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Proton pump inhibitors and risk of acute and chronic kidney disease: a retrospective cohort study

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Abstract

Background—Proton pump inhibitors (PPIs) have been linked to acute kidney injury (AKI) and chronic kidney disease (CKD); however, current evidence has only been evaluated in a small number of studies with short follow-up periods. This study examined the association between PPI use and risk of incident AKI and CKD in a large, population-based health-maintenance organization (HMO) cohort.

Methods—Patients aged 18 years or older, without evidence of pre-existing renal disease, started on PPI therapy, and continuously enrolled for at least 12 months between July 1993 and September 2008 were identified in an HMO database. Incidences of AKI and CKD were defined using documented International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes or a glomerular filtration rate less than 60 ml/min/1.73 m^2 after initiation of PPI therapy. Patients with AKI were followed for up to 90 days (cohort 1) and patients with CKD required at least 1 year of follow-up (cohort 2). Multivariable logistic regression analyses were used to adjust for differences in demographics (excluding race), comorbidities, and medication use between groups.

Results—In 93,335 patients in the AKI cohort, 16,593 of whom were exposed to PPIs, the incidence rate of AKI was higher in the PPI group than nonusers (36.4 vs. 3.54 per 1000 person-years, $p<0.0001$, respectively). In adjusted models, PPI exposure was associated with an increased risk of AKI (Adjusted Odds Ratio (aOR) 4.35; 95% Confidence Interval (CI) 3.14–6.04; $p<0.0001$). In 84,600 patients in the CKD cohort, 14,514 of whom were exposed to PPIs, the incidence rate of CKD was higher in the PPI group than nonusers (34.3 vs. 8.75 per 1000 person-years, $p<0.0001$, respectively). In adjusted models, PPIs were associated with a higher risk of CKD compared to controls (aOR 1.20; 95% CI 1.12–1.28; $p<0.0001$). Associations between PPI use and AKI and CKD persisted in propensity score-matched analyses.

Conclusion—Proton pump inhibitors use is associated with an increased risk of incident AKI and CKD. This relationship could have a considerable public health impact; therefore, health care provider education and deprescribing initiatives will be necessary to raise awareness and reduce health care burden.

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Keywords

Acute kidney injury; chronic kidney disease; observational study; proton pump inhibitors

Proton pump inhibitors (PPIs) are widely used to treat acid-related gastrointestinal disorders, with an estimated 113 million prescriptions filled in the United States in 2008, totaling $13.9 billion.[1] Although PPIs are one of the most commonly prescribed medications, 25% to 70% of these prescriptions are estimated to have no appropriate indication.[2] Indications such as gastroesophageal reflux disease require only short-term treatment with PPIs (i.e., up to 4–8 weeks), but chronic use appears to be common.[2–4] About 40% to 55% of primary care patients and up to 65% of hospitalized patients have no documented ongoing indications for PPIs.[5–8] Consequently, patients often take these medications without benefit and are therefore subject to unnecessary adverse events.

Proton pump inhibitors are generally considered to be a safe class of drugs; however, inappropriate prescribing can contribute to polypharmacy with its inherent risks of nonadherence, prescribing cascades, adverse reactions, medication errors, drug interactions, emergency department visits, and hospitalizations.[9, 10] Further, several observational studies have linked PPIs to adverse health outcomes including hip fractures, enteric infections, acute interstitial nephritis, and community-acquired pneumonia, as well as an increased risk of mortality among users.[11–15] A growing concern is that PPI use may be a risk factor for chronic kidney disease (CKD), potentially mediated by recurrent acute kidney injury (AKI).[16, 17] The mechanism for this relationship is currently unknown, however, possible mechanisms include development of acute interstitial nephritis, a hypersensitivity reaction that can lead to a decline in glomerular filtration rate and adverse renal outcomes.[18] Other possible mechanisms include inhibition of the lysosomal proton pump, with decreased nitric oxide synthesis and increased generation of superoxide anion, or hypomagnesemia, which could lead to increased secretion of inflammatory and atherogenic markers. PPIs have been shown to be associated with adverse kidney outcomes; however, a recent systematic review noted that this evidence was of low or insufficient quality.[19–23] Therefore, additional studies evaluating the relationship between PPI use and renal disease are necessary, especially considering the increasing global use of PPIs, as this relationship could pose a substantial disease and financial burden to health care systems.

The objective of this study was to determine the association between PPI use and incident AKI and CKD in a general population. A local health-maintenance organization (HMO) database was used to build two cohorts of new PPI users and additional cohorts for sensitivity analyses, including 1:1 propensity score-matched cohorts with predictor variables of age, gender, comorbidities, and concomitant medication use. In this way, the association between PPI exposure and risk of incident AKI and CKD was examined among persons without kidney disease at baseline.

Methods

Claims data from a local HMO in Western New York was used to examine the relationships between acute and chronic kidney disease and prescription PPI use. The database covered a

cohort of patients from July 1993 to September 2008 (192,936 individuals) and included outpatient, inpatient, laboratory, and prescription claims. Laboratory data included all tests performed along with the results of those tests. Pharmacy data included all pertinent patient demographics and medication dosing information regardless of pharmacy location or affiliation. This database has been used previously and is a generally complete claims record for covered patients.[24] Patient data were de-identified but patients could be linked across medical and prescription claims and years as long as the patient had coverage during these years. The University at Buffalo Institutional Review Board approved the study.

Study Cohorts and Patient Population

Two retrospective cohort studies were performed to evaluate the association between PPI prescription use and the development of the two outcomes of interest: AKI and CKD. Patients aged 18 years or older enrolled in the HMO during the study period were included in the study. All patients required at least 12 months of enrollment before the index date. Patients in the AKI cohort required at least 90 days of follow-up data, and patients in the CKD cohort required at least 12 months of follow-up data. Patients were excluded if they had evidence of pre-existing renal disease up to 12 months prior to the index date defined according to the presence of relevant International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes (Appendix 1). These inclusion and exclusion criteria assured that all patients had at least 12 months of claims data prior to renal disease onset. The index date for those exposed to PPIs was the date of first pharmacy prescription for these drugs and, for the nonexposed, the index date followed the first 12 months of claims.

