Original Investigation

Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease

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Editorial page 172

IMPORTANCE Proton pump inhibitors (PPIs) are among the most commonly used drugs worldwide and have been linked to acute interstitial nephritis. Less is known about the association between PPI use and chronic kidney disease (CKD).

OBJECTIVE To quantify the association between PPI use and incident CKD in a population-based cohort.

DESIGN, SETTING, AND PARTICIPANTS In total, 10 482 participants in the Atherosclerosis Risk in Communities study with an estimated glomerular filtration rate of at least 60 mL/min/1.73 m^2 were followed from a baseline visit between February 1, 1996, and January 30, 1999, to December 31, 2011. The data was analyzed from May 2015 to October 2015. The findings were replicated in an administrative cohort of 248 751 patients with an estimated glomerular filtration rate of at least 60 mL/min/1.73 m^2 from the Geisinger Health System.

EXPOSURES Self-reported PPI use in the Atherosclerosis Risk in Communities study or an outpatient PPI prescription in the Geisinger Health System replication cohort. Histamine$_2$ (H_2) receptor antagonist use was considered a negative control and active comparator.

MAIN OUTCOMES AND MEASURES Incident CKD was defined using diagnostic codes at hospital discharge or death in the Atherosclerosis Risk in Communities Study, and by a sustained outpatient estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 in the Geisinger Health System replication cohort.

RESULTS Among 10 482 participants in the Atherosclerosis Risk in Communities study, the mean (SD) age was 63.0 (5.6) years, and 43.9% were male. Compared with nonusers, PPI users were more often of white race, obese, and taking antihypertensive medication. Proton pump inhibitor use was associated with incident CKD in unadjusted analysis (hazard ratio [HR], 1.45; 95% CI, 1.11-1.90); in analysis adjusted for demographic, socioeconomic, and clinical variables (HR, 1.50; 95% CI, 1.14-1.96); and in analysis with PPI ever use modeled as a time-varying variable (adjusted HR, 1.35; 95% CI, 1.17-1.55). The association persisted when baseline PPI users were compared directly with H_2 receptor antagonist users (adjusted HR, 1.39; 95% CI, 1.01-1.91) and with propensity score–matched nonusers (HR, 1.76; 95% CI, 1.13-2.74). In the Geisinger Health System replication cohort, PPI use was associated with CKD in all analyses, including a time-varying new-user design (adjusted HR, 1.24; 95% CI, 1.20-1.28). Twice-daily PPI dosing (adjusted HR, 1.46; 95% CI, 1.28-1.67) was associated with a higher risk than once-daily dosing (adjusted HR, 1.15; 95% CI, 1.09-1.21).

CONCLUSIONS AND RELEVANCE Proton pump inhibitor use is associated with a higher risk of incident CKD. Future research should evaluate whether limiting PPI use reduces the incidence of CKD.

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Chronic kidney disease (CKD) affects approximately 13.6% of adults in the United States,[1] is associated with a substantially increased risk of death and cardiovascular events,[2] and accounts for a disproportionately large burden on the financial resources of Medicare.[1] The increasing prevalence of CKD among communities cannot be fully explained by trends in known risk factors, such as diabetes mellitus and hypertension, suggesting that other variables may contribute to the disease process.[3,4] Medication use may be a potential factor, particularly given tendencies toward polypharmacy.[5] Identifying iatrogenic risk factors for CKD may help to promote the rational use of medications and reduce the burden of CKD worldwide.

Proton pump inhibitors (PPIs) are one of the most commonly prescribed medications in the United States, and it has been estimated that between 25% and 70% of these prescriptions have no appropriate indication.[6] The duration of use frequently extends beyond recommended guidelines.[7,8] There is also a trend toward PPI use in infants and children.[9,10] Since the introduction of PPIs to the US market in 1990, several observational studies have linked PPI use to uncommon but serious adverse health outcomes, including hip fracture,[11] community-acquired pneumonia,[12] *Clostridium difficile* infection,[13] acute interstitial nephritis,[14,15] and acute kidney injury (AKI).[16-18] It is plausible that PPI use may also be a risk factor for CKD, potentially mediated by recurrent AKI,[19,20] or by hypomagnesemia, which has been associated with PPI use[21] and with incident CKD.[22] To our knowledge, no population-based studies have evaluated the association between PPI use and the risk of CKD.

