Do Proton Pump Inhibitors Cause Myocardial Infarction and Stroke? Time-Variant Analyses Can Resolve the Debate

To the Editor:

With broad advertisement and over-the-counter availability, global proton pump inhibitor (PPI) use is common (10%–21%) for the treatment of gastroesophageal reflux disease (GERD).[1,2] Unlike histamine 2 receptor antagonists (H2RA), PPIs impair endothelial nitric oxide synthase and vascular function that lead to inflammation, GERD, and thrombosis, and they may impair cardiac function.[3] With conflicting evidence, there is ongoing concern about whether PPIs increase the risk of cardiovascular disease (CVD), the leading cause of adult death and disability worldwide.[2–15]

Our nested case–control analyses of PPI use, and its recency and duration with first and second myocardial infarction (MI) and stroke events in the World Trade Center (WTC) General Responders Cohort, a multicenter open cohort, clarifies whether the relationship is causal. Evidence regarding the timing of PPI use and its association with CVD is scant with mixed results.[5,7,10,13,15] Five studies assessing the timing of PPI use included patients using antiplatelet agents, which confounds the associations of PPI and incident of CVD because antiplatelet agents are used for secondary prevention of recurrent CVD and treatment of other related conditions that may precipitate incident myocardial infarction and stroke.[5,7,10,13] These studies are also flawed by the lack of an unexposed comparison group,[5] comparison of cases to themselves before PPI use,[7,10] or very short–term assessment of medications use that cannot fairly assess causality of chronic conditions such as CVD.[5,7,15]

METHODS

Without access to medical records, this study assessed self-reported physician's diagnosis or treatment for first and second MI as well as stroke events, conditions that account for most CVD mortality,[12] from the WTC Health Program standardized medical monitoring visits (scheduled every 12–18 months) data.[16] Of 50,577 members providing written voluntary informed consent through December 31, 2021, 47,070 had essential demographic information. The analyses excluded 3.1% (n = 1462) reporting antiplatelet use, 1 person with unknown birth date, 7 who were <18 years at incident MI or stroke, and 412 with unknown earliest MI or stroke dates. Responders not reporting MI or stroke were classified as controls. Medication use reported in free-text fields was reviewed through visual inspection aided by Stedman Plus medical/pharmaceutical spell checker 2020. The recent analyses classified PPI use by its most recent use regardless of longer PPI use duration. The duration analyses classified PPI use by its longest duration. Medication dose was inconsistently reported and not analyzed. Those not reporting medication use were classified as nonusers.

Up to 4 controls were randomly selected from noncases and frequency matched without replacement to the case's 5 year age group, sex (male or female), first visit body mass index (BMI <25, 25–<30 and ≥30), and the cases' first and last monitoring visit dates plus/minus 3 years. Controls were assigned their matched case event ("index") dates. When possible, the BMI estimate used the average of the first 2 visits' height measurements. To retain continuity, second events are subsets of matched first events.

Fixed-effects, conditional, matched-pairs, logistic regression analyses were adjusted for GERD and H2RA use, major CVD comorbidity conditions, and for potential confounding before the index date.[17] Where possible, incomplete event dates were imputed (month's midpoint for day, June for month). All missing binary covariate data were derived using multiple imputation by logit chained equations except for "other heart disease," which was coded to the modal value (0).[18] Categorical missing was coded to their modal referent values (white n = 55, nonsmoker n = 15 and protective services n = 211).

Sensitivity analyses included the following: (1) replaced duration with the percent of preindex visits when PPI and H2RA were reported to estimate their cumulative use; (2) limited index dates to 2007–2021 when event dates may be recalled more accurately; and (3) distinguished program certified GERD, potentially a more objective measure, from solely self-reported GERD.

Descriptive and matching analyses were conducted using SPSS 28.0.1.1(15) (IBM Corp, Armonk, NY), and multiple imputation and regression analyses were conducted using Stata (StataCorp LLC. 2019. Stata Statistical Software: Release 16. College Station, TX).

The principles outlined in the Declaration of Helsinki 1975 as revised in 2013 and national and institutional committees' ethical standards on human experimentation were followed. The program's 5 clinical centers' and the data center's Institutional Review Board at the Icahn School of Medicine at Mount Sinai approved the research.

