Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD

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ABSTRACT

The association between proton pump inhibitors (PPI) use and risk of acute interstitial nephritis has been described. However, whether exposure to PPI associates with incident CKD, CKD progression, or ESRD is not known. We used Department of Veterans Affairs national databases to build a primary cohort of new users of PPI (n=173,321) and new users of histamine H_2-receptor antagonists (H_2 blockers; n=20,270) and followed these patients over 5 years to ascertain renal outcomes. In adjusted Cox survival models, the PPI group, compared with the H_2 blockers group, had an increased risk of incident eGFR<60 ml/min per 1.73 m^2 and of incident CKD (hazard ratio [HR], 1.22; 95% confidence interval [95% CI], 1.18 to 1.26; and HR, 1.28; 95% CI, 1.23 to 1.34, respectively). Patients treated with PPI also had a significantly elevated risk of doubling of serum creatinine level (HR, 1.53; 95% CI, 1.42 to 1.65), of eGFR decline >30% (HR, 1.32; 95% CI, 1.28 to 1.37), and of ESRD (HR, 1.96; 95% CI, 1.21 to 3.18). Furthermore, we detected a graded association between duration of PPI exposure and risk of renal outcomes among those exposed to PPI for 31–90, 91–180, 181–360, and 361–720 days compared with those exposed for ≤30 days. Examination of risk of renal outcomes in 1:1 propensity score-matched cohorts of patients taking H_2 blockers versus patients taking PPI and patients taking PPI versus controls yielded consistent results. Our results suggest that PPI exposure associates with increased risk of incident CKD, CKD progression, and ESRD.

J Am Soc Nephrol 27: 3153–3163, 2016. doi: 10.1681/ASN.2015121377

Numerous prior observations have suggested a relationship between exposure to proton pump inhibitors (PPI) and acute kidney injury and acute interstitial nephritis. Antoniou *et al.* conducted a population-based study involving Ontario residents aged 66 years and older who initiated PPI therapy and found an increased risk of both acute kidney injury and acute interstitial nephritis.[1] Klepser *et al.* built a nested case-control study using claims data from a private insurer in a single Midwestern state and also found a significant association between PPI use and acute kidney injury.[2] Blank *et al.* conducted a nested case-control study using routinely collected national health and drug dispensing data in New Zealand and found that current use of PPI was associated with increased risk of acute interstitial nephritis relative to past use.[3] Data from adverse event reporting systems suggest that PPI is a common cause of drug-induced acute interstitial nephritis.[4] While most patients recover kidney function, some may not fully recover and might develop CKD and progress to ESRD.[5,6]

While the association between PPI exposure and acute kidney disease has been well documented, it is unclear whether exposure to PPI is associated with

Received December 29, 2015. Accepted February 23, 2016.

Published online ahead of print. Publication date available at www.jasn.org.

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an increased risk of incident CKD and progression to ESRD.[4,7] In this report, we used national United States Department of Veterans Affairs (VA) databases to build a primary cohort of new users of PPI and new users of Histamine H_2-receptor antagonists (H_2 blockers), and additional cohorts for sensitivity analyses, including a 1:1 propensity score-matched cohort of PPI and H_2 blockers, a 1:1 propensity score-matched cohort of PPI, and a control group, and examined the association between PPI exposure and risk of incident CKD, CKD progression, and ESRD among United States veterans without kidney disease at baseline (baseline eGFR>60 ml/min per 1.73 m^2).

RESULTS

There were 20,270 and 173,321 participants in the H_2 blockers, and PPI groups, respectively (Figure 1). The demographic and health characteristics of the two groups are described in Table 1.

Association between PPI and Risk of eGFR<60 ml/min per 1.73 m^2, and Risk of CKD

The incident rate for eGFR<60 ml/min per 1.73 m^2 was 5408.24 (95% confidence interval [95% CI], 5248.96 to 5567.52) and 7241.27 (95% CI, 7176.61 to 7305.93) per 100,000 person-years for H_2 blockers and PPI groups, respectively (Table 2). Unadjusted Cox survival model results are provided in Supplemental Table 1. In Cox survival models adjusted for demographic, eGFR, clinical comorbid conditions, and other health characteristics, we evaluated the risk of incident eGFR<60 ml/min per 1.73 m^2; compared with users of H_2 blockers, the PPI group showed an increased risk (hazard ratio [HR], 1.22; 95% CI, 1.18 to 1.26) (Table 2).