The objective of this study was to quantify the association between PPI use and incident kidney disease in the general population. We hypothesized that PPI use is an independent risk factor for CKD and that the use of Histamine$_2$ (H_2) receptor antagonists, another common class of medications used to treat gastroesophageal reflux disease, is not. As a secondary outcome, we also evaluated the association between PPI use and AKI. Analyses were performed in the Atherosclerosis Risk in Communities (ARIC) study, a long-running population-based cohort, and were replicated in patients receiving care in the Geisinger Health System, an integrated health system in rural Pennsylvania.

Methods

Study Design and Setting of the ARIC Study

The ARIC study is a prospective cohort study of 15 792 adults 45 to 64 years old who were recruited as a population-based sample from 4 US communities (Forsyth, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland). Participants attended the first visit between January 12, 1987, and March 29, 1990, and attended subsequent visits at 3-year intervals until their fourth visit between February 1, 1996, and January 30, 1999. Visit 5 occurred between June 1, 2011, and August 30, 2013. The dates of our study analysis were from February 1, 1996 (ARIC study visit 4) to December 31, 2011. The ARIC study has been approved by the institutional review boards at the University of Minnesota (Minneapolis), The Johns Hopkins University (Baltimore, Maryland), Wake Forest University (Winston-Salem, North Carolina), University of North Carolina (Winston-Salem), University of Texas Health Sciences Center at Houston, and University of Mississippi Medical Center (Jackson). Participants provided written informed consent. All participants were followed up through an annual telephone survey and a review of community hospital discharge lists until December 31, 2011. Deaths were determined by a telephone survey of alternative contacts and surveillance of local newspaper obituaries, state death lists, and death certificates from the Department of Vital Statistics. Further details about the ARIC study cohort have been published previously.[23]

Participants in the ARIC Study

For the present study, we included the 11 656 participants who attended visit 4. The ratio of urinary albumin level to creatinine level, an important risk factor for CKD, was first obtained at this visit, and few participants reported PPI use before 1996. Participants who were missing data for the estimated glomerular filtration rate (eGFR) or the ratio of urinary albumin to creatinine (n = 215) or who had an eGFR of less than 60 mL/min/1.73 m^2 (n = 725) were excluded. Participants with missing data for years of education, health insurance status, cigarette smoking, body mass index (BMI), mean resting systolic blood pressure, use of antihypertensive or anticoagulant medication, or prevalent hypertension, diabetes mellitus, or cardiovascular disease (n = 234) were also excluded, resulting in a study population of 10 482 participants. The use of the full data set with multiple imputation for missing variables did not change the inference; therefore, we used the complete case analysis. The study population for the secondary outcome of AKI excluded persons with known end-stage renal disease (ESRD) or an eGFR of less than 15 mL/min/1.73 m^2 (n = 50). Therefore, it included some participants with an eGFR of less than 60 mL/min/1.73 m^2 but was otherwise similarly constructed (n = 11 145).

Measurement of Incident Kidney Disease in the ARIC Study

Incident CKD was defined by diagnostic codes that indicated CKD at hospital discharge (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]) or death (*ICD-10-CM*) or by incident ESRD, as determined through linkage with the United States Renal Data System registry.[24,25] In an earlier validation study[24] that used at least a 25% decline in the eGFR to less than 60 mL/min/1.73 m^2 at a follow-up outpatient visit as a reference standard for CKD, the sensitivity of diagnostic codes for defining CKD was 35.5%, and the specificity was 95.7%. Incident AKI was defined by hospitalization or death, with *ICD-9-CM* or *ICD-10-CM* diagnostic codes of 584.x or N17.x, respectively.[26] Participants who died before developing CKD, were lost to follow-up, or had disease-free survival to December 31, 2011, were censored.

Measurement of PPI Use and Other Covariates in the ARIC Study

The use of PPIs and H_2 receptor antagonists was measured at the baseline study visit through direct visual inspection of pill bottles for all medications used during the preceding 2 weeks. Exposure to antihypertensive, anticoagulant, aspirin, statin,

