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No Significant Association Between Proton Pump Inhibitor Use and Risk of Stroke After Adjustment for Lifestyle Factors and Indication

Long H. Nguyen,[1,2] Paul Lochhead,[1,2] Amit D. Joshi,[1,2] Yin Cao,[1,2,3] Wenjie Ma,[1,2] Hamed Khalili,[1,2] Eric B. Rimm,[3,4,5] Kathryn M. Rexrode,[6] and Andrew T. Chan[1,2,5,7,8]

[1]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [2]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [3]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; [4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; [5]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [6]Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and [7]Broad Institute of Massachusetts Institute of Technology and Harvard, Cambridge; [8]Department of Immunology and Infectious Disease, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

CLINICAL AT

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e21. Learning Objective: Upon completion of this CME activity, successful learners will be able to identify several limitations of prior investigations associating proton pump inhibitor (PPI) use with incidence of stroke, which may help to relieve patient concerns related to the interpretation of pharmacoepidemiologic studies.

BACKGROUND & AIMS: Proton pump inhibitors (PPI) are among the top 10 most prescribed medications worldwide. We investigated the association between PPI use and ischemic stroke. **METHODS:** We collected data on 68,514 women (mean age, 65 ± 7 years) enrolled in the Nurses' Health Study since 2000 and 28,989 men (mean age, 69 ± 8 years) in the Health Professionals Follow-up Study since 2004, without a history of stroke. We used Cox proportional hazards models to examine the association between risk of incident stroke and PPI use among participants. The primary end point was first incident stroke. **RESULTS:** In the 2 cohorts, we documented 2599 incident strokes (2037 in women and 562 in men) over a 12-year period, encompassing 949,330 person-years. After adjustment for established risk factors for stroke, PPI use was associated with a significant increase in risk of ischemic stroke (hazard ratio, 1.18; 95% confidence interval, 1.02–1.37). The association was reduced after we adjusted for potential indications for PPI use, including history of peptic ulcer disease, gastroesophageal reflux disease, or gastrointestinal bleeding, and prior use of histamine-2 receptor antagonist therapy (hazard ratio, 1.08; 95% confidence interval, 0.91–1.27). Regular PPI use was not associated with increased risk of stroke overall or hemorrhagic stroke. **CONCLUSIONS:** In an analysis of data from the Nurses' Health Study and the Health Professionals Follow-up Study, we did not find a significant association between PPI use and ischemic stroke, after accounting for indications for PPI use. Prior reports of an increased risk of stroke may be due to residual confounding related to chronic conditions associated with PPI use.

Keywords: Epidemiology; Reflux Treatment; Cardiovascular Disease; Drug.

Proton pump inhibitors (PPIs) are a potent class of agents used to suppress gastric acid secretion and are among the most commonly prescribed medications globally.[1] Presently, PPIs are routinely recommended for several gastrointestinal (GI) disorders, including gastroesophageal reflux disease (GERD), prophylaxis against peptic ulcer disease (PUD), and GI bleeding in susceptible populations, such as individuals on dual antiplatelet therapy for secondary prevention of cardiovascular disease.[2,3] Several studies have identified a potential association between PPI use and stroke, but have been limited by assessment of PPI use or stroke events through either retrospective recall or administrative claims,[4–9] the inclusion of only individuals with a history of cardiovascular disease,[6–12] use of composite cardiovascular disease outcome measures,[5,7,8,10–12] and a lack of detailed information on lifestyle risk factors for stroke or indications for PPI use.[4–13]

We examined the association between regular PPI therapy and the risk of incident stroke in men and women enrolled in 2 large cohorts in which detailed information on PPI use, as well as other potential health and lifestyle risk factors, was collected biennially.

Methods

Study Population

The Nurses' Health Study (NHS) is a prospective cohort study of 121,700 female registered nurses aged 30–55 years

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; GERD, gastroesophageal reflux disease; GI, gastrointestinal; H2RA, histamine-2 receptor antagonist; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; NHS, Nurses' Health Study; PPI, proton pump inhibitor; PUD, peptic ulcer disease.**

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

Proton pump inhibitors (PPI) are among the most frequently prescribed medications globally. Recent population-level studies suggest a possible association between PPI use and ischemic stroke.

NEW FINDINGS

An association between PPIs and ischemic stroke was not observed after accounting for several risk factors for ischemic stroke as well as clinical indications for PPI use.

LIMITATIONS

An observational study design and lack of PPI brand, dosage, and schedule information.