The incident rate for CKD (defined as two measurements of eGFR<60 ml/min per 1.73 m^2 at least 90 days apart) was 2569.86 (2463.30, 2676.43) and 3683.12 (95% CI, 3638.52 to 3727.72) per 100,000 person-years for H_2 blockers and PPI groups, respectively (Table 2). Adjusted survival models showed that the risk of CKD was increased in those exposed to PPI (HR, 1.28; 95% CI, 1.23 to 1.34). The attributable risk for incident eGFR<60 ml/min per 1.73 m^2 and incident CKD was 1.83% and 1.11%, respectively, and number needed to harm was 55 and 90, respectively.

Association between PPI and Risk of Kidney Disease Progression and ESRD

The incident rate of doubling of serum creatinine was 816.98 (758.86, 875.10) and 1387.02 (95% CI, 1360.81 to 1413.22) per 100,000 person-years for H_2 blockers and PPI groups, respectively. The incident rate for >30% decline in eGFR was 4533.25 (4391.86, 4674.64) and 6170.27 (95% CI, 6112.51 to 6228.03) per 100,000 person-years, respectively (Table 3). In adjusted survival models, risk of doubling of serum creatinine and eGFR decline >30% was significantly elevated in those treated with PPI (HR, 1.53; 95% CI, 1.42 to 1.65; and HR, 1.32; 95% CI, 1.28 to 1.37, respectively) (Table 3). The attributable risk for doubling of serum creatinine and >30% decline in eGFR was 0.57% and 1.63%, respectively, and number needed to harm was 175 and 61, respectively.

Incident rate for the outcome of ESRD was significantly higher among those treated with PPI compared with H_2 blockers (41.25 [95% CI, 36.79 to 45.70] and 26.50 [95% CI, 16.11 to 36.88] per 100,000 person-years, respectively). In adjusted survival models, the risk of ESRD was significantly increased in the PPI group (HR, 1.96; 95% CI, 1.21 to 3.18) (Table 3). Risk of ESRD, or >50% decline in eGFR was elevated in patients treated with PPI (HR, 1.47; 95% CI, 1.38 to 1.57) (Table 3). The attributable risk for ESRD and composite outcome of ESRD or >50% decline in eGFR was 0.01% and 0.66%, respectively, and number needed to harm was 6780 and 153, respectively.

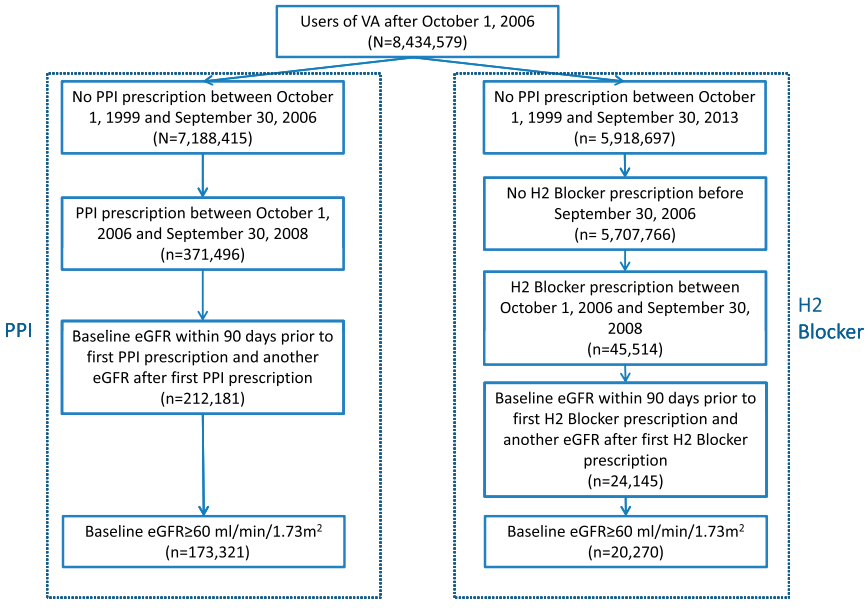

Figure 1. Flow diagram of cohort assembly of primary cohort of new users of PPI (*n*=173,321) and new users of H_2 blockers (20,270).

Duration of PPI Use and Risk of Renal Outcomes

We evaluated the association between duration of exposure and risk of renal outcomes among new users of PPI (*n*=173,321). Compared with those exposed for ≤30 days, there was a graded association between duration of exposure and risk of renal outcomes among those exposed for 31–90, 91–180, 181–360, and 361–720 days (Figure 2, Table 4).