Table 1. Baseline Characteristics of the Study Populations

Variable	Atherosclerosis Risk in Communities Study				Geisinger Health System Replication Cohort			
	PPI Users (n = 322)	H_2 Receptor Antagonist Users[a] (n = 956)	Nonusers (n = 9204)	*P* Value	PPI Users (n = 16 900)	H_2 Receptor Antagonist Users[a] (n = 6640)	Nonusers (n = 225 211)	*P* Value
Age, mean (SD), y	62.8 (5.5)	63.1 (5.5)	62.5 (5.6)	.008	50.0 (15.9)	50.3 (16.3)	49.5 (16.3)	<.001
Male sex, %	42.5	39.3	44.4	.01	43.2	42.6	43.5	.32
White race, %	86.0	84.2	77.9	<.001	94.6	96.4	95.5	<.001
Education ≥12 y, %	81.7	79.4	81.8	.18	NA	NA	NA	NA
Health insurance, %	92.2	88.9	85.6	<.001	NA	NA	NA	NA
Annual household income, %								
≥$25 000	72.0	66.4	66.2		NA	NA	NA	NA
<$25 000	23.6	29.7	29.7	.22	NA	NA	NA	NA
No response	4.3	3.9	4.2		NA	NA	NA	NA
eGFR, mean (SD), mL/min/1.73 m^2	87.8 (13.4)	86.5 (13.5)	88.9 (13.1)	<.001	94.9 (17.7)	95.2 (18.2)	96.0 (18.0)	<.001
Ratio of urinary albumin to creatinine, median (IQR), mg/g	4.0 (2.0-7.5)	3.6 (1.8-7.1)	3.7 (1.7-7.5)	.71	NA	NA	NA	NA
Cigarette smoking, %								
Current	11.5	15.5	15.2		25.7	26.1	23.9	
Former	48.4	44.2	43.2	.23	26.4	25.4	23.9	<.001
Never	40.1	40.3	41.6		47.9	48.5	52.2	
BMI, mean (SD)	29.4 (5.3)	29.4 (5.8)	28.7 (5.6)	<.001	30.8 (7.3)	30.8 (7.4)	30.2 (7.1)	<.001
Systolic blood pressure, mean (SD), mm Hg	126.5 (18.3)	128.2 (18.6)	127.0 (18.8)	.16	126.4 (15.8)	128.2 (16.7)	128.0 (17.7)	<.001
Prevalent medical condition, %								
Hypertension	54.3	50.0	44.8	<.001	33.3	34.0	30.2	<.001
Diabetes mellitus	14.9	18.0	15.6	.14	10.8	9.7	10.4	.06
Cardiovascular disease	13.7	14.1	10.8	.003	11.3	11.8	8.7	<.001
Concomitant medication use, %								
Antihypertensive	55.3	48.5	39.9	<.001	32.0	31.3	20.6	<.001
ACE-I/ARB	16.8	13.4	12.9	.12	15.5	13.4	9.6	<.001
Diuretic	16.1	12.1	9.6	<.001	13.8	12.6	8.3	<.001
Aspirin	64.9	67.6	54.9	<.001	7.8	5.9	3.9	<.001
Nonsteroidal anti-inflammatory drug	27.6	32.8	33.2	.11	13.9	14.4	9.5	<.001
Statin	20.2	13.6	10.3	<.001	13.9	11.7	6.1	<.001
Anticoagulant	1.9	2.8	1.7	.04	2.5	2.9	1.1	<.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; H_2, histamine$_2$; IQR, interquartile range; NA, not available; PPI, proton pump inhibitor.

[a] For the purposes of this table, participants using both a PPI and an H_2 receptor antagonist were classified as PPI users. In the Atherosclerosis Risk in Communities study, this represented 24 of the 322 PPI users. In the Geisinger Health System replication cohort, this represented 815 of the 6640 PPI users.

diuretic, and nonsteroidal anti-inflammatory medications was measured in the same way. Subsequent exposure to PPIs and H_2 receptor antagonists was obtained as part of the annual telephone follow-up, which included questions about medication use starting in September 2006. At each telephone follow-up from 2006 onward, participants were asked to assemble all medications they were taking and to "read the names of all the medications prescribed by a doctor."

Baseline plasma and urinary creatinine levels were measured by the modified kinetic Jaffé method.[24] The equation developed by the Chronic Kidney Disease Epidemiology Collaboration was used to calculate the eGFR.[27] The urinary albumin level was measured using a nephelometer (BN100; Dade Behring or IMMAGE; Beckman).[24] Three domains of socioeconomic status were measured, including self-reported highest level of education, health insurance status, and annual household income in the previous 12 months. Cigarette smoking status was defined categorically as a current, former, or never smoker at baseline, and the BMI was derived. Prevalent hypertension was defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or self-reported use of antihypertensive medication within the past 2 weeks. Prevalent diabetes mellitus was defined by a fasting blood glucose concentration of at least 126 mg/dL, a random glucose concentration of at least 200 mg/dL, self-report of a physician diagnosis of diabetes mellitus, or reported use of medication for diabetes in the past 2 weeks (to convert glucose concentration to millimoles per liter, multiply by 0.0555). Preva-

lent cardiovascular disease was defined as a composite outcome of prevalent coronary heart disease or stroke at visit 4.