Primary Exposure

The primary exposure was defined as a prescription claim for a PPI. Medications containing esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole were counted as PPIs. The medications were identified based on National Drug Codes (NDCs), or brand, and/or generic names.

Outcomes

The primary outcome for the AKI cohort was defined as a documented ICD-9-CM code of 584.X or an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 within 90 days after the index date. The primary outcome for the CKD cohort was defined as an inpatient or outpatient visit with an ICD-9-CM code of 585.X or an eGFR of less than 60 ml/min/1.73 m^2. End stage renal disease (ESRD) was also included as a CKD outcome, which was defined based on the presence of ICD-9-CM code 585.6 or documentation of receipt of dialysis (V45.11 or V56.X). All outcomes were ascertained from the time of cohort entry until last known follow-up within the database.

Covariates

Baseline covariates were ascertained up to 12 months prior to the index date for both the exposed and nonexposed groups. Covariates included age, sex, relevant comorbidities, and medication use. Comorbidities and medications were chosen based on their correlation with

kidney disease, PPI use, or overall health status. As a proxy for health status, comorbidities from the Charlson comorbidity index (obesity, diabetes, hypertension, hyperlipidemia, metastatic cancer, osteoarthritis, rheumatoid arthritis, liver disease, *Helicobacter pylori* infection, heart failure, peripheral vascular disease, cerebrovascular disease, and human immunodeficiency virus (HIV)) were included [Appendix 2].[25] Exposure to medications included histamine-2 (H_2)-receptor blockers, angiotensin-converting enzyme inhibitors (ACEs), angiotensin receptor blockers (ARBs), antibiotics, antivirals, nonsteroidal antiinflammatory drugs (NSAIDs), calcineurin inhibitors, and diuretics as evaluated using NDC codes and brand-generic names. All variables were extracted from inpatient, outpatient, and prescription claims data using appropriate ICD-9-CM, NDC, and brand-generic names. Use of over-the-counter (OTC) medications, including PPIs and H_2-receptor blockers, was not captured in this claims database.

Statistical Analysis

Baseline characteristics between groups were compared with the Student t test for continuous variables and the X_2-test for categorical variables. Incidence rates per 1000 person-years were computed for outcomes, and confidence intervals (CI) were estimated based on normal distributions. Logistic regression models were used to estimate the odds ratios (ORs) and 95% CIs for the association between PPI exposure and risk of renal outcomes (AKI and CKD). Each potential confounding factor was examined individually using a change-in-estimate criterion, and considered covariates as confounders if they changed the OR of interest by 10% or more.[26] For each identified confounder, separate 3-covariate logistic regression models examining the exposures' effects on the outcome were run, adjusted individually for each confounder. Then a multivariable logistic regression model including all identified confounders was run to estimate the fully modeled adjusted ORs of interest. A 2-tailed p value less than 0.05 was deemed statistically significant, and all analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Sensitivity Analyses

Additional analyses were performed to further explore the possibility of residual confounding factors. First, the risk of AKI and CKD among PPI users using H_2-receptor blockers as a negative control and active comparator was assessed, where medications that contained ranitidine, cimetidine, famotidine, or nizatidine were classified as H_2-receptor blockers based on their NDC or brand-generic name. In this analysis, the date of first pharmacy prescription for a PPI or H_2-receptor blocker was used as the index date. Second, the risk of renal outcomes in a 1:1 propensity score-matched cohort was examined. Propensity scores were calculated for each cohort using nonparsimonious logistic regression models with PPI exposure as the dependent variable, and predictor variables of age, gender, medical conditions (diabetes, cerebrovascular disease, heart failure, HIV, liver disease, metastatic cancer, obesity, osteoarthritis, rheumatoid arthritis, hypertension, hyperlipidemia, *H. pylori* infection, and peripheral vascular disease), and medication use (antibiotics, amphotericin B, antivirals, antiretrovirals, mesalamine, NSAIDs, ACE inhibitors, ARBs, diuretics, calcineurin inhibitors, and H_2-receptor blockers). Nearest-neighbor matching without replacement was used, with a caliper distance set as 0.2. Conditional logistic

regression models were used to examine the association between PPI and outcomes. Any variables that were not balanced following matching were included in the adjusted models.

Results

There were 93,335 patients in the AKI cohort and 84,600 patients in the CKD cohort. Cohort selection is detailed in Figure 1. Baseline characteristics of the AKI and CKD cohorts are described in **Tables** 1 **and** 2, respectively. The median follow-up was 6.8 years in the CKD cohort and 90 days in the AKI cohort. In both cohorts, PPI users were older at baseline and had higher prevalence of comorbidities compared to nonusers. PPI users also more frequently took an antibiotic, antiviral, NSAID, ACE inhibitor, ARB, diuretic, calcineurin inhibitor, or H_2-receptor blocker in the 12 months prior to the index date. The frequency of AKI and CKD events based on age and eGFR are described in Table 3. In both cohorts, the frequency of events were highest among those 65 years of age or older with a mild to moderate decrease in eGFR (range, 45–59 ml/min/1.73 m^2) reported most frequently.

Association between PPI Use and Risk of AKI

In the AKI cohort, there were 148 events (0.89%) among 16,593 patients exposed to PPIs and 67 events (0.09%) among 76,742 unexposed patients (Table 4). The incidence rate of AKI was higher in the PPI group than among nonusers (36.4 vs. 3.54 per 1000 person-years, $p<0.0001$, respectively). In the model adjusted for age, diabetes, heart failure, hypertension, fluoroquinolone use, ACE inhibitor use, ARB use, diuretic use, and H_2-receptor blocker use, PPI use was associated with a significantly increased risk of AKI (adjusted (a)OR 4.35; 95% CI 3.14–6.04; $p<0.0001$).

