cancer, cardiovascular diseases, respiratory diseases, and digestive diseases. Upon implementing lag times of up to 6 years, the associations were attenuated and no longer significant.

LIMITATIONS

We did not have information on PPI brand, dosage, and schedule. We were not able to adjust for specific medical conditions. Most of the study participants were White health professionals.

IMPACT

Our study is among the first to assess the potential for protopathic bias across a range of end points by applying successively longer lag times. Our results do not support positive associations between PPI use and mortality risks.

Methods

Study Population

We included participants from 2 ongoing US prospective cohorts. The Nurses' Health Study recruited 121,700 female registered nurses aged 30–55 years in 1976.[21] The Health Professionals Follow-up Study enrolled 51,529 male health professionals aged 40–75 years in 1986.[22] In both cohorts, questionnaires were mailed to participants at enrollment and every 2 years thereafter to obtain information on various lifestyle factors, medication use, and medical history. Diet was assessed using validated semiquantitative food frequency questionnaires beginning in 1980 in the Nurses' Health Study and in 1986 in the Health Professionals Follow-up Study, and updated every 4 years.[23,24]

For the current study, we used 2004 as the baseline for both cohorts when information on duration of prior PPI use was collected. We excluded participants who reported prior PPI use before the start of follow-up or had been diagnosed with upper gastrointestinal diseases, including gastroesophageal reflux disease, Barrett's esophagus, peptic ulcer disease, and gastrointestinal bleeding. After these exclusions, the final analytic cohort included 50,156 women and 21,731 men. The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Assessment of Proton Pump Inhibitor Use and Histamine-2 Receptor Antagonist Use

Information about PPI use was obtained from the biennial follow-up questionnaires starting in 2000 in the Nurses' Health Study and 2004 in the Health Professionals Follow-up Study and updated every 2 years. Participants were asked about

Abbreviations used in this paper: **HR, hazard ratio; H2RA, histamine-2 receptor antagonist; ICD-8, *International Classification of Diseases*, 8th revision; PPI, proton pump inhibitor.**

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regular use of PPIs in the past 2 years. Although examples of brand names were provided for reference (eg, Prilosec, Nexium, Prevacid, Protonix, and Aciphex), specific information on the brand, dose, and schedule was not queried. Duration of prior use (0–2 years, 3–5 years, 6–9 years, and ≥10 years) was asked in the 2004 questionnaire in both cohorts. Those who completed the medication section but did not report regular PPI use were considered nonusers for that 2-year period. If a participant did not return the questionnaire for a follow-up cycle, we carried forward PPI use status from the previous cycle. Duration of PPI use was also calculated through the sum of PPI use from baseline until the most recent cycle and categorized into nonusers, 1–2 years, 3–4 years, 5–6 years, and ≥7 years. Similarly, participants were asked about regular use of histamine-2 receptor antagonists (H2RAs) in the past 2 years in both cohorts, with examples of brand names provided for reference (eg, Tagamet, Zantac, and Pepcid).

Ascertainment of Death

The main outcome was death from all and different causes, occurring after the return of the 2004 questionnaire and before June 1, 2018. Deaths were usually reported by next of kin, the postal system, or identified by searching the National Death Index.[25,26] The cause of death was ascertained by review of death certificates and pertinent medical records. Deaths were grouped into several broad categories according to the *International Classification of Diseases*, 8th Revision (ICD-8),[27] including cancer (ICD-8 codes 140–209); cardiovascular diseases (ICD-8 codes 390–458); respiratory diseases (ICD-8 codes 460–519); digestive diseases (ICD-8 codes 520–577); renal diseases (ICD-8 codes 580–593); neurological diseases (ICD-8 codes 290, 340, 342, 348) (most cases could be attributed to dementia); and infectious diseases (ICD-8 codes 0–140). Consistent with prior analysis, the cause of death due to cancer was further subdivided into common causes of cancer-specific death with sufficient sample size for analysis, including lung cancer, upper gastrointestinal cancer (including cancer of the esophagus, stomach, and small intestine), colorectal cancer, non-Hodgkin's lymphoma, breast cancer, and ovarian cancer.[28]

Assessment of Covariates

Information on demographic and lifestyle characteristics, including smoking status, body mass index, physical activity, nonsteroidal anti-inflammatory drug use, and medical history, was assessed using the biennial questionnaires. Data on the Alternate Healthy Eating Index-2010[29] and alcohol intake were collected using semi-quantitative food frequency questionnaires.