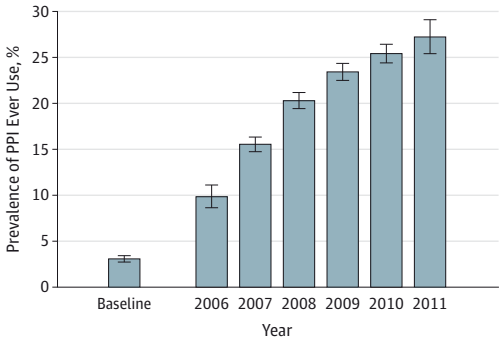
Geisinger Health System Replication Cohort

The replication cohort consisted of 248 751 patients with an outpatient eGFR of at least 60 mL/min/1.73 m^2 receiving care between February 13, 1997, and October 9, 2014, in the Geisinger Health System, a large rural health care system in central and northeastern Pennsylvania. Participants were selected at the earliest time point when they had both creatinine level and systolic blood pressure available. Incident CKD was defined as the first outpatient eGFR of less than 60 mL/min/1.73 m^2 that was sustained at all subsequent assessments of the eGFR or as the development of ESRD, which was ascertained through linkage to the United States Renal Data System registry. Incident AKI was defined as an *ICD-9-CM* code of 584.x, and death was ascertained through linkage to the National Death Index. Individuals who did not develop the outcome of interest were censored at their last follow-up or death. Medication use was determined by prescriber prescription within 90 days before baseline. The frequency of PPI use was categorized as once daily or twice daily according to the prescription and was assumed to be once daily if not specified. Comorbidities were captured by inpatient and outpatient billing codes.

Statistical Analysis

Baseline characteristics of PPI users and non-PPI users were compared using *t* tests for continuous variables and χ^2 tests for categorical variables. The Wilcoxon rank sum test was used for continuous variables that were not normally distributed. Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% CIs of incident CKD associated with PPI use. The proportional hazards assumption was tested using Schoenfeld residuals. Exposure to PPIs was modeled as a binary variable at baseline and in secondary analyses as a time-varying ever-use variable, in which a participant was considered an ever user at the first instance of PPI use and at all time points thereafter. In the ARIC study, time-varying PPI use represented baseline use, with updates in 2006 and yearly thereafter; in the replication cohort, it was evaluated by assessing all health care professional prescriptions throughout the study period. In the ARIC study, adjustment was performed for demographic variables (age, sex, race, and study center), socioeconomic status (health insurance and highest level of education), clinical measurements (baseline eGFR, logarithm of the ratio of urinary albumin to creatinine, cigarette smoking, mean systolic blood pressure, and BMI), prevalent comorbidities (diabetes mellitus and cardiovascular disease), and concomitant use of medications (antihypertensive medication and anticoagulant medication). Annual household income and concomitant use of nonsteroidal anti-inflammatory drugs, aspirin, diuretics, or statin medications were considered possible confounders a priori; however, they did not affect the results of adjusted analyses and were not included in the final model. In the replication cohort, fewer comorbidities were available; therefore, analyses were adjusted for age, sex, race, baseline eGFR, cigarette smoking, BMI, systolic blood pressure, diabetes mellitus, history of cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and nonsteroidal anti-inflammatory drug use. Subgroup analyses were performed, stratified by the median age, sex, race (in the ARIC study only), diabetes mellitus, and concomitant medication use.

Figure 1. Prevalence of Proton Pump Inhibitor (PPI) Ever Use Over Time in the Atherosclerosis Risk in Communities Study



In the replication cohort, the risk of CKD was also evaluated in once-daily and twice-daily PPI users. Similar analyses were performed for the secondary outcome of AKI. Absolute risk differences were estimated as the difference between the expected 10-year risk among PPI users and the expected 10-year risk had they not used PPIs.

Five sensitivity analyses were performed. First, the study population was limited to participants using H_2 receptor antagonists or PPIs, and the risk of kidney disease associated with PPI use was assessed using H_2 receptor antagonists as the active comparator. Second, the association between PPI use and incident kidney disease was examined in a propensity score–matched cohort, in which logistic regression was used to estimate the probability of PPI use based on observable predictors of PPI use, and controls not using PPIs were selected using 1:1 nearest-neighbor matching. Third, a new-user design was used, whereby the risk associated with time-varying PPI ever use was assessed only among persons not using PPIs at baseline.[28] Given that new use was not available until 2006 in the ARIC study, this analysis was performed only in the replication cohort. Fourth, the association between H_2 receptor antagonist use and incident kidney disease was assessed as a negative control. Fifth, persons with a baseline ratio of urinary albumin to creatinine exceeding 30 mg/g (or 1+ protein on dipstick in the replication cohort) were excluded from the study population. All analyses were performed using statistical software (Stata/IC, version 13.1; StataCorp LP).