The association seems to diminish with exposure exceeding 720 days.

Sensitivity Analyses

We examined the risk of renal outcomes in a 1:1 propensity score-matched cohort of new users of PPI (n=20,270) and new users of H_2 blockers (n=20,270). The flowchart for the cohort design is provided in Supplemental Figure 1; Supplemental Table 2 provides description of demographics and health characteristics. The standardized difference for age, race, sex distribution, clinical comorbid conditions, and heath characteristics was <0.1, indicating balance between the two groups (Supplemental Table 2). Examination of the association of PPI use and renal outcomes yielded results consistent with those shown in the primary analysis (Table 5).

We also examined the risk of renal outcomes in a 1:1 propensity matched cohort of new PPI users (n=173,321) and a control group (n=173,321) (see Concise Methods) (Supplemental Figure 2, Supplemental Table 3); the cohort was well balanced. Compared with the control group, patients treated with PPI exhibited an increased risk of renal outcomes, and results were consistent with those shown in the primary analyses (Table 6).

As a test of calibration, we evaluated the association between PPI exposure and the outcome of AKI. The intent of this analysis was to examine the presence of an association where *a priori* observations suggest that an association is expected.[1–3] The results suggest that patients in the PPI group have an increased risk of AKI (HR, 2.15; 95% CI, 2.00 to 2.32). To examine whether the association of PPI exposure and risk of chronic renal outcomes is mediated by occurrence of AKI, we controlled for AKI occurrence during exposure to acid-suppression therapy. The results suggest that associations remain significant (Table 7).

We evaluated the association of PPI exposure and risk of renal events in a number of additional sensitivity analyses where we: (*1*) included the number of eGFR measurements for each patient as a covariate (Supplemental Table 4), (*2*) included use of nonsteroidal anti-inflammatory drugs (NSAIDs), defined as exposure to NSAIDs for 30 days or more before (Supplemental Table 5A) and during time in cohort (Supplemental Table 5B) as a covariate, (*3*) included baseline microalbumin-to-creatinine ratio as a covariate in a subcohort of patients where data were available (n=29,059) (Supplemental Table 6), (*4*) included serum bicarbonate as a covariate (n=174,322) (Supplemental Table 7) and (*5*) included the angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB),

Table 1. Baseline characteristics of a cohort of new users of H2 blockers, and new users of PPI

Baseline Characteristics		H_2 Blockers (n=20,270)	PPI (n=173,321)	P Value
Age (SD)		55.40 (12.81)	56.85 (11.85)	P<0.001
Baseline eGFR in ml/min per 1.73 m^2 (SD)		86.98 (15.88)	86.56 (15.67)	P<0.001
Race	White (%)	15,937 (78.62)	137,174 (79.14)	P=0.01
	Black (%)	3,784 (18.67)	32,018 (18.47)	
	Other (%)	549 (2.71)	4,129 (2.38)	
Sex	Male (%)	18,929 (93.38)	161,259 (93.04)	P=0.07
	Female (%)	1,341 (6.62)	12,062 (6.96)	
Diabetes mellitus (%)		8,923 (44.02)	72,309 (41.72)	P<0.001
Hypertension (%)		15,814 (78.02)	136,782 (78.92)	P<0.01
Chronic lung disease (%)		7,951 (39.23)	66,955 (38.63)	P=0.10
Peripheral artery disease (%)		5,009 (24.71)	31,311 (18.07)	P<0.001
Cardiovascular disease (%)		8,459 (41.73)	71,807 (41.43)	P=0.41
Cerebrovascular disease (%)		4,596 (22.67)	26,457 (15.26)	P<0.001
Dementia (%)		5,058 (24.95)	32,380 (18.68)	P<0.001
Hyperlipidemia (%)		14,785 (72.94)	127,463 (73.54)	P=0.07
Hepatitis C (%)		1,198 (5.91)	14,892 (8.59)	P<0.001
HIV (%)		55 (0.27)	678 (0.39)	P<0.01
Gastroesophageal reflux disease (%)		3,767 (18.58)	86,804 (50.08)	P<0.001
Upper gastrointestinal tract bleeding (%)		246 (1.21)	7,898 (4.56)	P<0.001
Ulcer disease (%)		666 (3.29)	26,228 (15.13)	P<0.001
H. pylori infection (%)		22 (0.11)	4,052 (2.34)	P<0.001
Barrett esophagus (%)		15 (0.07)	3,207 (1.85)	P<0.001
Achalasia (%)		1 (0.00)	214 (0.12)	P<0.001
Stricture (%)		33 (0.16)	2,299 (1.33)	P<0.001
Esophageal adenocarcinoma (%)		3 (0.01)	291 (0.17)	P<0.001
Years of follow-up (IQR)		5.00 (5.00, 5.00)	5.00 (5.00, 5.00)	P<0.001
Days of having related prescription during follow-up (IQR)		90 (30, 270)	450 (90, 1260)	P<0.001

IQR, interquartile range.