IMPACT

Prior reports of increased risk for stroke with PPIs may be due to confounding related to conditions associated with use and should not deter PPI use in the appropriate setting.

at enrollment in 1976. The Health Professionals Follow-up Study (HPFS) is a prospective cohort study of 51,529 male health care professionals (dentists, optometrists, pharmacists, podiatrists, and veterinarians) aged 40–75 years at enrollment in 1986. Individuals in both cohorts have been followed using detailed biennial questionnaires to update information on lifestyle factors, medication use, and other exposures of interest, including validated self-assessments of physical activity and semi-quantitative food frequency questionnaires administered every 4 years.[14,15] Follow-up rates exceed 90% of available person-time. This study was approved by the human research committees at the Harvard T. H. Chan School of Public Health and the Brigham and Women's Hospital. Return of study questionnaires was considered to imply informed consent.

Assessment of Incident Stroke

The primary end point was first incident stroke. Upon report of stroke on a biennial questionnaire, we requested permission to review medical records. Physicians blinded to self-reported risk factor status reviewed the retrieved records. Stroke diagnoses were confirmed based on documentation of an episode characterized by a typical neurologic defect attributable to a cerebrovascular event of sudden and rapid onset for >24 hours or until death. Stroke was classified as ischemic (thrombotic, embolic, or non-hemorrhagic), hemorrhagic (intraparenchymal hemorrhage or subarachnoid hemorrhage), or unknown type, consistent with well-established criteria.[16] If medical records were not available, the case was considered probable. We included confirmed and probable cases for analysis. Deaths were confirmed by reporting from next of kin, coworkers, or postal authorities or by searching the National Death Index.

Assessment of Proton Pump Inhibitor Usage

Every 2 years since inception, participants have been asked to report medications they had used regularly in the preceding 2 years, including histamine-2 receptor antagonists (H2RAs), starting in 1980. Beginning in the year 2000 for the NHS and 2004 for the HPFS and for every subsequent 2-year period thereafter, participants were specifically asked whether they used PPIs regularly. While examples of brand names were provided for reference, specific information on brand, dose, and schedule was not specifically queried.

Assessment of Additional Covariates

Information on potential confounding factors, including age (continuous); smoking status (pack-years, continuous); menopausal hormone therapy in women (current vs never/past); body mass index (BMI, continuous); regular use of multivitamins (yes/no); aspirin; or nonsteroidal anti-inflammatory drug usage (≥2 tablets per week; yes/no for each); personal history of hypertension, hyperlipidemia, diabetes mellitus, or coronary heart disease (yes/no for each); and other medical diagnoses and lifestyle behaviors were updated biennially. Diet quality (Alternative Healthy Eating Index), alcohol intake (g/d, continuous), and physical activity (quintiles of metabolic equivalent task h/wk) were updated every 4 years. Further, information on several common indications for PPI usage, including history of PUD, GERD, or GI bleeding (each yes/no) were asked regularly. The validity of dietary assessment, anthropomorphic measurements, and physical activity has been reported previously.[14,17–22]

Statistical Analysis

We began follow-up with the date of return of the 2000 questionnaire in the NHS and the 2004 questionnaire in the HPFS, the questionnaire cycles in which PPI use was first queried. We excluded participants with a personal history of stroke or cancer before baseline and those with missing data on our exposure of interest. After these exclusions, the final study population consisted of 68,514 women and 28,989 men. Person-time for each participant was accrued from baseline to the date of first confirmed stroke, death from any cause, date of last returned questionnaire, or June 1, 2012 in NHS and January 1, 2012 in HPFS, whichever occurred first. Individuals were defined as PPI users if they responded that they regularly used PPI in the preceding 2 years. We employed Cox proportional hazards modeling using time-varying variables with the most updated information for PPI use and other covariates of interest before each 2-year time interval to calculate adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). We also examined PPI use and stroke risk according to strata of other risk factors. We also performed several sensitivity analyses to support our primary findings. The *Q*-test was used to test for heterogeneity in the association of PPI use and stroke between study cohorts and random-effects modeling was employed to produce summary estimates. SAS, version 9.4 (SAS Institute, Cary, NC) was used for all statistical analysis. All *P* values were 2-tailed with values ≤0.05 considered statistically significant.