Results

Study Population

In the ARIC study, 10 482 participants were followed up for a median of 13.9 years. In the replication cohort, 248 751 participants were followed up for a median of 6.2 years. At baseline in both cohorts, PPI users were more likely than nonusers to have a higher BMI and take antihypertensive, aspirin, or statin medications

Table 2. Proton Pump Inhibitor Use and the Risk of Incident Chronic Kidney Disease[a]

	Atherosclerosis Risk in Communities Study (n = 10 482)		Geisinger Health System Replication Cohort (n = 248 751)	
Variable	No. of Events	No. of Participants	No. of Events	No. of Participants
PPI users	56	322	1921	16 900
H_2 receptor antagonist users	158	956	1022	6640
Nonusers	1224	9204	27 204	225 221
Association Between PPI Use and Incident CKD	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Unadjusted baseline PPI use vs no PPI use	1.45 (1.11-1.90)	.006	1.20 (1.15-1.26)	<.001
Baseline PPI use vs no PPI use	1.50 (1.14-1.96)	.003	1.17 (1.12-1.23)	<.001
Time-varying PPI ever use vs never PPI use	1.35 (1.17-1.55)	<.001	1.22 (1.19-1.25)	<.001
Baseline PPI use vs baseline H_2 receptor antagonist use	1.39 (1.01-1.91)	.05	1.29 (1.19-1.40)	<.001
Baseline PPI use vs propensity score-matched no PPI use	1.76 (1.13-2.74)	.01	1.16 (1.09-1.24)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.24 (1.20-1.28)	<.001
Negative Control				
Baseline H_2 receptor antagonist use vs no H_2 receptor antagonist use	1.15 (0.98-1.36)	.10	0.93 (0.88-0.99)	.03

Abbreviations: CKD, chronic kidney disease; H_2, histamine$_2$; NA, not available; PPI, proton pump inhibitor.

[a] All analyses were adjusted unless otherwise specified. Adjustment variables for the Atherosclerosis Risk in Communities Study were age, sex, race, study center, education, health insurance status, baseline estimated glomerular filtration rate, ratio of urinary albumin to creatinine, smoking status, body mass index, systolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive medication use, and anticoagulant medication use. Adjustment variables for the Geisinger Health System replication cohort were age, sex, race, baseline estimated glomerular filtration rate, smoking status, body mass index, systolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and nonsteroidal anti-inflammatory drug use. Propensity score–matched analyses were adjusted for propensity scores only, which were estimated using the same variables.

(**Table 1**). The characteristics of H_2 receptor antagonist users were similar to those of PPI users. The prevalence of ever use of PPIs increased substantially during the follow-up period (**Figure 1**).

Association Between PPI Use and Kidney Disease in the ARIC Study

In the ARIC study, there were 56 incident CKD events among the 322 baseline PPI users (14.2 per 1000 person-years), and 1382 events among 10 160 baseline nonusers (10.7 per 1000 person-years). In unadjusted analysis, participants who used PPIs at baseline had 1.45 (95% CI, 1.11-1.90; P = .006) times the risk of incident CKD relative to that of nonusers (**Table 2**). The risk was similar after adjustment for potential confounders, including demographics, socioeconomic status, clinical measurements, prevalent comorbidities, and concomitant use of medications (HR, 1.50; 95% CI, 1.14-1.96; P = .003), as was the association when PPI use was modeled as a time-varying ever-use variable (HR, 1.35; 95% CI, 1.17-1.55; P < .001). Subgroup analyses were consistent with the primary results (**Figure 2**). The 10-year estimated absolute risk of CKD among the 322 baseline PPI users was 11.8% while the expected risk had they not used PPIs was 8.5% (absolute risk difference, 3.3%).

A slightly stronger association was seen between PPI use and AKI (**Table 3**). For example, in unadjusted analysis, participants who used PPIs at baseline had 1.72 (95% CI, 1.28-2.30; P < .001) times the risk of incident AKI relative to those who did not report use. The corresponding risks were similar after adjustment for potential confounders (HR, 1.64; 95% CI, 1.22-2.21; P < .001) and when PPI use was analyzed as a time-varying ever-use variable (HR, 1.49; 95% CI, 1.25-1.77; P < .001).