RESULTS

Frequency matching produced substantively similar study groups. Few responders took PPI within 30 days before the index dates (Table 1). Most cases with very recent PPI use had long-term PPI use. Only very recent (≤30 days) PPI use was associated with higher MI and

Table 1. Recency* of preindex date proton pump inhibitor use by PPI duration†.

	Duration					Duration				
	First event myocardial infarction cases					Second event myocardial infarction cases				
	None	≤1 yr	<7 yrs	≥7 yrs	Total	None	≤1 yr	<7 yrs	≥7 yrs	Total
Recency										
None	543	0	0	0	543	253	0	0	0	253
PPI ≤30 d	0	5	6	7	18	0	12	10	19	41
PPI 31–180 d	0	5	11	10	26	0	3	2	1	6
PPI ≥181 d	0	56	17	28	101	0	12	7	9	28
Total	543	66	34	45	688	253	27	19	29	328
	First event myocardial infarction controls					Second event myocardial infarction controls				
	None	≤1 yr	<7 yrs	≥7 yrs	Total	None	≤1 yr	<7 yrs	≥7 yrs	Total
None	2256	0	0	0	2256	1034	0	0	0	1034
PPI ≤30 d	0	1	8	13	22	0	6	6	10	22
PPI 31–180 d	0	25	23	40	88	0	19	18	20	57
PPI ≥181 d	0	205	76	98	379	0	106	46	45	197
Total	2256	231	107	151	2745	1034	131	70	75	1310
	First event stroke cases					Second event stroke cases				
	None	≤1 yr	<7 yrs	≥7 yrs	Total	None	≤1 yr	<7 yrs	≥7 yrs	Total
None	806	0	0	0	806	462	0	0	0	462
PPI ≤30 d	0	10	11	18	39	0	23	47	57	127
PPI 31–180 d	0	11	20	21	52	0	4	7	5	16
PPI ≥181 d	0	86	49	59	194	0	34	27	31	92
Total	806	107	80	98	1091	462	61	81	93	697
	First event stroke controls					Second event stroke controls				
	None	≤1 yr	<7 yrs	≥7 yrs	Total	None	≤1 yr	<7 yrs	≥7 yrs	Total
None	3316	0	0	0	3316	1954	0	0	0	1954
PPI ≤30 d	0	10	14	22	46	0	11	15	12	38
PPI 31–180 d	0	48	61	97	206	0	45	38	77	160
PPI ≥181 d	0	359	182	236	777	0	257	153	209	619
Total	3316	417	257	355	4345	1954	313	206	298	2771

*Recency = the most proximate preindex date of use minus the index date.
†Duration = the most proximate preindex use date minus the most distant use date.

stroke risk; less recent and longer PPI use was associated with no or diminished risks (Table 2). Less adjusted and the sensitivity results were very similar (data not shown).

DISCUSSION AND CONCLUSIONS

The study reveals biologically implausible associations, where only very recent PPI use increased the risk of MI and stroke, which are chronic diseases that generally develop over years. The results also counter a dose–response relationship as nearly all responders with very recent PPI use had much longer use, which was associated with null or lower risks. Both MI and stroke involve broad physiologic processes, and impending events may produce symptoms that prompt PPI use, providing some explanation of our and other studies' associations identified with recent use.[3,17] Self-reported MI and stroke validity is generally good.[20] The ample longitudinal data supported matching and statistical adjustment that strengthened

Table 2. Adjusted* odds ratios for proton pump inhibitor use,† recency,‡ and duration§.