Results

Cohort Characteristics

At baseline, among the 97,503 participants (68,514 women and 28,989 men; mean age, 69 ± 8 years), 6.5% of women and 16.1% of men reported regular PPI use. The rate of PPI use at that time was comparable to the rate of other US populations.[23–25] Participants who were regular PPI users at baseline tended to have higher rates of chronic medical conditions, including history of hypertension,

hyperlipidemia, coronary artery disease, and diabetes mellitus, as well as lower levels of physical activity expenditure (Table 1). Among women, regular PPI users were more likely to have higher BMI and a history of menopausal hormone use. As expected, PPI users had considerably higher rates of prior PUD, GERD, GI bleeding, or use of H2RAs.

Proton Pump Inhibitor Use and Incident Stroke

Over 12 years encompassing 949,330 person-years of follow-up, we documented 2599 incident strokes (2037 in women and 562 in men). In age-adjusted models comparing PPI users to nonusers, there was no observed difference in the summary estimate of risk for total stroke (HR, 1.11; 95% CI, 1.00–1.24) or hemorrhagic stroke (HR, 1.00; 95% CI, 0.72–1.38; Table 2). We did observe a statistically significant difference in age-adjusted risk for ischemic stroke (HR, 1.25; 95% CI, 1.08–1.46). This association was attenuated somewhat, but remained statistically significant after multivariable adjustment for smoking status, BMI, physical activity, dietary quality, alcohol use, menopausal hormone use in women, multivitamin use, regular aspirin use, regular non-aspirin nonsteroidal anti-inflammatory drug use, and personal history of hypertension, hyperlipidemia, coronary artery disease, or diabetes (HR, 1.18; 95% CI, 1.02–1.37).

To address the possibility that clinical indications for PPI use may confound the association of PPI use with ischemic stroke, we conducted additional analyses adjusting for several indications for PPI use, including history of PUD, GERD, GI bleeding, or use of H2RAs. With this additional adjustment, the association between PPI use and ischemic stroke was further attenuated (HR, 1.08; 95% CI, 0.91–1.27). Of note, there was no single indication that was the dominant source of confounding.

Given their shared indications of use, we examined the influence of H2RA use on risk for stroke. In age-adjusted analyses, regular users of H2RAs were at modestly increased risk of total stroke, though this was attenuated in multivariate testing. There was no apparent association between H2RA use and ischemic stroke (Supplementary Table 1). There was no clear association between duration of PPI use and risk of ischemic stroke ($P_{trend} = .18$; Table 3).

We evaluated potential differences in the association between regular PPI use and stroke according to strata of known stroke risk factors. The estimates for risk of ischemic stroke among PPI users did not appear to differ according to several stroke risk factors, including subgroups defined by age, regular aspirin use, hypertension, or hyperlipidemia. However, the association of PPI use with ischemic stroke appeared to be of greater magnitude among participants with obesity, or a history of diabetes or coronary heart disease, though formal tests for interaction were not statistically significant (Table 4; all $P_{interaction} \geq .10$).

To ensure that PPI use was not predictive of later stroke development, we performed a 2-year lag analysis in which exposure information was derived 2 questionnaire cycles

Table 1. Age-Standardized Baseline Characteristics According to Proton Pump Inhibitor Use

	Nurses' Health Study (2000)		Health Professionals Follow-up Study (2004)	
Characteristic	Non-user (n = 64,055)	Regular user (n = 4459)	Non-user (n = 24,326)	Regular user (n = 4663)
Age, *y*, mean (SD)	65.7 (7.1)	65.7 (7.1)	69.9 (8.6)	69.9 (8.5)
Smoking, %				
Never	45	42	53	49
Past	46	51	44	48
Current	9	7	3	3
Exercise, *MET-h/wk*, mean (SD)	17.5 (22.1)	13.9 (18.2)	45.4 (47.3)	40.4 (45.2)
BMI, kg/m^2, mean (SD)	26.6 (5.3)	28.3 (5.8)	25.6 (4.9)	25.9 (4.9)
Regular ASA usage, %	26	24	59	62
Regular NSAID usage, %	28	29	18	20
Past/current PMH, %	46	52	NA	NA
AHEI score	50.0 (9.6)	49.4 (9.4)	52.4 (10.8)	51.8 (10.5)
Hypertension, %	47	63	49	60
Hyperlipidemia, %	59	73	59	68
Coronary heart disease, %	3	5	9	12
Diabetes mellitus, %	8	11	10	11
GERD, %	8	37	23	72
Prior PUD, %	9	28	9	22
Prior GI bleed, %	2	6	4	8
Past/current H2RA usage, %	15	66	12	49

NOTE. Values are standardized to the age distribution of the study population. Regular use of either ASA or NSAIDs defined as ≥2 tablets per week. PMH use measured only among post-menopausal females.
AHEI, Alternative Healthy Eating Index; MET, metabolic-equivalent task; NSAID, nonsteroidal anti-inflammatory drug; PMH, post-menopausal hormone.