Association between PPI Use and Risk of CKD

In the CKD cohort, there were 2370 events (15.3%) among 14,514 PPI users and 4501 (6.42%) events among 70,086 nonusers (Table 5). The incidence rate of CKD was significantly higher in patients exposed to PPIs compared to non-PPI users (34.3 vs. 8.75 per 1000 person-years, $p<0.0001$, respectively). In the model adjusted for age, diabetes, hypertension, hyperlipidemia, ACE inhibitor use, diuretic use, and H_2-receptor blocker use, PPI use was associated with a 1.2-times risk of incident CKD relative to nonusers (aOR 1.20; 95% CI 1.12–1.28; $p<0.0001$).

Sensitivity Analyses

Results of our first sensitivity analyses examining the risk of AKI and CKD associated with PPIs at baseline using H_2-receptor blockers as a negative control and active comparator are displayed in Table 6. There were 89,524 patients in the AKI cohort, of which 9736 were exposed to PPIs and 11,397 were exposed to H_2-receptor blockers. Patients receiving both a PPI and an H_2-receptor blocker on the index date were excluded (n=82). The incidence rate of AKI among PPI users was higher than controls (46.5 vs. 3.74 per 1000 person-years, $p<0.0001$) and H_2-receptor blocker users (46.5 vs. 9.26 per 1000 person-years, $p<0.0001$), respectively. PPI use was associated with an increased risk of AKI compared to non-PPI users (aOR 4.31; 95% CI 3.05–6.09; $p<0.0001$), consistent with the primary analysis. PPI

use was also associated with an increased risk of AKI when compared directly to H_2-receptor blocker use (aOR 3.78; 95% CI 2.44–5.84; p<0.0001). After adjusting for confounders, H_2-receptor blockers were not associated with an increased risk of AKI (aOR 1.16; 95% CI 0.72–1.85; p=0.55).

In the CKD cohort, 80,909 patients were included with 8192 exposed to PPIs and 10,843 exposed to H_2-receptor blockers. Sixty-six patients taking both a PPI and H_2-receptor blocker on the index date were excluded. The incidence rate of CKD was higher among PPI users than controls (34.0 vs. 8.32 per 1000 person-years, p<0.0001) and H_2-receptor blocker users (34.0 vs. 21.0 per 1000 person-years, p<0.0001), respectively. The association between risk of CKD among PPI users compared to that of nonusers (aOR 1.18; 95% CI 1.09–1.28; p<0.0001) was similar to the primary analysis. Use of H_2-receptor blockers at baseline was associated with an increased risk of CKD (aOR 1.49; 95% CI 1.39–1.60; p<0.0001) and, when comparing PPI users to H_2-receptor blocker users, the risk of CKD was similar between groups in unadjusted models (OR 0.97; 95% CI 0.89–1.05; p=0.48) and decreased in adjusted models (aOR 0.81; 95% CI 0.74–0.89; p<0.0001).

Baseline characteristics of the propensity-matched AKI and CKD cohorts are described in **Tables** 1 **and** 2. Results were consistent with the primary analyses (**Tables** 4 **and** 5). PPI use was associated with an increased incidence of AKI compared with nonusers (33.7 vs. 8.48 per 1000 person-years, p<0.0001, respectively) and an increased risk of AKI (OR 3.93; 95% CI 2.61–5.93; p<0.0001). The PPI users had an increased incidence of CKD compared to nonusers (30.5 vs. 16.5 per 1000 person-years, p<0.0001, respectively), and PPI use was associated with an increased risk of CKD (OR 1.20; 95% CI 1.11–1.29; p<0.0001), consistent with adjusted models in the primary analysis (Table 5).

Discussion

In this longitudinal, retrospective cohort study of more than 190,000 patients, baseline PPI use was independently associated with a 20% higher risk of incident CKD after adjusting for demographics, comorbidities, and concomitant medications. There was a 4-fold increase in the risk of AKI among those exposed to PPIs. These results were consistent within a propensity-matched analysis and when directly compared with the use of H_2-receptor blockers. Our results are in general agreement with previous results on this topic and strengthen existing evidence of an association between PPI exposure and the development of kidney disease.

These results expand on the findings of recent observational cohort studies. One study evaluated the relationship between PPIs and CKD in two cohorts: 10,482 participants in the Arthrosclerosis Risk in Communities study and 248,751 patients in the Geisinger Health System.[19] In both cohorts, participants who used PPIs at baseline had a significantly increased risk of incident CKD compared with nonusers. Similarly, another study built a cohort of 173,321 new users of PPIs within the Department of Veterans Affairs national databases and followed these patients over 5 years.[20] There was a relationship between PPI exposure and increased risk of incident CKD, CKD progression, and ESRD. Our study adds to the existing literature by describing an association between PPI use and incidence of CKD

over a long period within an HMO database. The consistency of our findings with previous observations suggests the need to judiciously prescribe PPIs. Given the high prevalence of PPI use, overuse, and long-term adverse outcomes, a focus on PPI deprescribing is necessary to reduce PPI burden and harm.

Although these findings support a relationship between PPI exposure and incident AKI, the precision of the estimate (i.e., CI) is limited by the number of AKI cases. The CI ranged from 3.14 to 6.04, suggesting that PPIs could increase the odds of AKI development by as much as 6-fold. Of note, this relationship persisted within a propensity score-matched cohort, as the multivariable-adjusted OR for PPI exposure was 3.93 (95% CI 2.61–5.93). AKI in PPI users is likely to be underdiagnosed given that PPIs are often viewed as safe and well-tolerated medications. A heightened awareness among health care professionals of the adverse outcomes associated with PPIs is a necessary first step to modify PPI overutilization.