Statistical Analysis

Person-years were accrued from the date of return of the baseline questionnaire to the date of death or the end of follow-up (June 1, 2018 for both cohorts), whichever occurred first. We employed Cox proportional hazards models stratified by age, cohort, and questionnaire cycle, and adjusted for confounders to estimate the hazard ratios (HRs) and 95% CIs for mortality comparing PPI use and nonuse. Confounders selected *a priori* included smoking status, body mass index, physical activity, Alternate Healthy Eating Index-2010,[29] alcohol intake, regular nonsteroidal anti-inflammatory drug use, H2RA use in the past, history of cancer, myocardial infarction, stroke, hypertension, diabetes mellites, hypercholesterolemia, gastroesophageal reflux disease, Barrett's esophagus, peptic ulcer disease, gastrointestinal bleeding, and chronic obstructive pulmonary disease. To minimize the influence of protopathic bias, we used a modified lag-time approach, which was adapted from prior studies.[19,20] Instead of excluding the period preceding the index date from PPI use assessment, a period before each questionnaire cycle was excluded from the assessment of PPI use. We considered 2-year, 4-year, and 6-year lag times based on the structure of our data (2-year interval). For example, in a 2-year lag-time analysis, we used the exposure status in 2004 to model mortality risks starting in 2006; in a 4-year lag-time analysis, we used the exposure status in 2004 to model mortality risks starting in 2008, and so on. Figure 1 illustrates this approach. To assess the cumulative exposure of PPIs, we examined the associations between duration of PPI use and mortality risks. The models were adjusted for the same confounders listed above.

For sensitivity analysis, we excluded participants who reported H2RA use before the start of follow-up and applied an active-comparator study design.[30] First, we estimated the HRs and 95% CIs for mortality comparing PPI use, H2RA use, and nonuse of both medications. Second, we compared the mortality risks between PPI users and H2RA users, with H2RA users as the reference group and further employed the lag-time approach.

We conducted all analyses using SAS software, version 9.4 (SAS Institute, Cary, NC). All statistical tests were 2-sided; $P < .05$ indicated statistical significance.

Results

Study Population

Our study included 50,156 women and 21,731 men contributing to 831,407 person-years during a median of 13.8 years of follow-up. We confirmed 22,125 deaths, including 4592 deaths from cancer, 5404 from cardiovascular diseases, and 12,129 deaths from other causes (including respiratory diseases, digestive diseases, renal diseases, neurologic diseases, infectious diseases, and other less common medical conditions). Among study participants, 10,998 women (21.9%) and 2945 men (13.6%) initiated PPI use at some point during the study period and, during that course, PPI use increased from 6.1% to 10.0% in women and from 2.5% to 7.0% in men (Figure 2). The age-standardized characteristics of study participants according to PPI use in the 2 cohorts are summarized in Table 1. Mean age at baseline for women and men was 68.9 years and 68.0 years, respectively. PPI use was associated with higher rates of H2RA use in the past. Compared with nonusers of PPIs, PPI users were more likely to have cancer, cardiovascular diseases (myocardial infarction and stroke), and various medical conditions. Similar distributions could be observed when examining characteristics by H2RA use (Supplementary Table 1).

Proton Pump Inhibitor Use and All-Cause and Cause-Specific Mortality

Compared with nonusers of PPIs, PPI users had a significantly higher risk of all-cause mortality after adjusting