Table 2. Risk of Stroke Events by Current Use of Proton Pump Inhibitor Therapy

Variable	Non-user	Regular user
Total stroke		
NHS		
Cases/person-years	1,707/635,985	330/110,756
Age-adjusted, HR (95% CI)	1 (ref)	1.14 (1.01–1.29)
Model 1,[a] HR (95% CI)	1 (ref)	1.07 (0.95–1.21)
Model 2,[b] HR (95% CI)	1 (ref)	1.01 (0.89–1.16)
HPFS		
Cases/person-years	467/170,856	95/31,733
Age-adjusted, HR (95% CI)	1 (ref)	1.03 (0.82–1.29)
Model 1,[a] HR (95% CI)	1 (ref)	1.00 (0.80–1.25)
Model 2,[b] HR (95% CI)	1 (ref)	0.89 (0.69–1.14)
Total		
Cases/person-years	2,174/806,841	425/142,489
Age-adjusted, HR (95% CI)	1 (ref)	1.11 (1.00–1.24)
Model 1,[a] HR (95% CI)	1 (ref)	1.06 (0.95–1.17)
Model 2,[b] HR (95% CI)	1 (ref)	0.99 (0.88–1.11)
Ischemic stroke		
NHS		
Cases/person-years	811/635,985	169/110,756
Age-adjusted, HR (95% CI)	1 (ref)	1.27 (1.07–1.51)
Model 1,[a] HR (95% CI)	1 (ref)	1.18 (0.99–1.40)
Model 2,[b] HR (95% CI)	1 (ref)	1.08 (0.89–1.30)
HPFS		
Cases/person-years	225/170,856	56/31,733
Age-adjusted, HR (95% CI)	1 (ref)	1.21 (0.90-1.62)
Model 1,[a] HR (95% CI)	1 (ref)	1.18 (0.88-1.60)
Model 2,[b] HR (95% CI)	1 (ref)	1.08 (0.77-1.51)
Total		
Cases/person-years	1,036/806,841	225/142,489
Age-adjusted, HR (95% CI)	1 (ref)	1.25 (1.08–1.46)
Model 1,[a] HR (95% CI)	1 (ref)	1.18 (1.02–1.37)
Model 2,[b] HR (95% CI)	1 (ref)	1.08 (0.91–1.27)
Hemorrhagic stroke		
NHS		
Cases/person-years	223/635,985	36/110,756
Age-adjusted, HR (95% CI)	1 (ref)	0.94 (0.65–1.35)
Model 1,[a] HR (95% CI)	1 (ref)	0.97 (0.67–1.40)
Model 2,[b] HR (95% CI)	1 (ref)	0.94 (0.63–1.39)
HPFS		
Cases/person-years	50/170,856	12/31,733
Age-adjusted, HR (95% CI)	1 (ref)	1.19 (0.63–2.25)
Model 1,[a] HR (95% CI)	1 (ref)	1.12 (0.59–2.15)
Model 2,[b] HR (95% CI)	1 (ref)	0.79 (0.38–1.63)
Total		
Cases/person-years	273/806,841	48/142,489
Age-adjusted, HR (95% CI)	1 (ref)	0.99 (0.72–1.36)
Model 1,[a] HR (95% CI)	1 (ref)	1.01 (0.73–1.38)
Model 2,[b] HR (95% CI)	1 (ref)	0.90 (0.64–1.27)

HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study.
[a]Model 1: adjusted for age (continuous), smoking status (never <5, 5–20, 20–40, >40 pack-years), alcohol intake (g/d, continuous), BMI (continuous), physical activity (metabolic-equivalent task/wk, continuous), Alternative Healthy Eating Index scores (continuous), menopausal hormone use (among women, current vs past/never), multivitamin use, regular aspirin use, regular non-aspirin nonsteroidal anti-inflammatory use, history of hypertension, hyperlipidemia, coronary artery disease, or diabetes.
[b]Model 2: Model 1 + history of PUD (ever/never), history of GERD (ever/never), history of GI bleeding (ever/never), history of H2RA usage (ever/never).