	First MI		Second MI		First stroke		Second stroke	
	n = 3433		n = 1638		n = 5436		n = 3468	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
PPI use								
Preindex PPI*	1.01 (0.76–1.34)	0.944	0.74 (0.49–1.12)	0.161	0.96 (0.78–1.18)	0.707	0.92 (0.72–1.17)	0.502
Preindex GERD*	1.07 (0.83–1.36)	0.609	1.7 (1.20–2.41)	0.003	1.13 (0.94–1.36)	0.191	1.34 (1.07–1.68)	0.011
Preindex H2*	0.59 (0.37–0.92)	0.021	0.39 (0.21–0.75)	0.004	0.77 (0.58–1.02)	0.067	0.75 (0.54–1.03)	0.072
Recency								
No PPI	Referent							
PPI recency ≤30 d	2.75 (1.34–5.62)	0.006	3.48 (1.71–7.07)	0.001	3.10 (1.85–5.17)	≤0.001	11.03 (6.99–17.42)	≤0.001
PPI recency 31–180 d	0.84 (0.49–1.44)	0.525	0.39 (0.15–1.02)	0.056	0.86 (0.61–1.23)	0.416	0.31 (0.17–0.56)	≤0.001
PPI recency ≥180 d	0.94 (0.69–1.27)	0.684	0.39 (0.23–0.68)	0.001	0.87 (0.70–1.09)	0.236	0.44 (0.32–0.60)	≤0.001
GERD	1.08 (0.84–1.38)	0.549	1.80 (1.26–2.57)	0.001	1.14 (0.95–1.38)	0.158	1.43 (1.13–1.81)	0.003
No H2RA	Referent							
H2RA recency ≤30 d	0.27 (0.03–2.41)	0.241	0.71 (0.20–2.43)	0.58	1.13 (0.40–3.19)	0.815	3.19 (1.36–7.46)	0.008
H2RA recency 31–180 d	0.78 (0.29–2.11)	0.63	0.60 (0.12–2.90)	0.52	0.64 (0.32–1.29)	0.212	0.34 (0.10–1.16)	0.085
H2RA recency ≥181 d	0.57 (0.34–0.95)	0.031	0.22 (0.09–0.57)	0.002	0.71 (0.51–0.99)	0.042	0.53 (0.33–0.84)	0.007
Duration								
No PPI	Referent							
PPI duration ≤1 yr	1.00 (0.71–1.41)	0.992	0.64 (0.37, 1.11)	0.11	0.94 (0.73–1.22)	0.658	0.64 (0.46–0.89)	0.009
PPI duration <7 yrs	1.07 (0.67–1.70)	0.791	0.82 (0.42, 1.60)	0.555	1.03 (0.76–1.41)	0.829	1.32 (0.95–1.84)	0.101
PPI duration ≥7 yrs	0.98 (0.63–1.53)	0.94	0.86 (0.47–1.57)	0.623	0.92 (0.68–1.24)	0.583	1.00 (0.72–1.39)	0.999
GERD	1.07 (0.83–1.37)	0.603	1.69 (1.19–2.41)	0.004	1.13 (0.94–1.37)	0.189	1.31 (1.04–1.64)	0.022
No H2RA	Referent							
H2RA duration ≤1 yr	0.52 (0.29–0.94)	0.029	0.27 (0.12–0.62)	0.002	0.75 (0.51–1.10)	0.14	0.73 (0.47–1.12)	0.149
H2RA duration <7 yrs	0.65 (0.26–1.63)	0.359	1.48 (0.42–5.27)	0.543	0.65 (0.37–1.12)	0.122	0.67 (0.37–1.20)	0.179
H2RA duration ≥7 yrs	0.74 (0.29–1.89)	0.533	0.38 (0.09–1.51)	0.168	0.96 (0.56–1.66)	0.886	0.85 (0.46–1.57)	0.593

*Up to 4 controls matched to the case's 5-year age group, sex (male or female), first visit body mass index (BMI <25, 25–<30 and ≥30), and the cases' first and last monitoring visit dates plus/minus 3 years. Controls were assigned their matched case event ("index") dates. Preindex PPI adjusted for preindex date GERD, H2RA use, major risk factors (diabetes, hypertension, and high cholesterol), potential confounding including posttraumatic stress disorder (civilian PTSD checklist scores ≥44[19]), cancer, occupation, and first response participation on September 11, 2001, symptoms of an impending event (chest pain, heart palpitations), and other heart disease before the index date and whether the initial visit data form included information on myocardial infarction or stroke.

†Yes = 1; no = 0.

‡Recency = the most proximate preindex date of use minus the index date.

§Duration = the most proximate preindex use date minus the most distant use date.