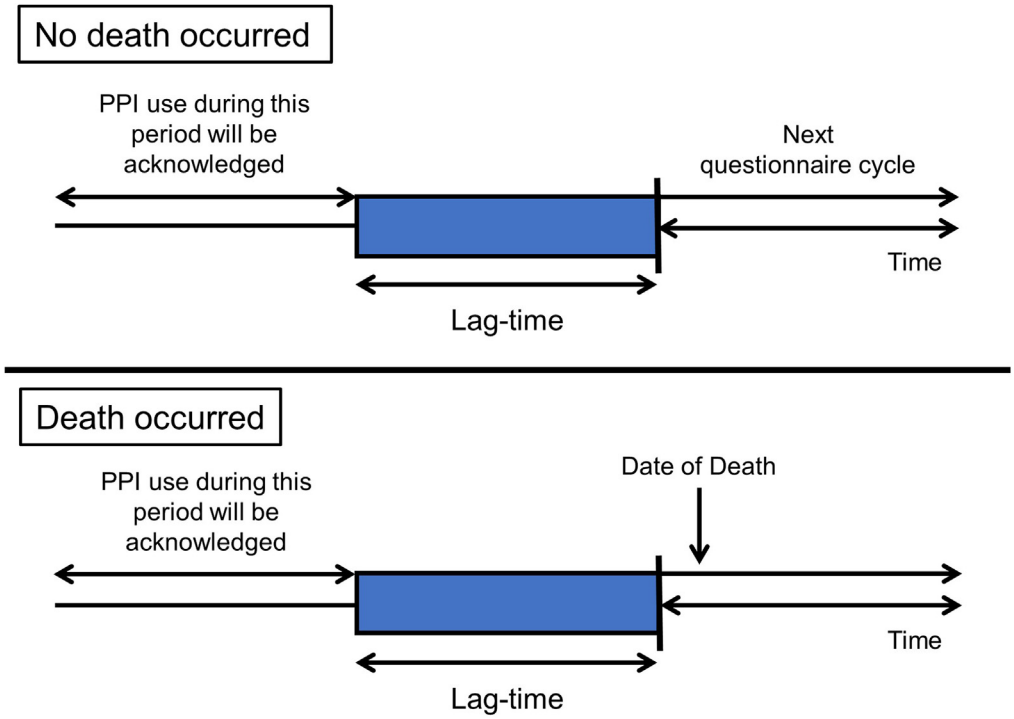

Figure 1. The lag-time approach. A period preceding each questionnaire cycle was excluded from the assessment of PPI use.

for time-varying confounding (HR, 1.19; 95% CI, 1.13–1.24) (Table 2). PPI use was also associated with increased risks of cause-specific mortality, including due to cancer (HR, 1.30; 95% CI, 1.17–1.44), cardiovascular diseases (HR, 1.13; 95% CI, 1.02–1.26), respiratory diseases (HR, 1.32; 95% CI, 1.12–1.56), digestive diseases (HR, 1.50; 95% CI, 1.10–2.05), and renal diseases (HR, 2.09; 95% CI, 1.50–2.90). We did not observe an association between PPI use and mortality due to neurologic diseases (HR, 1.01; 95% CI, 0.88–1.16) and infectious diseases (HR, 1.31; 95% CI, 0.96–1.78). When we applied successively longer lag times, we found overall attenuation of the associations. Ultimately, a 6-year lag time resulted in reduced HRs for all-cause mortality (HR, 1.04; 95% CI, 0.97–1.11) and mortality due to cancer (HR, 1.07; 95% CI, 0.89–1.28), cardiovascular diseases (HR, 0.94; 95% CI, 0.81–1.10), respiratory diseases (HR, 1.20; 95% CI, 0.95–1.50), and digestive diseases (HR, 1.38; 95% CI, 0.88–2.18). In contrast, PPI users remained at a significantly elevated risk for mortality due to renal diseases (HR, 2.45; 95% CI, 1.59–3.78).

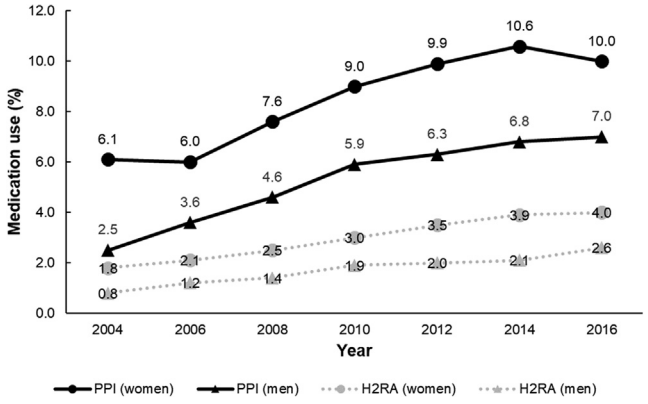

Figure 2. PPI use and H2RA use in women and men during the study period (2004–2018).