(approximately 4 years) before the follow-up interval. The association of PPI use with ischemic stroke was not materially altered (multivariable HR, 0.93; 95% CI, 0.77–1.12).

Discussion

In this prospective investigation, we observed an association between regular PPI use and risk of ischemic stroke in age-adjusted models and multivariate models adjusting for known risk factors for ischemic stroke that was consistent with the findings of prior reports. However, additional adjustment for factors that may be associated with initiation and continuation of PPI therapy, including history of peptic ulcer disease, GERD, GI bleeding, and use of H2RA therapy substantially attenuated the association. Taken together, these data suggest that the association of PPI use with ischemic stroke may be due to residual confounding by factors associated with the indication for PPI use.

Our finding of a modestly increased risk for ischemic stroke associated with regular PPI use that was subsequently attenuated after further adjustment for several indications for PPI use may be explained by confounding from factors incompletely accounted for in our multivariable model. For example, the metabolic syndrome is a shared risk factor between GERD and ischemic stroke. Thus, adjusting for GERD may better control for confounding associated with the metabolic syndrome, which is not completely accounted for with adjustment for cardiac risk factors.

The risk of ischemic stroke and PPI therapy has been previously studied most often in the context of populations with established cardiovascular disease at baseline or as part of a composite outcome inclusive of other vascular events, including myocardial infarction. Our findings contrast with 2 recent publications that specifically focused on PPI use and ischemic stroke, including results from a retrospective case-control study of the Taiwan National Insurance Database, which observed a modestly increased risk for first-time ischemic stroke within a 120-day period of initiating PPI use.[4] In their propensity-based analysis, Wang et al[4] found that PPI use was associated with an age-adjusted increased risk for ischemic stroke (HR, 1.36; 95% CI, 1.14–1.62) which appeared to be of somewhat stronger magnitude than the age-adjusted risk that we observed (HR, 1.25; 95% CI, 1.08–1.46). This may be due to the shorter follow-up period (120 days) compared to our study. With shorter follow-up, the likelihood of confounding by clinical indications for PPI use may be more evident. For example, more acute health issues associated with near-term PPI use may also be associated with stroke. In fact, in their nested case-control analysis, which extended the follow-up period, the observed risk for ischemic stroke actually weakened with increasing duration of therapy. Finally, although propensity score matching was employed in the analyses, factors contributing to the score were limited to chronic conditions, such as diabetes, chronic kidney disease, drug abuse, physical limitation, autoimmune disease, and history of cancer. Therefore, confounding by factors associated with PPI use or the likelihood of receiving acid-suppression therapy may still have occurred.