Our results add to a growing list of concerning side effects and adverse outcomes associated with PPIs including hypomagnesemia, vitamin B12 deficiency, fractures, pneumonia, and *Clostridium difficile* infection.[11, 12, 27, 28] An increased risk of any side effect from these medications is concerning, especially considering that up to 70% of patients are taking PPIs without a valid indication.[2] There is a clear need to decrease inappropriate PPI usage. To help achieve this goal, evidence-based clinical practice guidelines have been published to aid clinicians in deprescribing PPIs.[9] Deprescribing may involve reducing the dosage, using “as needed” dosing, or stopping acid reduction therapy altogether in certain eligible patients. Although deprescribing is an essential part of best prescribing practices, several barriers exist in everyday practice. These include personal factors (i.e., maintaining relationships with patients and colleagues), sociocultural factors (i.e., medical culture of prescribing), and organizational factors (i.e., fast pace and competing demands of practice).[29] Interventions focused on safer PPI prescribing are necessary and should consider these influences.

This study had several strengths. We included a large, representative sample of patients over 15 years. Our comprehensive data source allowed us to collect information on laboratory values in addition to medication usage and comorbidities, which allowed accurate assessment of outcomes, exposures, and confounders. The study yielded robust results supported by multiple sensitivity analyses, which showed that the findings may be generalizable.

A limitation, as with all observational studies, is the risk of residual confounding factors. To account for this, we adjusted for multiple confounders and performed several sensitivity analyses, including a propensity-matched cohort. However, several potential confounders could not be evaluated. Race was unspecified for a significant proportion of patients, so we were unable to include this variable in the study. In addition, we could not account for OTC PPI and H_2-receptor blocker use, so it is possible that some patients who used OTC products were misclassified as nonusers. Of note, omeprazole was the first PPI to become available OTC in 2003, whereas H_2-receptor blockers (cimetidine and famotidine) were available OTC from 1995.[30] We were also unable to account for other factors that could contribute to the development of kidney injury on the index date, including volume depletion.

Additionally, there were limitations related to the use of claims data in the study. We were unable to assess whether patients were actually taking the medications they had filled. This is of particular concern for patients who may have had prescriptions filled automatically, especially through mail order, though we did not have information on the type of pharmacy that dispensed the PPI. Finally, there may have been surveillance bias. Patients receiving PPI therapy may have had more frequent contact with the health care system, so may have been more likely to receive testing that would indicate AKI or CKD. This would have led to an overestimation of risk of renal outcomes in PPI-exposed patients compared to non-exposed patients.

Conclusion

In summary, PPIs are frequently used drugs that are independently associated with AKI and CKD. A focus on health care provider education and deprescribing initiatives will be necessary to raise awareness and reduce PPI overutilization. Further studies are necessary to confirm our findings and provide evidence of a causal relationship, as well as to fully determine the mechanism by which PPIs may cause renal injury.

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Appendix 1.: Pre-existing renal disease to be excluded

Disease	ICD-9-CM
Hypertensive renal disease	403.XX
Acute glomerulonephritis	580.XX
Nephrotic syndrome	581.XX
Chronic glomerulonephritis	582.XX
Nephritis and nephropathy	583.XX
Acute renal failure	584.XX
Chronic renal failure	585.XX
Renal failure, unspecified	586.XX
Impaired renal function disease not elsewhere classifiable	588.89
Unspecified disorder of kidney and ureter	593.9
Kidney transplant	V42.0
Dialysis	V45.1, V56.X

Appendix 2.: Identification of variables

Covariate	ICD-9-CM
Obesity	278.0

Covariate	ICD-9-CM
Diabetes	250.xx
Hypertension	401.0, 401.1, 401.9
Hyperlipidemia	272.0, 272.1, 272.2, 272.4
Metastatic cancer	196.x-199.x
Osteoarthritis	715.xx
Rheumatoid arthritis	714.xx
Liver disease	571.xx
H. pylori infection	041.86
Heart failure	428
Peripheral vascular disease	443.9
Cerebrovascular disease	430–438
HIV	042–044.9