For cancer-specific mortality, PPI use was associated with significantly increased risks of mortality due to lung cancer (HR, 1.38; 95% CI, 1.11–1.72), upper gastrointestinal cancer (HR, 1.68; 95% CI, 1.27–2.23), colorectal cancer (HR, 1.44; 95% CI, 1.00–2.08), and ovarian cancer (HR, 1.94; 95% CI, 1.32–2.84) (Table 3). Similar to the analysis of overall cancer, the associations with mortality according to specific cancers were attenuated after applying successively longer lag times. Risks of death from upper gastrointestinal cancer (HR, 1.06; 95% CI, 0.73–1.54) and colorectal cancer (HR, 1.27; 95% CI, 0.83–1.95) were attenuated upon applying a 2-year lag time; no significant association between PPI use and mortality due to lung cancer (HR, 1.16; 95% CI, 0.84–1.60) and ovarian cancer (HR, 0.57; 95% CI, 0.26–1.25) was found once a 4-year lag time was applied.

Duration of Proton Pump Inhibitor Use and All-Cause and Cause-Specific Mortality

Table 4 presents the associations between duration of PPI use and mortality risks. For all-cause mortality and mortality due to cancer, cardiovascular diseases, respiratory diseases, and digestive diseases, the greatest HRs were seen mostly in those who reported using PPIs for 1–2 years. Longer duration of PPI use did not confer higher risks for these end points. In contrast, a potential trend toward greater HRs with longer duration of PPI use was

Table 1. Age-Standardized Characteristics of Study Participants According to Proton Pump Inhibitor Use During Follow-Up

Characteristic	Women (n = 50,156)			Men (n = 21,731)		
	All	PPI nonusers	PPI users	All	PPI nonusers	PPI users
Age at baseline, *y*, mean (SD)	68.9 (6.9)	69.0 (6.9)	67.8 (6.6)	68.0 (8.0)	68.0 (8.1)	68.1 (7.7)
White, %	91.3	91.4	90.4	95.0	94.9	96.0
Smoking status, %						
Never smokers	49.3	49.5	47.0	54.4	54.6	49.6
Past smokers	47.4	47.0	50.7	42.7	42.4	48.1
Current smokers	3.3	3.5	2.3	2.9	3.0	2.3
Body mass index, kg/m^2, mean (SD)	25.8 (5.3)	25.7 (5.2)	26.6 (5.4)	25.9 (3.9)	25.9 (3.9)	26.3 (4.1)
Physical activity, *MET-h/wk*, mean (SD)	18.6 (14.8)	18.8 (14.9)	16.6 (13.5)	34.4 (23.2)	34.6 (23.3)	32.3 (21.6)
Alternate Healthy Eating Index-2010, mean (SD)	49.6 (8.9)	49.7 (8.9)	48.9 (8.5)	51 (9.4)	51 (9.4)	50.8 (9.1)
Alcohol intake, *g/d*, mean (SD)	5.8 (8.6)	5.8 (8.6)	5.4 (8.2)	11.3 (12.6)	11.3 (12.6)	11.5 (12.5)
Regular NSAID use, %	67.2	66.9	69.6	55.7	55.5	59.6
H2RA use in the past, %	10.7	9.1	26.9	6.8	5.7	23.7
Physical examination in the past 2 y, %	76.5	76.8	74.0	69.1	69.2	68.1
Medical condition, %						
Cancer	23.1	22.8	25.7	25.1	24.8	30.3
Myocardial infarction	5.4	5.3	7.1	10.2	10.0	12.9
Stroke	3.7	3.6	4.6	4.2	4.2	4.7
Hypertension	64.3	63.4	73.4	57.0	56.4	67.0
Diabetes mellitus	12.7	12.4	15.4	13.1	12.9	16.7
Hypercholesterolemia	72.1	71.4	79.2	64.9	64.4	73.0
Chronic obstructive pulmonary disease	9.3	8.9	13.2	3.8	3.8	5.2

NOTE. Characteristics of study participants are presented according to PPI use. All variables are standardized to the age distribution of the study population except for age. Values are presented as mean (SD) for continuous variables and percentage of participants for categorical variables. Values for all variables except age were calculated during follow-up.
MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug.

observed in mortality due to renal diseases; the HR of 1.68 (95% CI, 1.19–2.38) for 1–2 years gradually increased to 2.42 (95% CI, 1.23–4.77) for ≥7 years of PPI use. There were no apparent trends for mortality due to neurologic diseases and infectious diseases.