Table 3. Relative Risk of Stroke Events by Duration of Proton Pump Inhibitor Use

Variable	Years of regular PPI use			
	0	1–2	>2	P_{trend}*
Total stroke				
NHS				
Cases/person-years	1,561/588,264	228/80,461	248/78,017	
Age-adjusted, HR (95% CI)	1 (ref)	1.11 (0.96–1.27)	1.16 (1.01–1.34)	.31
Model 1,[a] HR (95% CI)	1 (ref)	1.06 (0.92–1.23)	1.07 (0.93–1.24)	.49
Model 2,[b] HR (95% CI)	1 (ref)	1.00 (0.86–1.16)	0.98 (0.84–1.15)	.81
HPFS				
Cases/person-years	426/160,018	62/22,433	74/20,139	
Age-adjusted, HR (95% CI)	1 (ref)	0.94 (0.72–1.24)	1.21 (0.94–1.57)	.34
Model 1,[a] HR (95% CI)	1 (ref)	0.93 (0.71–1.22)	1.18 (0.91–1.53)	.40
Model 2,[b] HR (95% CI)	1 (ref)	0.86 (0.65–1.14)	1.05 (0.78–1.40)	.32
Total				
Cases/person-years	1,987/748,282	290/102,894	502/98,156	
Age-adjusted, HR (95% CI)	1 (ref)	1.07 (0.94–1.21)	1.18 (1.04–1.33)	.18
Model 1,[a] HR (95% CI)	1 (ref)	1.03 (0.91–1.17)	1.10 (0.97–1.25)	.35
Model 2,[b] HR (95% CI)	1 (ref)	0.97 (0.85–1.10)	1.00 (0.87–1.14)	.51
Ischemic stroke				
NHS				
Cases/person-years	729/588,264	135/80,461	116/78,017	
Age-adjusted, HR (95% CI)	1 (ref)	1.42 (1.18–1.72)	1.28 (1.04–1.57)	.40
Model 1,[a] HR (95% CI)	1 (ref)	1.37 (1.13–1.65)	1.18 (0.95–1.45)	.28
Model 2,[b] HR (95% CI)	1 (ref)	1.27 (1.04–1.55)	1.07 (0.84–1.35)	.13
HPFS				
Cases/person-years	208/160,018	34/22,433	39/20,139	
Age-adjusted, HR (95% CI)	1 (ref)	1.04 (0.72–1.50)	1.37 (0.96–1.96)	.91
Model 1,[a] HR (95% CI)	1 (ref)	1.00 (0.69–1.45)	1.32 (0.92–1.89)	.89
Model 2,[b] HR (95% CI)	1 (ref)	0.96 (0.65–1.40)	1.19 (0.79–1.79)	.97
Total				
Cases/person-years	937/748,282	169/102,894	155/98,156	
Age-adjusted, HR (95% CI)	1 (ref)	1.27 (0.94–1.71)	1.30 (1.09–1.55)	.48
Model 1,[a] HR (95% CI)	1 (ref)	1.22 (0.91–1.64)	1.21 (1.01–1.45)	.32
Model 2,[b] HR (95% CI)	1 (ref)	1.16 (0.89–1.50)	1.09 (0.89–1.34)	.18
Hemorrhagic stroke				
NHS				
Cases/person-years	208/588,264	19/80,461	32/78,017	
Age-adjusted, HR (95% CI)	1 (ref)	0.69 (0.42–1.12)	1.12 (0.76–1.64)	.11
Model 1,[a] HR (95% CI)	1 (ref)	0.70 (0.43–1.14)	1.16 (0.78–1.71)	.08
Model 2,[b] HR (95% CI)	1 (ref)	0.68 (0.41–1.12)	1.09 (0.69–1.70)	.09
HPFS				
Cases/person-years	47/160,018	7/22,433	8/20,139	
Age-adjusted, HR (95% CI)	1 (ref)	0.92 (0.41–2.07)	1.27 (0.58–2.76)	.40
Model 1,[a] HR (95% CI)	1 (ref)	0.86 (0.38–1.93)	1.21 (0.55–2.67)	.29
Model 2,[b] HR (95% CI)	1 (ref)	0.59 (0.25–1.41)	0.77 (0.32–1.85)	.33
Total				
Cases/person-years	255/748,282	26/102,894	40/98,156	
Age-adjusted, HR (95% CI)	1 (ref)	0.74 (0.49–1.13)	1.14 (0.81–1.62)	.07
Model 1,[a] HR (95% CI)	1 (ref)	0.74 (0.49–1.12)	1.17 (0.82–1.66)	.04
Model 2,[b] HR (95% CI)	1 (ref)	0.66 (0.42–1.01)	1.01 (0.68–1.51)	.06

[a]Model 1: adjusted for age (continuous), smoking status (never <5, 5–20, 20–40, >40 pack-years), cumulative average alcohol intake (g/d, continuous), cumulative average BMI, cumulative average physical activity (metabolic-equivalents/wk), cumulative average Alternative Healthy Eating Index score (continuous), post-menopausal hormone use (only in NHS, current vs past/never), cumulative years of multivitamin use, regular aspirin use, and regular non-aspirin nonsteroidal anti-inflammatory drug use, duration of personal history of hypertension, hyperlipidemia, coronary heart disease, or diabetes.
[b]Model 2: Model 1 + history of PUD (ever/never), history of GERD (ever/never), history of GI bleeding (ever/never), history of H2RA usage (ever/never).
*P_{trend} calculated as linear trend among PPI users.