Table 2. Association between PPI and risk of eGFR<60 ml/min per 1.73 m^2, and risk of CKD

Outcome		H_2 Blockers (*n*=20,270)	PPI (*n*=173,321)
Incident eGFR<60 ml/min per 1.73 m^2	Number of events (%)	4,429 (21.85)	48,171 (27.79)
	Incident rate (95% CI)	5408.24 (5248.96 to 5567.52)	7241.27 (7176.61 to 7305.94)
	HR (95% CI)	1.0	1.22 (1.18 to 1.26)
Incident chronic kidney disease	Number of events (%)	2,234 (11.02)	26,193 (15.11)
	Incident rate (95% CI)	2569.86 (2463.30 to 2676.43)	3683.12 (3638.52 to 3727.72)
	HR (95% CI)	1.0	1.28 (1.23 to 1.34)

Incident rate as incident per 100,000 person-years.
HRs were obtained from Cox models adjusted for baseline eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *H. pylori* infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma.

Table 3. Association between PPI and risk of kidney disease progression and risk of ESRD

Outcome		H2 Blockers (*n*=20,270)	PPI (*n*=173,321)
Doubling of serum creatinine	Number of events (%)	759 (3.74)	10,766 (6.21)
	Incident rate (95% CI)	816.98 (758.86 to 875.10)	1387.02 (1360.81 to 1413.22)
	HR (95% CI)	1.0	1.53 (1.42 to 1.65)
>30% decline in eGFR	Number of events (%)	3,949 (19.48)	43,842 (25.30)
	Incident rate (95% CI)	4533.25 (4391.86 to 4674.64)	6170.27 (6112.51 to 6228.03)
	HR (95% CI)	1.0	1.32 (1.28 to 1.37)
ESRD	Number of events (%)	25 (0.12)	329 (0.19)
	Incident rate (95% CI)	26.50 (16.11 to 36.88)	41.25 (36.79 to 45.70)
	HR (95% CI)	1.0	1.96 (1.21 to 3.18)
ESRD or >50% decline in eGFR	Number of events (%)	947 (4.67)	12,952 (7.47)
	Incident rate (95% CI)	1024.27 (959.03 to 1089.51)	1679.40 (1650.48 to 1708.32)
	HR (95% CI)	1.0	1.47 (1.38 to 1.57)

Incident rate as incident per 100,000 person-years.
HRs were obtained from Cox models adjusted for baseline eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *H. pylori* infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma.

defined as exposure to ACEI or ARB for 30 days or more before (Supplemental Table 8A) and during (Supplemental Table 8B) time in cohort as a covariate in the models. The results remained consistent in all sensitivity analyses.

DISCUSSION

This study leverages the availability of a national comprehensive database in an integrated network of health systems to examine the association between PPI exposure and long-term renal outcomes. Among users of acid-suppression therapy, H_2 blockers and PPI—2 classes of drugs generally prescribed for similar indications—we have shown that exposure to PPI is associated with increased risk of development of CKD, progression of kidney disease, and risk of ESRD. The results also suggest a graded relationship between duration of exposure and risk of renal outcomes. The results were consistent in multiple sensitivity analyses, including an assessment of risk in a 1:1 propensity score-matched and balanced cohort of H_2 blocker and PPI users where risk of renal outcomes was significantly elevated in patients treated with PPI compared with those treated with H_2 blockers, and a 1:1 propensity score-matched and balanced cohort of PPI users and controls where risk of renal outcomes was significantly increased in PPI users.