Sensitivity Analysis

We conducted sensitivity analyses to test whether our results were robust. Except for all-cause mortality and mortality due to other causes, PPI users and H2RA users showed similar HRs for mortality compared with nonusers of PPIs and H2RAs (Supplementary Table 2). We then used H2RA users as the reference group to directly compare the mortality risks between PPI users and H2RA users. Compared with H2RA users, PPI users were at higher risks of all-cause mortality (HR, 1.14; 95% CI, 1.03–1.27) and mortality due to other causes (HR, 1.21; 95% CI, 1.05–1.40) (Supplementary Table 3). Upon applying successively longer lag times, we found that the associations with all-cause mortality and mortality due to other causes gradually attenuated to null.

Discussion

In this large prospective study of women and men, PPI use was associated with an increase in the risks of all-cause and cause-specific mortality, including mortality due to cancer, cardiovascular diseases, respiratory diseases, digestive diseases, and renal diseases. However, these associations were largely attenuated after applying lag times, and the excess mortality risks were not observed with longer duration of PPI use, except for mortality due to renal diseases, a finding that should be interpreted with caution, given the lack of information on potential confounders for renal diseases. Furthermore, we did not observe an increase in mortality risks associated with the use of PPIs compared with H2RAs with successively longer lag times. Taken together, our results do not support positive associations between PPI use and all-cause mortality and mortality due to major causes.

Our null results are supported by 1 randomized controlled trial[31] and several observational studies,[32,33] in which no increased risk of death was found with PPI use. Nonetheless, the randomized controlled trial[31] was restricted to a highly selected population (ie, patients with

Table 2. Hazard Ratios (95% CIs) for All-Cause and Cause-Specific Mortality According to Proton Pump Inhibitor Use

	Lag time[a]							
	No lag		2 y		4 y		6 y	
Cause of death	No. of events	HR (95% CI)[b]	No. of events	HR (95% CI)[b]	No. of events	HR (95% CI)[b]	No. of events	HR (95% CI)[b]
All causes								
PPI nonusers	20,092	1 (reference)	18,661	1 (reference)	16,634	1 (reference)	14,205	1 (reference)
PPI users	2033	1.19 (1.13–1.24)	1726	1.10 (1.04–1.15)	1301	1.04 (0.98–1.11)	950	1.04 (0.97–1.11)
Cancer								
PPI nonusers	4141	1 (reference)	3594	1 (reference)	2879	1 (reference)	2136	1 (reference)
PPI users	451	1.30 (1.17–1.44)	323	1.17 (1.03–1.31)	212	1.08 (0.94–1.26)	132	1.07 (0.89–1.28)
Cardiovascular diseases								
PPI nonusers	4946	1 (reference)	4554	1 (reference)	4032	1 (reference)	341 2	1 (reference)
PPI users	458	1.13 (1.02–1.26)	388	1.03 (0.92–1.15)	296	1.00 (0.88–1.13)	207	0.94 (0.81–1.10)
Respiratory diseases								
PPI nonusers	1628	1 (reference)	1499	1 (reference)	1327	1 (reference)	1122	1 (reference)
PPI users	188	1.32 (1.12–1.56)	178	1.32 (1.11–1.57)	129	1.19 (0.98–1.45)	96	1.20 (0.95–1.50)
Digestive diseases								
PPI nonusers	379	1 (reference)	353	1 (reference)	299	1 (reference)	256	1 (reference)
PPI users	54	1.50 (1.10–2.05)	48	1.44 (1.04–2.00)	39	1.67 (1.16–2.39)	23	1.38 (0.88–2.18)
Renal diseases								
PPI nonusers	293	1 (reference)	274	1 (reference)	245	1 (reference)	202	1 (reference)
PPI users	51	2.09 (1.50–2.90)	41	1.90 (1.32–2.73)	35	1.88 (1.27–2.78)	29	2.45 (1.59–3.78)
Neurologic diseases								
PPI nonusers	3256	1 (reference)	3174	1 (reference)	3003	1 (reference)	2728	1 (reference)
PPI users	233	1.01 (0.88–1.16)	206	0.87 (0.75–1.01)	162	0.89 (0.77–1.04)	135	0.83 (0.69–1.00)
Infectious diseases								
PPI nonusers	417	1 (reference)	394	1 (reference)	353	1 (reference)	308	1 (reference)
PPI users	54	1.31 (0.96–1.78)	50	1.30 (0.94–1.79)	39	1.33 (0.93–1.90)	19	0.78 (0.48–1.28)