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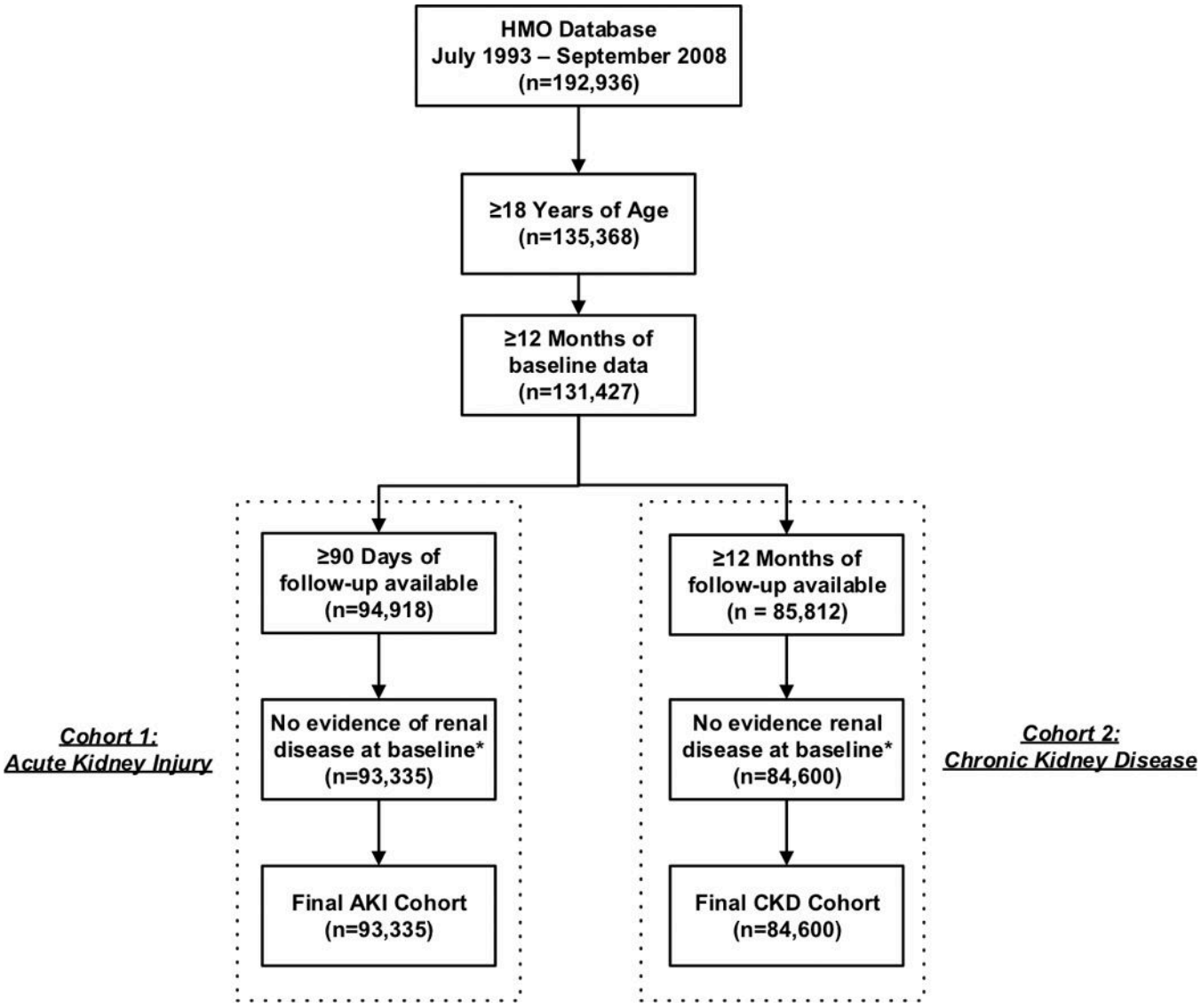

Figure 1.

Flow chart of cohort assembly within the acute kidney injury and chronic kidney disease cohorts (Abb. AKI, acute kidney injury; CKD, chronic kidney disease; HMO, health maintenance organization). [a]Patients were excluded if they had evidence of pre-existing renal disease up to 12 months prior to the index date defined based on the presence of relevant ICD-9-CM codes (Appendix2)

Table 1.

Baseline characteristics of new PPI users within the AKI cohort and the propensity-matched AKI cohort

	AKI Cohort				Propensity-Matched AKI Cohort			
Characteristic, n (%)	**All patients (n = 93,335)**	**PPI (n = 16,593)**	**No PPI (n = 76,742)**	**p value**	**All Patients (n = 27,778)**	**PPI (n = 13,889)**	**No PPI (n = 13,889)**	**p value**
Age, years, mean (SD)	44.1 (16.7)	53.2 (17.4)	42.1 (15.9)	<0.0001	51.1 (17.0)	51.4 (17.2)	50.9 (16.8)	0.017
Gender								
Female	55,676 (59.6)	10,376 (62.5)	45,300 (59.0)	<0.0001	17,036 (61.3)	8551 (61.6)	8485 (61.1)	0.44
Medical Conditions								
Diabetes	4842 (5.19)	1810 (10.9)	3032 (3.95)	<0.0001	2547 (9.17)	1292 (9.30)	1255 (9.04)	0.44
CVD	1520 (1.63)	878 (5.29)	642 (0.84)	<0.0001	999 (3.60)	533 (3.84)	466 (3.36)	0.031
Heart Failure	1224 (1.31)	782 (4.71)	442 (0.58)	<0.0001	792 (2.85)	442 (3.18)	350 (2.52)	0.0009
HIV	43 (0.05)	15 (0.09)	28 (0.04)	0.0033	19 (0.07)	11 (0.08)	8 (0.06)	0.49
Liver Disease	263 (0.28)	134 (0.81)	129 (0.17)	<0.0001	174 (0.63)	89 (0.64)	85 (0.61)	0.76
Metastatic Cancer	339 (0.36)	208 (1.25)	131 (0.17)	<0.0001	245 (0.88)	127 (0.91)	118 (0.85)	0.56
Obesity	1734 (1.86)	480 (2.89)	1254 (1.63)	<0.0001	761 (2.74)	361 (2.60)	400 (2.88)	0.15
Osteoarthritis	3081 (3.30)	1365 (8.23)	1716 (2.24)	<0.0001	1842 (6.63)	949 (6.83)	893 (6.43)	0.18
Rheumatoid Arthritis	782 (0.84)	400 (2.41)	382 (0.50)	<0.0001	505 (1.82)	259 (1.86)	246 (1.77)	0.56
Hypertension	13,316 (14.3)	4536 (27.3)	8780 (11.4)	<0.0001	6973 (25.1)	3411 (24.6)	3562 (25.7)	0.037