The results of our study further expand on the findings of a recently reported observational cohort study by Lazarus *et al.*[8] The investigators followed 10,482 participants in the Atherosclerosis Risk in Communities Study and assessed the association between self-reported PPI use and the risk of incident CKD defined by diagnostic codes that indicated CKD at hospital discharge or death or by incident ESRD as determined through linkage with United States Renal Database System. In adjusted analyses, they found that participants who used PPIs at baseline had a significantly increased risk of incident CKD compared with nonusers. Similar associations were seen in the Geisinger Health System replication cohort of 248,751 participants, where incident CKD was defined as sustained eGFR<60 ml/min per 1.73 m^2 or development of ESRD. In addition, twice-daily PPI dosing was shown to be associated with a higher risk of CKD than once-daily dosing. The study by Lazarus *et al.*, and this study, reached remarkably similar conclusions using comparable study designs but in unrelated, population-based cohorts. Our study adopted a new user design, on the basis of pharmacy records, where the primary

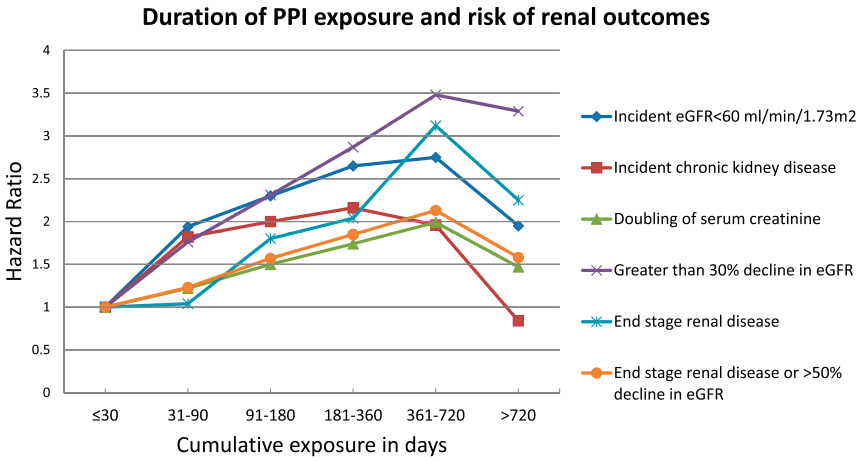

Figure 2. Duration of PPI exposure and risk of renal outcomes among PPI users (*n*=173,321).

outcomes for incident CKD and CKD progression were defined using actual laboratory parameters (not ICD-9 codes). In addition to reporting an association between PPI and the risk of incident CKD, our results demonstrate that PPI use is also associated with an increased risk of CKD progression (doubling of serum creatinine, eGFR decline >30%) and ESRD; furthermore, we show a graded association between duration of exposure and risk of renal outcomes. The constellation of findings in our study lends further validity to the observations reported by Lazarus *et al.*, further elucidates our understanding of the expanding spectrum of renal adverse events associated with PPI use, and suggests the need to exercise judicious use of PPI, limit exposure to the minimum dose necessary, and for close monitoring of renal function during PPI use.[9]

PPI are widely used and generally perceived as safe; they are often overprescribed, started inappropriately during a hospital stay, and their use extended for long-term duration without appropriate medical indication.[10–12] Strid *et al.* examined the use of acid-suppressant drugs in patients with CKD and concluded that acid-suppression therapy is often prescribed without adequate indication, where PPI were the most common drug class used for acid suppression.[13] Because of the wide use of PPI, the findings in this study may have public health relevance, in that, while seemingly benign, PPI use may be significantly associated with an increased risk of serious renal outcomes. We also note that, while the associations are significant, the incident rate of CKD, doubling of serum creatinine, eGFR decline >30%, and ESRD is relatively infrequent; therefore, while pharmacovigilance about safety of any approved therapeutic is a meritorious approach, the findings should not deter from prescription and use of PPI where medically indicated.

Recent examples that are relevant to PPI exposure and adverse outcomes include reports on risk of hypomagnesemia associated with PPI use among those admitted to intensive care units and in a population-based cohort study.[14,15] It is notable that the risk of hypomagnesemia in PPI users was not observed in clinical trials and postmarketing studies. Randomized controlled trials are often undertaken in an idealized setting, are generally underpowered, and do not cover a sufficiently prolonged span of time to detect untoward events that may be rare and/or require a long time course for disease progression to manifest. The Food and Drug Administration postmarketing safety surveillance systems for drug and therapeutic biologic products are passive and rely on data obtained from manufacturers or through voluntary physician and consumer reporting.[16] The systems may not capture long-term untoward outcomes.[16] The newly established Sentinel Initiative aims to leverage the increasing availability of 'Big Data' and significant advances in analytics to proactively and systematically detect adverse signals associated with prescription medications and to uncover latent adverse events that are relatively rare and would not otherwise be observed in randomized clinical trials, postmarketing studies, or be captured through the passive surveillance mechanisms.[16–18] The Sentinel Initiative, however, is informed (and often prompted) by observations (or signals) from clinical literature. Our results may help facilitate further discussion on PPI exposure and the risk of renal outcomes and, more broadly, on the role the scientific community could play in comprehensively fulfilling the promise of the Sentinel Initiative to protect and promote public health.[17,19,20]