Association Between PPI Use and Kidney Disease in the Replication Cohort

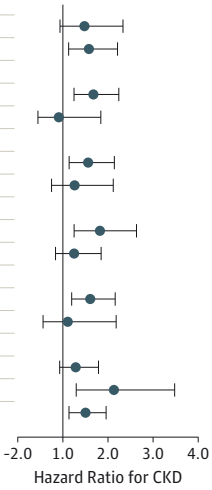
In the replication cohort, there were 1921 incident CKD events among 16 900 baseline PPI users (20.1 per 1000 person-years) and 28 226 events among 231 851 baseline nonusers (18.3 per 1000 person-years). Proton pump inhibitor use was significantly associated with incident CKD in unadjusted analyses (HR, 1.20; 95% CI, 1.15-1.26; P < .001), in adjusted analyses (adjusted HR, 1.17; 95% CI, 1.12-1.23; P < .001), and when estimated using a time-varying ever-use model (adjusted HR, 1.22; 95% CI, 1.19-1.25; P < .001) (Table 2). Twice-daily PPI dosing (adjusted HR, 1.46; 95% CI, 1.28-1.67; P < .001) was associated with a higher risk of CKD than once-daily dosing (adjusted HR, 1.15; 95% CI, 1.09-1.21; P < .001). The 10-year absolute risk of CKD among the 16 900 baseline PPI users was 15.6%, and the expected risk had they not used PPIs was 13.9% (absolute risk difference, 1.7%).

Similar associations were seen with incident AKI (Table 3). Proton pump inhibitor use resulted in a higher risk of incident AKI in unadjusted analysis (HR, 1.30; 95% CI, 1.21-1.40;

Figure 2. Association Between Proton Pump Inhibitor Use and Incident Kidney Disease Stratified By Subgroups

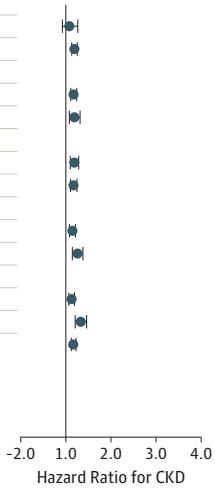
Atherosclerosis Risk in Communities Study

	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	556	5468	20	164
Old	882	5014	36	158
Race				
White	1060	8253	48	277
Black	378	2229	8	45
Diabetes mellitus				
No	982	8826	41	274
Yes	456	1656	15	48
Sex				
Male	757	4596	30	137
Female	681	5886	26	185
ACE-I/ARB use				
No	1148	9116	47	268
Yes	290	1366	9	54
Diuretics use				
No	1205	9433	38	272
Yes	233	1049	18	50
Overall	1438	10482	56	322

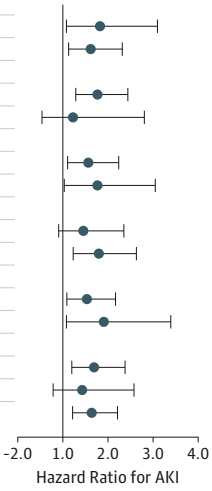


Geisinger Health System Replication Cohort

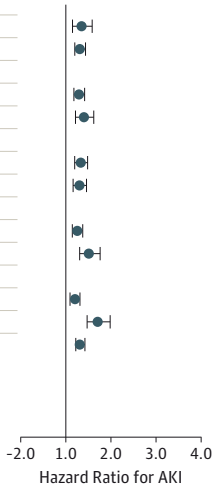
	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	2761	127542	1175	8518
Old	27386	121209	1746	8382
Diabetes mellitus				
No	22907	222829	1463	15081
Yes	7240	25922	458	1819
Sex				
Male	12808	108070	721	7304
Female	17339	140681	1200	9596
ACE-I/ARB use				
No	24694	223579	1380	14277
Yes	5453	25172	541	2623
Diuretics use				
No	25055	226879	1408	14569
Yes	5092	21872	513	2331
Overall	30147	248751	1921	16900



	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	326	5617	15	174
Old	634	5528	32	184
Race				
White	1731	8768	41	309
Black	229	2377	6	49
Diabetes mellitus				
No	655	9316	33	300
Yes	305	1829	14	58
Sex				
Male	492	4891	18	151
Female	468	6254	29	207
ACE-I/ARB use				
No	734	9574	34	294
Yes	226	157	13	64
Diuretics use				
No	777	9903	36	294
Yes	183	1242	11	64
Overall	960	11145	47	358