Hyperlipidemia	7539 (8.08)	2793 (16.8)	4746 (6.18)	<0.0001	4468 (16.1)	2104 (15.2)	2364 (17.0)	<0.0001
H. pylori	77 (0.08)	67 (0.40)	10 (0.01)	<0.0001	35 (0.13)	25 (0.18)	10 (0.07)	0.011
PVD	479 (0.51)	242 (1.46)	237 (0.31)	<0.0001	299 (1.08)	161 (1.16)	138 (0.99)	0.18
Medications								
Aminoglycoside	12 (0.01)	9 (0.05)	3 (0.00)	<0.0001	6 (0.02)	3 (0.02)	3 (0.02)	0.66
Cephalosporin	6563 (7.03)	1890 (11.4)	4673 (6.09)	<0.0001	2929 (10.5)	1434 (10.3)	1495 (10.8)	0.23
Fluoroquinolone	3939 (4.22)	1907 (11.5)	2032 (2.65)	<0.0001	2524 (9.09)	1257 (9.05)	1267 (9.12)	0.83
Macrolide	9100 (9.75)	3111 (18.8)	5989 (7.80)	<0.0001	4742 (17.1)	2307 (16.6)	2435 (17.5)	0.041
Penicillin	18,009 (19.3)	4562 (27.5)	13,447 (17.5)	<0.0001	7193 (25.9)	3574 (25.7)	3619 (26.1)	0.54
Penicillinase-resistant	353 (0.38)	52 (0.31)	301 (0.39)	0.13	86 (0.31)	50 (0.36)	36 (0.26)	0.13
Sulfa	6026 (6.46)	1733 (10.4)	4293 (5.59)	<0.0001	2691 (9.69)	1319 (9.50)	172 (9.88)	0.28
Tetracycline	1177 (1.26)	305 (1.84)	872 (1.14)	<0.0001	395 (1.42)	220 (1.58)	175 (1.26)	0.023
Vancomycin	25 (0.03)	14 (0.08)	11 (0.01)	<0.0001	14 (0.05)	8 (0.06)	6 (0.04)	0.59
Nitrofurantoin	1177 (1.26)	355 (2.14)	822 (1.07)	<0.0001	513 (1.85)	257 (1.85)	256 (1.84)	0.96
Amphotericin B	11 (0.01)	7 (0.04)	4 (0.01)	0.0009	8 (0.03)	5 (0.04)	3 (0.02)	0.73
Antiviral	1179 (1.26)	377 (2.27)	802 (1.05)	<0.0001	573 (2.06)	283 (2.04)	290 (2.09)	0.77
Antiretroviral	9 (0.01)	4 (0.02)	5 (0.01)	0.059	4 (0.01)	2 (0.01)	2 (0.01)	1.0
Mesalamine	173 (0.19)	95 (0.57)	78 (0.10)	<0.0001	118 (0.42)	63 (0.45)	55 (0.40)	0.46
NSAID	19,396 (20.8)	5894 (35.5)	13,502 (17.6)	<0.0001	9223 (33.2)	4505 (32.4)	4718 (34.0)	0.0067
ARB	954 (1.02)	587 (3.54)	367 (0.48)	<0.0001	662 (2.38)	352 (2.53)	310 (2.23)	0.099
ACE Inhibitor	6748 (7.23)	3026 (18.2)	3722 (4.85)	<0.0001	4346 (15.7)	2143 (15.4)	2203 (15.9)	0.32
Diuretic	7749 (8.30)	3545 (21.4)	4204 (5.48)	<0.0001	4957 (17.9)	2439 (17.6)	2518 (18.1)	0.22