The mechanism(s) underpinning the observed associations are not clear; several studies have suggested an association between PPI exposure and acute interstitial nephritis.[1,3,4,6] PPI-induced acute interstitial nephritis is thought to be a cell-mediated immune response that maybe idiosyncratic, and likely represents a class effect and does not seem dose-dependent.[4,21] It has been reported that 30–70% of patients with acute interstitial nephritis did not fully recover renal function, likely due to rapid development of interstitial fibrosis shortly after onset of the acute inflammatory process, especially in the setting of delayed diagnosis or treatment.[4,5] This incomplete recovery of renal function, possibly along with chronic interstitial nephritis, leads to CKD and potentially CKD progression and ESRD.[6,22] The relationship between AKI and subsequent development of CKD is supported by multiple observations, suggesting an important and growing role of AKI in the global epidemiology of CKD and ESRD and a bidirectional nexus between AKI and CKD and progression to ESRD.[23–25] In our analyses, we observed that the association of PPI and renal outcomes remained significant even after controlling for AKI, suggesting that the described associations may be independent of clinically

Table 4. Duration of exposure to PPI and risk of renal outcomes among new users of PPI (n=173,321)

Duration		Less or Equal to 30 Days	31–90 Days	91–180 Days	181–360 Days	361–720 Days	>720 days
Incident eGFR<60 ml/min per 1.73 m^2	*n* (%)	25,912 (14.95)	31,192 (18.00)	18,889 (10.90)	20,770 (11.98)	23,446 (13.53)	53,112 (30.64)
	HR (95% CI)	1	1.94 (1.88 to 2.00)	2.30 (2.22 to 2.39)	2.65 (2.56 to 2.74)	2.75 (2.66 to 2.85)	1.95 (1.87 to 2.02)
Incident CKD	*n* (%)	23,621 (13.63)	29,886 (17.24)	18,338 (10.58)	20,148 (11.62)	23,293 (13.44)	58,035 (33.48)
	HR (95% CI)	1	1.82 (1.74 to 1.89)	2.00 (1.91 to 2.10)	2.16 (2.06 to 2.26)	1.96 (1.87 to 2.06)	0.84 (0.79 to 0.89)
Doubling of serum creatinine	*n* (%)	19,602 (11.31)	27,234 (15.71)	16,989 (9.80)	19,116 (11.03)	23,603 (13.62)	66,777 (38.53)
	HR (95% CI)	1	1.22 (1.13 to 1.30)	1.50 (1.39 to 1.62)	1.74 (1.61 to 1.87)	1.99 (1.85 to 2.14)	1.47 (1.37 to 1.59)
>30% decline in eGFR	*n* (%)	22,751 (13.13)	29,291 (16.90)	18,209 (10.51)	20,444 (11.80)	24,371 (14.06)	58,255 (33.61)
	HR (95% CI)	1	1.76 (1.70 to 1.83)	2.31 (2.22 to 2.40)	2.87 (2.76 to 2.99)	3.48 (3.34 to 3.61)	3.29 (3.17 to 3.42)
ESRD	*n* (%)	18,529 (10.69)	26,469 (15.27)	16,649 (9.61)	18,792 (10.84)	23,500 (13.56)	69,382 (40.03)
	HR (95% CI)	1	1.04 (0.70 to 1.56)	1.80 (1.18 to 2.75)	2.04 (1.33 to 3.12)	3.12 (2.07 to 4.71)	2.25 (1.46 to 3.47)
ESRD or >50% decline in eGFR	*n* (%)	19,799 (11.42)	27,349 (15.78)	17,105 (9.87)	19,248 (11.11)	23,695 (13.67)	66,125 (38.15)
	HR (95% CI)	1	1.23 (1.16 to 1.31)	1.57 (1.47 to 1.69)	1.85 (1.72 to 1.98)	2.13 (1.99 to 2.28)	1.58(1.47 to 1.69)