[a]For a modified lag-time approach, we considered 2-year, 4-year, and 6-year lag times based on the structure of our data. For example, in a 2-year lag-time analysis, we used the exposure status in 2004 to model mortality risk starting in 2006; in a 4-year lag-time analysis, we used the exposure status in 2004 to model mortality risk starting in 2008, and so on.
[b]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 nonsteroidal anti-inflammatory drug use; H2RA use in the past; and 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.

stable cardiovascular disease and peripheral artery disease) and limited by short follow-up. The large cohort study of 1.9 million older adult Medicare enrollees[32] only examined all-cause mortality, and not cause-specific deaths. Although the prospective study of 0.44 million UK Biobank participants[33] investigated all-cause and cause-specific mortality, it relied on adjustment for general health (overall health rating and longstanding illness), suggesting any positive associations were primarily due to residual confounding. This study did not properly account for protopathic bias or examine mortality due to renal diseases. As such, our study expands upon existing evidence and provides more robust evidence examining the associations between PPI use and mortality.

Findings from our initial analysis without considering lag times are consistent with prior observational studies that showed associations of PPI use with higher risks for all-cause mortality[6–8] and mortality due to cancer (especially lung cancer, upper gastrointestinal cancer, colorectal cancer, and ovarian cancer),[8–10] cardiovascular diseases,[5,11] respiratory diseases,[12] digestive diseases,[13–17] and renal diseases.[8,18] We conducted a prospective study of 2 nationwide cohorts with long-term follow-up of more than 10 years. Upon applying lag times of up to 6 years, the excess mortality risks associated with PPI use were largely attenuated. This highlights the importance of carefully controlling for the influence of protopathic bias. Moreover, in our duration analysis, we found that the highest HRs were observed mostly among those who used PPIs for less than 2 years, and the magnitude of HRs steadily decreased with longer duration of PPI use. This can be seen in mortality due to cancer and cardiovascular diseases, conditions in which PPIs are frequently used both therapeutically for gastrointestinal symptoms and prophylactically to prevent

Table 3. Hazard Ratios (95% CIs) for Cancer-Specific Mortality According to Proton Pump Inhibitor Use

	Lag time[a]					
	No lag		2 y		4 y	
Cause of death	No. of events	HR (95% CI)[b]	No. of events	HR (95% CI)[b]	No. of events	HR (95% CI)[b]
Lung cancer						
PPI nonusers	868	1 (reference)	736	1 (reference)	574	1 (reference)
PPI users	106	1.38 (1.11–1.72)	74	1.30 (1.01–1.68)	45	1.16 (0.84–1.60)
Upper gastrointestinal cancer[c]						
PPI nonusers	450	1 (reference)	391	1 (reference)	306	1 (reference)
PPI users	64	1.68 (1.27–2.23)	34	1.06 (0.73–1.54)	29	1.32 (0.87–2.02)
Colorectal cancer						
PPI nonusers	331	1 (reference)	285	1 (reference)	225	1 (reference)
PPI users	37	1.44 (1.00–2.08)	26	1.27 (0.83–1.95)	19	1.24 (0.75–2.04)
Non-Hodgkin lymphoma						
PPI nonusers	287	1 (reference)	254	1 (reference)	190	1 (reference)
PPI users	22	1.09 (0.69–1.72)	20	1.23 (0.76–1.98)	14	1.28 (0.72–2.28)
Breast cancer (women)						
PPI nonusers	368	1 (reference)	314	1 (reference)	251	1 (reference)
PPI users	40	1.21 (0.86–1.71)	33	1.22 (0.83–1.78)	22	1.08 (0.69–1.71)
Ovarian cancer (women)						
PPI nonusers	194	1 (reference)	165	1 (reference)	145	1 (reference)
PPI users	36	1.94 (1.32–2.84)	27	2.02 (1.31–3.12)	7	0.57 (0.26–1.25)