	AKI Cohort				Propensity-Matched AKI Cohort			
Characteristic, n (%)	**All patients (n = 93,335)**	**PPI (n = 16,593)**	**No PPI (n = 76,742)**	**p value**	**All Patients (n = 27,778)**	**PPI (n = 13,889)**	**No PPI (n = 13,889)**	**p value**
Calcineurin Inhibitor	24 (0.03)	15 (0.09)	9 (0.01)	<0.0001	15 (0.05)	9 (0.06)	6 (0.04)	0.44
H_2-Blocker	6226 (6.67)	4301 (25.9)	1925 (2.51)	<0.0001	4230 (15.2)	2328 (16.8)	1902 (13.7)	<0.0001

Abbreviations: ACE inhibitor, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CVD, cerebrovascular disease; H_2-blocker, histamine-2 receptor blocker; HIV, human immunodeficiency virus; *H. pylori*, *Helicobacter pylori* infection; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors; PVD, peripheral vascular disease; SD, standard deviation

Table 2.

Baseline characteristics of new PPI users within the CKD cohort and the propensity-matched CKD cohort

	CKD Cohort				Propensity-Matched CKD Cohort			
Characteristic, n (%)	**All patients (n = 84,600)**	**PPI (n = 14,514)**	**No PPI (n = 70,086)**	**p value**	**All Patients (n = 24,186)**	**PPI (n = 12,093)**	**No PPI (n = 12,093)**	**p value**
Age, years, mean (SD)	44.2 (16.7)	53.4 (17.2)	42.4 (16.0)	<0.0001	51.6 (16.9)	51.6 (17.0)	51.6 (16.8)	0.90
Gender								
Female	50,442 (59.6)	9115 (62.8)	41,327 (59.0)	<0.0001	14,853 (61.4)	7457 (61.7)	7396 (61.2)	0.42
Medical Conditions								
Diabetes	4381 (5.18)	1575 (10.9)	2806 (4.00)	<0.0001	2275 (9.41)	1160 (9.59)	1115 (9.22)	0.32
CVD	1351 (1.60)	756 (5.21)	595 (0.85)	<0.0001	879 (3.63)	455 (3.76)	424 (3.51)	0.29
Heart Failure	1075 (1.27)	665 (4.58)	410 (0.58)	<0.0001	706 (2.92)	379 (3.13)	327 (2.70)	0.047
HIV	39 (0.05)	15 (0.10)	24 (0.03)	0.0004	21 (0.09)	9 (0.07)	12 (0.10)	0.51
Liver Disease	207 (0.24)	102 (0.70)	105 (0.15)	<0.0001	132 (0.55)	72 (0.60)	60 (0.50)	0.29
Metastatic Cancer	261 (0.31)	141 (0.97)	120 (0.17)	<0.0001	175 (0.72)	87 (0.72)	88 (0.73)	0.94
Obesity	1587 (1.88)	428 (2.95)	1159 (1.65)	<0.0001	665 (2.75)	329 (2.72)	336 (2.78)	0.78
Osteoarthritis	2833 (3.35)	1224 (8.43)	1609 (2.30)	<0.0001	1657 (6.85)	834 (6.90)	823 (6.81)	0.78
Rheumatoid Arthritis	707 (0.84)	354 (2.44)	353 (0.50)	<0.0001	445 (1.84)	229 (1.89)	216 (1.79)	0.53
Hypertension	12,186 (14.4)	4019 (27.7)	8167 (11.7)	<0.0001	6230 (25.8)	3014 (24.9)	3216 (26.6)	0.003
Hyperlipidemia	6789 (8.02)	2511 (17.3)	4278 (6.10)	<0.0001	3992 (16.5)	1896 (15.7)	2096 (17.3)	0.0005
H. pylori	65 (0.08)	59 (0.41)	6 (0.01)	<0.0001	21 (0.09)	15 (0.12)	6 (0.05)	0.049
PVD	428 (0.51)	207 (1.43)	221 (0.32)	<0.0001	258 (1.07)	134 (1.11)	124 (1.03)	0.53
Medications								
Aminoglycoside	9 (0.01)	6 (0.04)	3 (0.00)	0.0013	6 (0.02)	3 (0.02)	3 (0.02)	0.66
Cephalosporin	6022 (7.12)	1670 (11.5)	4352 (6.21)	<0.0001	2560 (10.6)	1260 (10.4)	1300 (10.8)	0.40
Fluoroquinolone	3394 (4.01)	1607 (11.1)	1787 (2.55)	<0.0001	2134 (8.82)	1082 (8.95)	1052 (8.70)	0.49
Macrolide	8206 (9.70)	2727 (18.8)	5479 (7.82)	<0.0001	4124 (17.1)	2024 (16.7)	2100 (17.4)	0.19
Penicillin	16,659 (19.7)	4098 (28.2)	12,561 (17.9)	<0.0001	6404 (26.5)	3146 (26.0)	3258 (26.9)	0.10
Penicillinase-resistant	337 (0.40)	49 (0.34)	288 (0.41)	0.20	78 (0.32)	43 (0.36)	35 (0.29)	0.36
Sulfa	5690 (6.73)	1603 (11.0)	4087 (5.83)	<0.0001	2436 (10.07)	1203 (9.95)	1233 (10.2)	0.52
Tetracycline	1100 (1.30)	281 (1.94)	819 (1.17)	<0.0001	391 (1.62)	211 (1.74)	180 (1.49)	0.11
Vancomycin	24 (0.03)	13 (0.09)	11 (0.02)	<0.0001	12 (0.05)	5 (0.04)	7 (0.06)	0.56
Nitrofurantoin	1070 (1.26)	312 (2.15)	758 (1.08)	<0.0001	447 (1.85)	230 (1.90)	217 (1.79)	0.53
Amphotericin B	7 (0.01)	5 (0.03)	2 (0.00)	0.0023	3 (0.01)	1 (0.01)	2 (0.02)	1.0
Antiviral	1051 (1.24)	321 (2.21)	730 (1.04)	<0.0001	464 (1.92)	221 (1.83)	243 (2.01)	0.30
Antiretroviral	6 (0.01)	2 (0.01)	4 (0.01)	0.28	3 (0.01)	1 (0.01)	2 (0.02)	1.0
Mesalamine	159 (0.19)	89 (0.61)	70 (0.10)	<0.0001	104 (0.43)	54 (0.45)	50 (0.41)	0.69
NSAID	17,915 (21.2)	5270 (36.3)	12,645 (18.0)	<0.0001	8183 (33.8)	4029 (33.3)	4154 (34.4)	0.089
ARB	808 (0.96)	500 (3.44)	308 (0.44)	<0.0001	572 (2.37)	302 (2.50)	270 (2.23)	0.18
ACE Inhibitor	6102 (7.21)	2638 (18.2)	3464 (4.94)	<0.0001	3826 (15.8)	1895 (15.7)	1931 (16.0)	0.52
Diuretic	7004 (8.28)	3088 (21.3)	3916 (5.59)	<0.0001	4385 (18.1)	2152 (17.8)	2233 (18.5)	0.18

	CKD Cohort				Propensity-Matched CKD Cohort			
Characteristic, n (%)	**All patients (n = 84,600)**	**PPI (n = 14,514)**	**No PPI (n = 70,086)**	**p value**	**All Patients (n = 24,186)**	**PPI (n = 12,093)**	**No PPI (n = 12,093)**	**p value**
Calcineurin Inhibitor	21 (0.02)	13 (0.09)	8 (0.01)	<0.0001	12 (0.05)	6 (0.05)	6 (0.05)	1.0
H_2-Blocker	5896 (6.97)	4066 (28.0)	1830 (2.61)	<0.0001	4044 (16.7)	2236 (18.5)	1808 (15.0)	<0.0001

Abbreviations: ACE inhibitor, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CVD, cerebrovascular disease; H_2-blocker, histamine-2 receptor blocker; HIV, human immunodeficiency virus; *H. pylori*, *Helicobacter pylori* infection; NSAID, nonsteroidal antiinflammatory drug; PPI, proton pump inhibitors; PVD, peripheral vascular disease; SD, standard deviation

Table 3.