HRs were obtained from Cox models adjusted for PPI duration, baseline eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *H. pylori* infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma.
Beginning of follow up (T0) was defined as the date of last use of PPI before event occurrence.
PPI duration was computed between first PPI prescription date and T0.

detectable AKI episodes and may be either the result of subclinical or unrecognized AKI or chronic indolent, but progressive, renal injury. PPI use may also cause severe hypomagnesemia,[14,15] which is associated with faster eGFR decline in CKD patients and in patients with type 2 diabetes mellitus,[26–28] progression to ESRD in diabetic nephropathy,[29] decreased renal allograft survival,[30] and, more recently, incident CKD.[31] While our study did not examine this mechanistic link, it is hypothetically plausible that hypomagnesemia may mediate or partially explain the observed associations in this report.[31]

The results show a graded association between duration of exposure and risk of renal outcomes; however, the association seems to weaken in those exposed for more than 720 days, which is most likely a reflection of a survivorship bias—a phenomenon commonly referred to in pharmacoepidemiology as "depletion of susceptibles," *i.e.,* those remaining in the cohort are likely resistant to the effect of PPI on renal outcomes.[32–34] In this study, we examined the risk of renal outcomes in a cohort design of new users of PPI and H_2 blockers, a category of therapeutics (acid-suppression therapy) generally prescribed for similar medical indications which may reduce confounding by indication bias; we built multivariate Cox survival models adjusting for known confounders. While our study is sufficiently large, and the outcome is not particularly rare, we further tested the sensitivity of the results to changes in cohort design (and specification of statistical models) where associations were examined in two propensity score-matched and balanced cohorts (H_2 blockers versus PPI, and PPI versus control).[35] The results obtained using propensity score analyses were similar to those obtained using multivariate Cox regression analyses (*i.e.,* were robust to changes in epidemiologic design), consistent with observations by Strümer *et al.* that, in most large studies, propensity score analyses do not yield substantially different risk estimates from conventional multivariate methods.[36] Winklemeyer and Kurth note a limitation of both approaches, in that they cannot account for unmeasured and unknown confounders and suggest that traditional multivariate regression adjustment is preferable in pharmacoepidemiology studies when the sample size is sufficiently large and the outcome is not rare.[37]

Our study has a number of limitations. The cohort included mostly older white male United States' veterans, thus the results may not be generalizable to less narrowly defined populations. The imperfect nature of administrative data and the retrospective design of the study may also lead to sampling bias and inaccurate measurements of the predictor variables. In order to minimize such measurement bias, we used definitions of comorbid illnesses that are validated for use in VA administrative data.[38] In our analyses, we considered drug exposure as PPI prescription; since PPI is available over the counter in the United States, it is possible that some patients in this cohort may have obtained and used PPI without prescription. However, owing to financial considerations, this is not highly likely, and if it occurred in some

Table 5. Risk of renal events in a 1:1 propensity score-matched cohort of new users of PPI (n=20,270) and new users of H2 blockers (n=20,270)

Outcome		H2 Blockers (*n*=20,270)	PPI (*n*=20,270)
Incident eGFR<60 ml/min per 1.73 m^2	Number of events (%)	4,429 (21.85)	5,204 (25.67)
	Incident rate (95% CI)	5408.24 (5249.96 to 5567.52)	6563.33 (6385.01 to 6741.65)
	HR (95% CI)	1.0	1.23 (1.17 to 1.30)
Incident CKD	Number of events (%)	2,234 (11.02)	2,776 (13.70)
	Incident rate (95% CI)	2569.86 (2463.30 to 2676.43)	3294.88 (3172.31 to 3417.44)
	HR (95% CI)	1.0	1.28 (1.18 to 1.38)
Doubling of serum creatinine	Number of events (%)	759 (3.74)	1,185 (5.85)
	Incident rate (95% CI)	816.98 (758.86 to 875.10)	1300.96 (1226.89 to 1375.03)
	HR (95% CI)	1.0	1.63 (1.47 to 1.81)
>30% decline in eGFR	Number of events (%)	3,949 (19.48)	4,762 (23.49)
	Incident rate (95% CI)	4533.25 (4391.86 to 4674.64)	5669.45 (5508.42 to 5830.47)
	HR (95% CI)	1.0	1.32 (1.25 to 1.39)
ESRD	Number of events (%)	25 (0.12)	38 (0.19)
	Incident rate (95% CI)	26.50 (16.11 to 36.88)	40.69 (27.75 to 53.63)
	HR (95% CI)	1.0	1.48 (0.49 to 4.50)
ESRD or >50% decline in eGFR	Number of events (%)	947 (4.67)	1433 (7.07)
	Incident rate (95% CI)	1024.27 (959.03 to 1089.51)	1582.80 (1500.85 to 1664.75)
	HR (95% CI)	1.0	1.59 (1.45 to 1.74)