[a]For a modified lag-time approach, we considered 2-year, 4-year, and 6-year lag times based on the structure of our data. For example, in a 2-year lag-time analysis, we used the exposure status in 2004 to model mortality risk starting in 2006; in a 4-year lag-time analysis, we used the exposure status in 2004 to model mortality risk starting in 2008, and so on.
[b]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 nonsteroidal anti-inflammatory drug use; H2RA use in the past; and 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.
[c]Upper gastrointestinal cancer includes cancer of the esophagus, stomach, and small intestine.

gastrointestinal injury due to chronic nonsteroidal anti-inflammatory drug use.[34,35] Thus, mortality due to these conditions within a few years of initiation of PPIs may be attributable to protopathic bias. Other medical conditions, many of which are not PPI indications, were also more prevalent in PPI users, which might result in increased risk of death from such conditions. Notably, in a sensitivity analysis, we implemented an active-comparator study design comparing the mortality risks among PPI users and H2RA users. Without lag time, PPI users were at increased risks of all-cause mortality and mortality due to causes other than cancer and cardiovascular diseases compared with H2RA users. Decreased strengths of associations were observed after introducing 2-year and 4-year lag times. This confirmed our main findings and suggested PPIs might be preferred over H2RAs in sicker patients with comorbid conditions.

In contrast to our analyses of mortality due to other causes, associations between PPI use and risk of death from renal diseases persisted, despite applying lag times. In addition, the duration analysis showed a potential relationship between increasing duration of PPI use and higher risk of mortality due to renal diseases. Importantly, such increased mortality risk could not be established in this study because we did not have reliable data on renal diseases and, therefore, could not adjust for confounding in the models. Nonetheless, evidence from prior observational studies has linked PPI use to various renal end points, including acute interstitial nephritis,[36,37] chronic kidney disease,[38–41] end-stage renal disease,[39] and mortality due to renal diseases.[8,18] Taken together, although our study and prior observational studies cannot prove causation, they support the need for further studies examining the risk of mortality due to renal diseases in patients using PPIs.

This study has multiple strengths. First, our long-term follow-up of more than 10 years and repeated assessment of PPI use allowed analyses incorporating lag times and increasing exposure duration to account for protopathic bias. Second, our cohort collected extensive information about potential confounding lifestyle factors that often is not available in administrative claims databases. Third, we further used an active-comparator study design to test

Table 4. Hazard Ratios (95% CIs) for All-Cause and Cause-Specific Mortality According to Duration of Proton Pump Inhibitor Use[a]

	PPI use				
Cause of death	Nonusers	1–2 y	3–4 y	5–6 y	≥7 y
All causes	1 (reference)	1.21 (1.15–1.27)	1.03 (0.95–1.11)	1.05 (0.94–1.17)	0.94 (0.83–1.06)
Cancer	1 (reference)	1.37 (1.24–1.52)	1.13 (0.94–1.36)	0.91 (0.68–1.21)	1.05 (0.77–1.44)
Cardiovascular diseases	1 (reference)	1.12 (1.01–1.24)	0.92 (0.77–1.11)	0.97 (0.76–1.24)	0.87 (0.66–1.14)
Respiratory diseases	1 (reference)	1.46 (1.24–1.71)	1.17 (0.89–1.54)	1.29 (0.90–1.85)	1.07 (0.70–1.63)
Digestive diseases	1 (reference)	1.56 (1.14–2.12)	1.62 (1.04–2.54)	1.09 (0.50–2.38)	1.32 (0.63–2.76)
Renal diseases	1 (reference)	1.68 (1.19–2.38)	1.45 (0.80–2.62)	1.74 (0.83–3.65)	2.42 (1.23–4.77)
Neurologic diseases	1 (reference)	0.85 (0.73–1.00)	0.89 (0.72–1.10)	1.11 (0.87–1.42)	1.11 (0.90–1.38)
Infectious diseases	1 (reference)	1.14 (0.82–1.58)	1.38 (0.88–2.15)	1.45 (0.81–2.60)	0.74 (0.32–1.70)

[a]HRs (95% CIs) were calculated using 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 nonsteroidal anti-inflammatory drug use; H2RA use in the past; and 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.

whether there was residual bias when using H2RA users as the reference group.