Table 4. Risk of Ischemic Stroke and Regular Proton Pump Inhibitor Use by Strata

Characteristic	Non-user		Regular PPI user		$P_{INTERACTION}$
	Cases/ person-years	NHS+HPFS Multivariable HR (95% CI)	Cases/ person-years	NHS+HPFS Multivariable HR (95% CI)	
Age					
≤65 y	160/266,802	1 (ref)	31/39,949	1.27 (0.81–2.00)	.90
>65 y	876/540,040	1 (ref)	194/102,540	1.06 (0.89–1.27)	
BMI					
<30 kg/m^2	843/653,970	1 (ref)	162/106,854	0.98 (0.81–1.19)	.43
≥30 kg/m^2	193/152,871	1 (ref)	63/35,636	1.55 (1.10–2.19)	
Regular aspirin use					
No	552/475,719	1 (ref)	105/80,488	0.97 (0.77–1.24)	.16
Yes	484/331,122	1 (ref)	120/62,002	1.16 (0.92–1.46)	
Coronary heart disease					
No	942/767,318	1 (ref)	193/132,774	1.03 (0.86, 1.23)	.45
Yes	94/39,523	1 (ref)	32/9,715	1.56 (0.79–3.11)	
Hypertension					
No	272/359,117	1 (ref)	48/44,872	1.19 (0.80–1.76)	.69
Yes	764/447,724	1 (ref)	177/97,619	1.06 (0.88–1.27)	
Diabetes					
No	858/721,936	1 (ref)	169/122,931	0.98 (0.81–1.19)	.10
Yes	178/84,904	1 (ref)	56/19,559	1.57 (1.07–2.29)	
Hyperlipidemia					
No	313/275,612	1 (ref)	41/32,953	1.03 (0.71–1.49)	.39
Yes	723/531,229	1 (ref)	184/109,536	1.09 (0.91–1.31)	

NOTE. Multivariable model adjusted for age (continuous), smoking status (never <5, 5−20, 20−40, >40 pack-years), alcohol intake (g/d, continuous), BMI (continuous), physical activity (metabolic-equivalent task/wk, continuous), Alternative Healthy Eating Index scores (continuous), menopausal hormone use (among women, current vs. past/never), multivitamin use, regular aspirin use, regular non-aspirin nonsteroidal anti-inflammatory drug use, history of hypertension, hyperlipidemia, coronary artery disease, or diabetes. history of PUD (ever/never), history of GERD (ever/never), history of GI bleeding (ever/never), history of H2RA usage (ever/never).

In a separate investigation leveraging Danish national registry data, Sehested et al[5] found that PPI use determined by pharmacy records was associated with ischemic stroke (HR, 1.13; 95% CI, 1.09–1.19) based on billing data after adjustment for several indications for therapy, including PUD, GI hemorrhage, and GERD,[5] Further, they noted this association was more apparent with high-dose PPI (HR, 1.31; 95% CI, 1.21–1.42). Our results may have differed because our PPI exposure was based on self-report, which more likely captured actual intake, and our stroke end points were based on adjudicated medical record review, which is less prone to misclassification. Furthermore, in our analysis, we also adjusted for H2RA usage, which may further account for unmeasured confounding. Although we acknowledge that we lacked dosage information, which precludes direct comparison with Sehested et al, their study notably used a limited definition of dose based only within a 6-month inclusion period. Additionally, study inclusion criteria required a history of elective gastroscopy, raising the possibility of selection bias as well as lead-in bias, as subjects were likely exposed to PPI therapy before study baseline, limiting generalizability. For example, >40% of individuals in this study filled a PPI prescription without accounting for over-the-counter usage during the 6-year follow-up period, a relatively high number compared to the general population.

Our study includes several strengths. First, compared to prior analyses, we had prospective, biennially updated collection of both PPI use and several important potential stroke risk factors. Second, our long-term follow-up and rigorous adjudication of stroke events is a significant advantage over prior case-control studies of large claims databases, which rely on discharge coding, and may be inaccurate. Third, in this group of health professionals, ascertainment of PPI use by self-reporting is likely to be a more accurate reflection of actual use, including prescription and over-the-counter sources, compared with studies based on prescription data alone. Finally, we had the ability to adjust for other potential indications for PPI use.

We acknowledge several limitations of this study. PPI users differed from nonusers in many attributes, including a higher burden of chronic medical conditions. As with any observational study design, there remains the possibility of additional residual and unmeasured confounding. However, we did adjust for many more available potential confounding variables in our analysis than comparable studies, which substantially attenuated modestly significant associations. Finally, we did not collect information on PPI brand, dosage, and schedule, although most studies have suggested any potential association is a class effect not associated with any one specific drug. However, Sehested et al[5] did observe a

stronger association with high-dose PPI therapy, which we were unable to directly assess.

In this prospective study of 2 large, population-based cohorts, regular PPI therapy was not associated with an increase in the risk of incident ischemic stroke after adjustment for multiple stroke risk factors and potential indications for PPI use. These findings suggest that previously reported associations relating PPI therapy and ischemic stroke or other adverse events may have resulted from residual confounding, highlighting the need for caution in the interpretation of pharmacoepidemiologic data in which modest associations are detected.