Frequency of acute kidney injury and chronic kidney disease stratified by age and GFR categories

			Acute Kidney Injury[a]			Chronic Kidney Disease[b]		
		Age (years)	**18–39**	**40–64**	**≥65**	**18–39**	**40–64**	**≥65**
		No. of events (%)	**7**	**72**	**104**	**418**	**2410**	**3162**
	Description	**eGFR Range**						
GFR Categories[c] (ml/min/1.73 m^2)	Mildly to moderately decreased	45–59	6 (86)	62 (86)	80 (77)	382 (91)	2163 (89)	2491 (79)
	Moderately to severely decreased	30–44	1 (14)	9 (13)	19 (18)	25 (6)	217 (9)	576 (18)
	Severely decreased	15–29	0	1 (1)	4 (4)	9 (2.2)	27 (1.1)	92 (2.9)
	Kidney failure	<15	0	0	1 (1)	2 (0.48)	3 (0.12)	3 (0.1)

Abbreviations: eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcomes

Data are presented as n (%)

[a] This includes 183 AKI events identified based on the estimated GFR of the total 215 AKI events

[b] This includes 5036 CKD events identified based on the estimated GFR of the total 6871 CKD events

[c] GFR categories are based on the CKD nomenclature within the KDIGO Clinical Practice Guidelines[27]

Table 4.

Incidence rates and odds ratios for PPI use and risk of acute kidney injury

	AKI Cohort		Propensity-Matched AKI Cohort	
	PPI Users (n = 16,593)	PPI Nonusers (n = 76,742)	PPI Users (n = 13,889)	PPI Nonusers (n = 13,889)
Number of events (%)	148 (0.89)	67 (0.09)	115 (0.83)	29 (0.21)
Incident rate per 1000 person-years	36.4	3.54	33.7	8.48
	Odds Ratio (95% CI)	**p value**	**Odds Ratio (95% CI)**	**p value**
Unadjusted PPI use vs. no PPI use	10.3 (7.71 – 13.8)	<0.0001	3.99 (2.65 – 6.00)	<0.0001
PPI use vs. no PPI use	4.35 (3.14 – 6.04) [a]	<0.0001	3.93 (2.61– 5.93) [b]	<0.0001

Abbreviations: AKI, acute kidney injury; PPI, proton pump inhibitors; CI, confidence interval; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; H_2, histamine-2; NSAIDs, nonsteroidal anti-inflammatory drugs

[a] Adjusted for age, diabetes, heart failure, hypertension, and use of fluoroquinolones, ACE inhibitors, ARBs, diuretics, and H_2-receptor blockers

[b] Adjusted for age, cerebrovascular disease, heart failure, hypertension, hyperlipidemia, and use of macrolides, tetracyclines, NSAIDs, and H_2-receptor blockers

Table 5.

Incidence rates and odds ratios for PPI use and risk of chronic kidney disease

	CKD Cohort		Propensity-Matched CKD Cohort	
	PPI Users (n = 14,514)	**PPI Nonusers (n = 70,086)**	**PPI Users (n = 12,093)**	**PPI Nonusers (n = 12,093)**
Number of events (%)	2370 (15.3)	4501 (6.42)	1710 (14.1)	1500 (12.4)
Incidence rate per 1000 person-years	34.3	8.75	30.5	16.5
	Odds Ratio (95% CI)	**p value**	**Odds Ratio (95% CI)**	**p value**
Unadjusted PPI use vs. no PPI use	2.84 (2.70 – 3.00)	<0.0001	1.16 (1.08 – 1.25)	<0.0001
PPI use vs. no PPI use	1.20 (1.12 – 1.28) [a]	<0.0001	1.20 (1.11 – 1.29) [b]	<0.0001

Abbreviations: CKD, chronic kidney disease; PPI, proton pump inhibitor; CI, confidence interval; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; H_2, histamine-2

[a] Adjusted for age, diabetes, hypertension, hyperlipidemia, and use of ACE inhibitors, diuretics, and H_2-receptor blockers

[b] Adjusted for heart failure, hypertension, hyperlipidemia, *H. pylori* infection, and use of H_2-receptor blockers

Table 6.

PPI use and risk 00of incident acute kidney injury or chronic kidney disease – sensitivity analyses

	AKI Cohort			CKD Cohort		
	PPI Users (n = 9736)	**H_2-Receptor Blocker Users (n = 11,397)**	**Nonusers (n = 68,391)**	**PPI Users (n = 8192)**	**H_2-Receptor Blocker Users (n = 10,843)**	**Nonusers (n = 61,874)**
Number of events (%)	111 (1.14)	26 (0.23)	63 (0.09)	1159 (14.2)	1572 (14.5)	3638 (5.88)
Incident rate per 1000 person-years	46.5	9.26	3.74	34.0	21.0	8.32
	Odds Ratio (95% CI)		**p value**	**Odds Ratio (95% CI)**		**p value**
Unadjusted PPI use vs. no PPI use	12.6 (9.25 – 17.2)		<0.0001	2.63 (2.45 – 2.82)		<0.0001
PPI use vs. no PPI use	4.31 (3.05 – 6.09) †		<0.0001	1.18 (1.09– 1.28) ‡		<0.0001
Unadjusted H_2-receptor blocker use vs. no H_2-receptor blocker use	2.50 (1.58 – 3.95)		<0.0001	2.71 (2.54 – 2.88)		<0.0001
H_2-receptor blocker use vs. no H_2-receptor blocker use	1.16 (0.72 – 1.85) †		0.55	1.49 (1.39 – 1.60) ‡		<0.0001
Unadjusted PPI use vs. H_2-receptor blocker use	5.05 (3.29 – 7.75)		<0.0001	0.97 (0.89 – 1.05)		0.48
PPI use vs. H_2-receptor blocker use	3.78 (2.44 – 5.84) *a*		<0.0001	0.81 (0.74 – 0.89) *b*		<0.0001

Abbreviations: CKD, chronic kidney disease; AKI, acute kidney injury; PPI, proton pump inhibitor; CI, confidence interval; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; H_2, histamine-2

*a*Adjusted for adjusted for age, diabetes, cerebrovascular disease, heart failure, hypertension, hyperlipidemia, and use of fluoroquinolones, ACE inhibitors, ARBs, and diuretics

*b*Adjusted for age, diabetes, hypertension, hyperlipidemia, and use of ACE inhibitors, and diuretics