	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	2033	127542	168	8518
Old	8143	121209	560	8382
Diabetes mellitus				
No	7226	222829	516	15081
Yes	2950	25922	212	1819
Sex				
Male	5804	108070	384	7304
Female	4372	140681	344	9596
ACE-I/ARB use				
No	8398	223579	517	14277
Yes	1778	25172	211	2623
Diuretics use				
No	8568	226879	512	14569
Yes	1608	21872	216	2331
Overall	10176	248751	728	16900



Young refers to an age that is below the cohort median (62 years in the Atherosclerosis Risk in Communities study and 50 years in the Geisinger Health System replication cohort). ACE-I indicates angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; and PPI, proton pump inhibitor.

P < .001), adjusted analysis (HR, 1.31; 95% CI, 1.22-1.42; P < .001), and time-varying ever-use analysis (adjusted HR, 1.54; 95% CI, 1.47-1.60; P < .001). Twice-daily PPI dosing (adjusted HR, 1.62; 95% CI, 1.32-1.98; P < .001) was associated with a higher risk of AKI than once-daily dosing (adjusted HR, 1.28; 95% CI, 1.18-1.39; P < .001).

Sensitivity Analyses

When compared directly with H_2 receptor antagonist use, PPI use was associated with incident CKD in the ARIC study (adjusted HR, 1.39; 95% CI, 1.01-1.91; P = .05) and in the replication cohort (adjusted HR, 1.29; 95% CI, 1.19-1.40; P < .001). Baseline PPI use was also associated with incident CKD in propensity score–matched analyses (HR, 1.76; 95% CI, 1.13-2.74; P = .01 in the ARIC study and HR, 1.16; 95% CI, 1.09-1.24; P < .001 in the replication cohort) and in the new-user analysis (adjusted HR, 1.24; 95% CI, 1.20-1.28; P < .001). The use of H_2 receptor antagonists was not associated with increased risk of incident CKD in either cohort (adjusted HR, 1.15; 95% CI, 0.98-1.36; P = .10 in the ARIC

Table 3. Proton Pump Inhibitor Use and the Risk of Incident Acute Kidney Injury[a]

	Atherosclerosis Risk in Communities Study (n = 11 145)		Geisinger Health System Replication Cohort (n = 248 751)	
Variable	No. of Events	No. of Participants	No. of Events	No. of Participants
PPI users	47	358	728	16 900
H_2 receptor antagonist users	104	1053	347	6640
Nonusers	809	9734	9101	225 211
Association Between PPI Use and Incident AKI	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Unadjusted baseline PPI use vs no PPI use	1.72 (1.28-2.30)	<.001	1.30 (1.21-1.40)	<.001
Baseline PPI use vs no PPI use	1.64 (1.22-2.21)	<.001	1.31 (1.22-1.42)	<.001
Time-varying PPI ever use vs never PPI use	1.49 (1.25-1.77)	<.001	1.54 (1.47-1.60)	<.001
Baseline PPI use vs baseline H_2 receptor antagonist use	1.58 (1.05-2.40)	.03	1.30 (1.13-1.48)	<.001
Baseline PPI use vs propensity score-matched no PPI use	2.00 (1.24-3.22)	.005	1.29 (1.16-1.43)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.66 (1.57-1.75)	<.001
Negative Control				
Baseline H_2 receptor antagonist use vs no H_2 receptor antagonist use	1.03 (0.84-1.26)	.78	0.98 (0.89-1.10)	.78

Abbreviations: AKI, acute kidney injury; H_2, histamine$_2$; NA, not available; PPI, proton pump inhibitor.

[a] All analyses were adjusted unless otherwise specified. Adjustment variables for the Atherosclerosis Risk in Communities Study were age, sex, race, study center, education, health insurance status, baseline estimated glomerular filtration rate, ratio of urinary albumin to creatinine, smoking status, body mass index, systolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive medication use, and anticoagulant medication use. Adjustment variables for the Geisinger Health System replication cohort were age, sex, race, baseline estimated glomerular filtration rate, smoking status, body mass index, systolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and nonsteroidal anti-inflammatory drug use. Propensity score–matched analyses were adjusted for propensity scores only, which were estimated using the same variables.

study and adjusted HR, 0.93; 95% CI, 0.88-0.99, $P = .03$ in the replication cohort). Similar results were obtained when persons with baseline albuminuria were excluded (adjusted HR, 1.45; 95% CI, 1.09-1.96; $P = .01$ in the ARIC study and adjusted HR, 1.19; 95% CI, 1.13-1.25; $P < .001$ in the replication cohort). Sensitivity analyses using AKI as an outcome were also consistent (Table 3).