H2RA, histamine 2 receptor antagonist.

internal validity and minimized selection and follow-up bias. Adjustment for the major known CVD comorbidities and confounding provide indirect adjustment for other medication use. Except for being mostly male, the sample characteristics including the prevalence of major CVD risk factors are similar to the US population.[17]

Analysis of the recency and duration of PPI use, excluding people who have used antiplatelet therapy, in studies with unexposed referent groups could clarify the nature of the associations of PPI use and CVD and resolve the ongoing debate.

Human participant protection

The WTC Health Program research has been approved by the Institutional Review Boards of the Rutgers University Environmental and Occupational Health Sciences Institute; NYU School of Medicine; Icahn School of Medicine at Mount Sinai; Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; and Stony Brook University Department of Medicine; the WTC Health Program General Responder Data Center conducted the data analysis at the the Icahn School of Medicine at Mount Sinai.

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REFERENCES

1. Eusebi LH, Ratnakumaran R, Yuan Y, et al. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. *Gut*. 2018;67:430–440.
2. Lee TJ, Fennerty MB, Howden CW. Systematic review: is there excessive use of proton pump inhibitors in gastro-oesophageal reflux disease? *Aliment Pharm Ther*. 2004;20: 1241–1251.
3. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PLoS One*. 2015;10:e0124653.
4. Cardoso RN, Benjo AM, DiNicolantonio JJ, et al. Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: an updated meta-analysis. *Open Heart*. 2015;2:e000248.
5. Casula M, Scotti L, Galimberti F, et al. Use of proton pump inhibitors and risk of ischemic events in the general population. *Atherosclerosis*. 2018;277:123–129.
6. Charlot M, Ahlehoff O, Norgaard ML, et al. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use A nationwide cohort study. *Ann Intern Med*. 2010;153:378–386.
7. Chui CSL, Cheung KS, Brown JP, et al. Proton pump inhibitors and myocardial infarction: an application of active comparators in a self-controlled case series. *Int J Epidemiol*. 2023;52:899–907.
8. Farhat N, Fortin Y, Haddad N, et al. Systematic review and meta-analysis of adverse cardiovascular events associated with proton pump inhibitors used alone or in combination with antiplatelet agents. *Crit Rev Toxicol*. 2019;49:215–261.
9. GBD Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–1222.
10. Juurlink DN, Dormuth CR, Huang AJ, et al. Proton pump inhibitors and the risk of adverse cardiac events. *PLoS One*. 2013;8:e84890.
11. Melloni C, Washam JB, Jones WS, et al. Conflicting results between randomized trials and observational studies on the impact of proton pump inhibitors on cardiovascular events when coadministered with dual antiplatelet therapy: systematic review. *Circ Cardiovasc Qual Outcomes*. 2015;8:47–55.
12. Nowbar AN, Gitto M, Howard JP, et al. Mortality from ischemic heart disease. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005375.
13. Qian Y, Jick S. Proton-pump inhibitor use and myocardial infarction: a nested case-control study in the UK clinical practice research datalink. *Epidemiology*. 2020;31: 423–431.
14. Shiraev TP, Bullen A. Proton pump inhibitors and cardiovascular events: a systematic review. *Heart Lung Circ*. 2018;27:443–450.
15. Wang YF, Chen YT, Luo JC, et al. Proton-pump inhibitor use and the risk of first-time ischemic stroke in the general population: a nationwide population-based study. *Am J Gastroenterol*. 2017;112:1084–1093.
16. Dasaro CR, Holden WL, Berman KD, et al. Cohort profile: World trade center Health program general responder cohort. *Int J Epidemiol*. 2017;46:e9.
17. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American heart association. *Circulation*. 2019;139:e56–e528.
18. Zhang Z. Multiple imputation with multivariate imputation by chained equation (MICE) package. *Ann Transl Med*. 2016;4:30.
19. Ruggiero KJ, Del Ben K, Scotti JR, et al. Psychometric properties of the PTSD checklist-civilian version. *J Trauma Stress*. 2003;16:495–502.
20. Machon M, Arriola L, Larranaga N, et al. Validity of self-reported prevalent cases of stroke and acute myocardial infarction in the Spanish cohort of the EPIC study. *J Epidemiol Community Health*. 2013;67:71–75.