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.2017.12.006.

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Reprint requests
Address requests for reprints to: Andrew T. Chan, MD, MPH, Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, GRJ-825C, Boston, Massachusetts 02114. e-mail: achan@partners.org; fax: (617) 724-6832.

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Supplementary Table 1. Risk of Stroke Events by Current Use of Histamine-2 Receptor Antagonist Therapy

Variable	Non-user	Regular user
Total stroke		
NHS		
Cases/person-years	1,858/693,941	179/52,800
Age-adjusted, HR (95% CI)	1 (ref)	1.19 (1.02−1.39)
Model 1,[a] HR (95% CI)	1 (ref)	1.10 (0.94−1.29)
Model 2,[b] HR (95% CI)	1 (ref)	1.07 (0.91−1.25)
HPFS		
Cases/person-years	525/191,215	37/11,374
Age-adjusted, HR (95% CI)	1 (ref)	1.21 (0.86−1.70)
Model 1,[a] HR (95% CI)	1 (ref)	1.18 (0.84−1.65)
Model 2,[b] HR (95% CI)	1 (ref)	1.13 (0.80−1.60)
Total		
Cases/person-years	2,383/885,156	216/64,174
Age-adjusted, HR (95% CI)	1 (ref)	1.19 (1.04−1.37)
Model 1,[a] HR (95% CI)	1 (ref)	1.11 (0.97−1.29)
Model 2,[b] HR (95% CI)	1 (ref)	1.08 (0.93−1.24)
Ischemic stroke		
NHS		
Cases/person-years	895/693,941	85/52,800
Age-adjusted, HR (95% CI)	1 (ref)	1.16 (0.93−1.45)
Model 1,[a] HR (95% CI)	1 (ref)	1.06 (0.85−1.33)
Model 2,[b] HR (95% CI)	1 (ref)	1.00 (0.79−1.26)
HPFS		
Cases/person-years	263/191,215	18/11,374
Age-adjusted, HR (95% CI)	1 (ref)	1.19 (0.73−1.93)
Model 1,[a] HR (95% CI)	1 (ref)	1.15 (0.71−1.87)
Model 2,[b] HR (95% CI)	1 (ref)	1.06 (0.64−1.74)
Total		
Cases/person-years	1,158/885,156	103/64,174
Age-adjusted, HR (95% CI)	1 (ref)	1.17 (0.95−1.43)
Model 1,[a] HR (95% CI)	1 (ref)	1.08 (0.88−1.32)
Model 2,[b] HR (95% CI)	1 (ref)	1.01 (0.82−1.25)
Hemorrhagic stroke		
NHS		
Cases/person-years	239/693,941	20/52,800
Age-adjusted, HR (95% CI)	1 (ref)	1.04 (0.66−1.65)
Model 1,[a] HR (95% CI)	1 (ref)	1.07 (0.68−1.70)
Model 2,[b] HR (95% CI)	1 (ref)	1.08 (0.67−1.73)
HPFS		
Cases/person-years	58/191,215	4/11,374
Age-adjusted, HR (95% CI)	1 (ref)	1.17 (0.42−3.26)
Model 1,[a] HR (95% CI)	1 (ref)	1.23 (0.44−3.46)
Model 2,[b] HR (95% CI)	1 (ref)	1.03 (0.36−2.94)
Total		
Cases/person-years	297/885,156	24/64,174
Age-adjusted, HR (95% CI)	1 (ref)	1.06 (0.70−1.62)
Model 1,[a] HR (95% CI)	1 (ref)	1.10 (0.72−1.67)
Model 2,[b] HR (95% CI)	1 (ref)	1.07 (0.69−1.65)

[a]Model 1: adjusted for age (continuous), smoking status (never <5, 5−20, 20−40, >40 pack-years), alcohol intake (g/d, continuous), BMI (continuous), physical activity (metabolic-equivalent task/wk, continuous), Alternative Healthy Eating Index scores (continuous), menopausal hormone use (among women, current vs past/never), multivitamin use, regular aspirin use, regular non-aspirin nonsteroidal anti-inflammatory drug use, history of hypertension, hyperlipidemia, coronary artery disease, or diabetes.

[b]Model 2: Model 1 + history of PUD (ever/never), history of GERD (ever/never), history of GI bleeding (ever/never), history of PPI usage (ever/never).