Discussion

In a prospective community-based cohort of more than 10 000 adults, we found that baseline use of PPIs was independently associated with a 20% to 50% higher risk of incident CKD, after adjusting for several potential confounding variables, including demographics, socioeconomic status, clinical measurements, prevalent comorbidities, and concomitant use of medications. The observed association persisted when PPI exposure was modeled as a time-varying ever-use variable and was replicated in a separate administrative cohort of 248 751 individuals. The risk was specific to PPI medications because the use of H_2 receptor antagonists, which are prescribed for the same indication as PPIs, was not independently associated with CKD. Similar findings were demonstrated for the outcome of AKI and collectively suggest that PPI use is an independent risk factor for CKD and for AKI.

Previous studies[14-18] have also identified an association between PPI use and AKI, most specifically in the form of acute interstitial nephritis. Our study adds to the existing literature by describing an association between PPI use and incident CKD. We note that our study is observational and does not provide evidence of causality. However, a causal relationship between PPI use and CKD could have a considerable public health effect given the widespread extent of use. More than 15 million Americans used prescription PPIs in 2013, costing more than $10 billion.[29] Study findings suggest that up to 70% of these prescriptions are without indication[6] and that 25% of long-term PPI users could discontinue therapy without developing symptoms.[30] Indeed, there are already calls for the reduction of unnecessary use of PPIs.[31]

Observational cohort studies represent one of the best methods to study adverse effects of medications used in real-world settings. However, several limitations inherent in observational design must be considered. First, unlike a randomized clinical trial, participants who are prescribed PPIs may be at a higher risk of CKD for reasons unrelated to their PPI use. For example, PPI users in both the ARIC study and the replication cohort were more likely to be obese, have a diagnosis of hypertension, and carry a greater burden of prescribed medications. In recognition of this potential bias, we performed adjustment for multiple confounders, including BMI, hypertension, diabetes mellitus, and concomitant medication use, compared PPI users directly with H_2 receptor antagonist users, and conducted propensity score–matched analyses. Each of these sensitivity

analyses showed a consistent association between PPI use and a higher risk of CKD.

A second limitation of our study is the potential for surveillance bias, whereby outcome assessment might have occurred more often in persons using PPIs. In the ARIC study, incident CKD was detected using hospitalization discharge codes, while outpatient creatinine levels were used in the replication cohort. However, the association between PPI use and new CKD persisted after accounting for predictors of more frequent contact with the medical system such as insurance status and comorbid illness. A third limitation is the low sensitivity of hospital discharge codes for diagnosing CKD in the ARIC study. However, the study results were replicated in the Geisinger Health System cohort, in which CKD was defined by direct laboratory measurements. Fourth, the inclusion of baseline PPI users can invoke selection bias, whereby baseline users represent a special group of PPI users who tolerate the medication without the development of CKD. In our study, there were few prevalent PPI users at baseline, which should lead to less bias.[32] In addition, the results were replicated in a new-user design in the replication cohort, in which baseline PPI users were excluded. A fifth potential limitation is that neither PPI nor H_2 receptor antagonist use was captured as directly observed therapy. In recent years, both have become available over the counter in the United States. Therefore, medication exposure in the ARIC study and the replication cohort may have been misclassified.

Notable strengths of the ARIC study include a large representative community-based sample, baseline visits occurring soon after PPIs were introduced into the United States, visual confirmation of medications used, comprehensive data pertaining to potential confounders, and close monitoring for more than 13 years of follow-up. Sensitivity analyses, including a time-varying exposure model, propensity score matching, and replication in a large second cohort, showed robust results. We also demonstrated specificity to PPI use rather than H_2 receptor antagonist use.

Conclusions

In summary, we found that PPI use is an independent risk factor for CKD and AKI, but H_2 antagonist use is not. Further research is required to investigate whether PPI use itself causes kidney damage and, if so, the underlying mechanisms of this association.

ARTICLE INFORMATION

Correction: This article was corrected on February 29, 2016, to fix a typographical error in Table 2.

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Study concept and design: Lazarus, Chen, Chang, Grams.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lazarus, Grams.
Critical revision of the manuscript for important intellectual content: All authors.
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