We acknowledge several limitations. First, we did not collect information on PPI brand, dosage, and schedule. However, most studies have suggested that any potential association is a class effect not related to any one specific drug.[42] Second, the number of events for certain outcomes in PPI users was relatively small compared with other studies, especially when applying longer lag times. Nonetheless, we examined the trend of the point estimates and not just the statistical significance. Moreover, there were still sufficient cases in non-PPI users. If an association truly existed, the number of cases in PPI users and non-PPI users should be balanced for the association to remain statistically significant in spite of the lag times. Third, we did not have data on all potential confounding medical conditions. Inability to adjust for specific medical conditions might lead to residual confounding (bias away from the null). This is especially relevant to mortality due to renal diseases, as the positive association with PPI use was a notable exception to our null findings for other causes of death. Finally, our study participants were mostly White health professionals. Further studies are needed for other racial, ethnic, and socioeconomic groups.

Patients with various medical conditions may use PPIs before death, which leads to protopathic bias when evaluating mortality risks in PPI users. We used a modified lag-time approach and found no association between PPI use and all-cause mortality and mortality due to major causes after accounting for protopathic bias. Despite the lack of association with risks of death, it remains prudent to recommend the use of these agents to patients with appropriate indications and for the minimally effective duration.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2022.06.067.

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Conflicts of interest
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Supplementary Table 1. Age-Standardized Characteristics of Study Participants According to Histamine-2 Receptor Antagonist Use During Follow-Up

Characteristic	Women (n = 50,156)			Men (n = 21,731)		
	All	H2RA nonusers	H2RA users	All	H2RA nonusers	H2RA users
Age at baseline, *y*, 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^2, 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-h/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 2 y, %	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

NOTE. Characteristics of study participants are presented according to H2RA use. All variables are standardized to the age distribution of the study population, except for age. Values are presented as mean (SD) for continuous variables and percentage of participants for categorical variables. Values for all variables except age were calculated during follow-up.
MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug.

Supplementary Table 2. Hazard Ratios (95% CIs) for All-Cause and Cause-Specific Mortality According to Proton Pump Inhibitor Use and Histamine-2 Receptor Antagonist Use

Cause of death	Nonusers of PPIs and H2RAs		PPI users		H2RA users	
	No. of events	HR (95% CI)[a]	No. of events	HR (95% CI)[a]	No. of events	HR (95% CI)[a]
All causes	18,440	1 (reference)	1657	1.25 (1.19–1.32)	473	1.09 (0.99–1.20)
Cancer	3842	1 (reference)	386	1.40 (1.25–1.56)	105	1.29 (1.05–1.57)
Cardiovascular diseases	4508	1 (reference)	365	1.18 (1.06–1.33)	120	1.11 (0.91–1.34)
Other[b]	10,090	1 (reference)	906	1.23 (1.15–1.33)	248	1.02 (0.90–1.16)

[a]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 nonsteroidal anti-inflammatory drug use; and 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.
[b]Other includes respiratory diseases, digestive diseases, renal diseases, neurologic diseases, infectious diseases, and other less common medical conditions.

Supplementary Table 3. Hazard Ratios (95% CIs) for All-Cause and Cause-Specific Mortality According to Proton Pump Inhibitor Use in an Active-Comparator Analysis

	Lag time[a]					
	No lag		2 y		4 y	
Cause of death	No. of events	HR (95% CI)[b]	No. of events	HR (95% CI)[b]	No. of events	HR (95% CI)[b]
All causes						
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)
Cancer						
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)
Cardiovascular diseases						
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)
Other[c]						
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)

[a]For a modified lag-time approach, we considered 2-year, 4-year, and 6-year lag times based on the structure of our data. For example, in a 2-year lag-time analysis, we used the exposure status in 2004 to model mortality risk starting in 2006; in a 4-year lag-time analysis, we used the exposure status in 2004 to model mortality risk starting in 2008, and so on.

[b]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 nonsteroidal anti-inflammatory drug use; and 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.

[c]Other includes respiratory diseases, digestive diseases, renal diseases, neurologic diseases, infectious diseases, and other less common medical conditions.