Incident rate as incident per 100,000 person-years.
HRs were obtained from Cox models adjusted for baseline eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper GI tract bleeding, ulcer disease, *H. pylori* infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma.

patients, it will have biased the results against the primary hypothesis and resulted in underestimation of risk. While we report attributable risk to PPI use and number needed to harm, these numbers should not be extrapolated or otherwise generalized to other cohorts or the general population. The study has a number of strengths, including the use of national large-scale data from a network of integrated health systems which was captured during routine medical care which minimizes selection bias. We evaluated multiple outcomes in the continuum of CKD evolution, including development of CKD, progression of CKD, and the definite and terminal renal outcome of ESRD. We have taken

Table 6. Risk of renal events in a 1:1 propensity matched cohort of new PPI users (173,321) and a control group (n=173,321)

Outcome		Control (*n*=173,321)	PPI (*n*=173,321)
Incident eGFR<60 ml/min per 1.73 m^2	Number (%)	35,759 (20.63)	48,171 (27.79)
	Incident rate (95% CI)	5105.97 (5053.05 to 5158.90)	7241.27 (7176.61 to 7305.93)
	HR (95% CI)	1.0	1.57 (1.54 to 1.60)
Incident CKD	Number (%)	17,426 (10.05)	26,193 (15.11)
	Incident rate (95% CI)	2359.99 (2323.96 to 2394.01)	3683.12 (3638.52 to 3727.72)
	HR (95% CI)	1.0	1.81 (1.76 to 1.86)
Doubling of serum creatinine	Number (%)	6,039 (3.48)	10,766 (6.21)
	Incident rate (95% CI)	770.38 (750.95 to 789.81)	1387.02 (1360.81 to 1413.22)
	HR (95% CI)	1.0	1.86 (1.80 to 1.93)
>30% decline in eGFR	Number (%)	31,781 (18.34)	43,842 (25.30)
	Incident rate (95% CI)	4255.67 (4208.88 to 4302.46)	6170.27 (6112.51 to 6228.03)
	HR (95% CI)	1.0	1.67 (1.64 to 1.70)
ESRD	Number (%)	219 (0.13)	329 (0.19)
	Incident rate (95% CI)	27.60 (23.94 to 31.25)	41.25 (36.79 to 45.70)
	HR (95% CI)	1.0	1.61 (1.26 to 2.04)
ESRD or >50% decline in eGFR	Number (%)	7,410 (4.28)	12,952 (7.47)
	Incident rate (95% CI)	949.13 (927.52 to 970.74)	1679.40 (1650.48 to 1708.32)
	HR (95% CI)	1.0	1.83 (1.77 to 1.89)

Incident rate as incident per 100,000 person-years.
HRs were obtained from Cox models adjusted for baseline eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *H. pylori* infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma.

Table 7. Risk of renal events in models additionally adjusted for AKI during exposure to acid-suppression therapy

Outcome		H_2 Blockers (n=20,270)	PPI (n=173,321)
Incident eGFR<60 ml/min per 1.73 m^2	Number of patients with AKI during exposure to acid-suppression therapy (%)	690 (3.40)	10,903 (6.29)
	HR (95% CI)	1	1.20 (1.16 to 1.24)
Incident CKD	Number of patients with AKI during exposure to acid-suppression therapy (%)	710 (3.50)	12,170 (7.02)
	HR (95% CI)	1	1.28 (1.22 to 1.34)
Doubling of serum creatinine	Number of patients with AKI during exposure to acid-suppression therapy (%)	749 (3.70)	14,620 (8.44)
	HR (95% CI)	1	1.42 (1.32 to 1.54)
>30% decline in eGFR	Number of patients with AKI during exposure to acid-suppression therapy (%)	720 (3.55)	11,797 (6.81)
	H R (95% CI)	1	1.28 (1.24 to 1.33)
ESRD	Number of patients with AKI during exposure to acid-suppression therapy (%)	760 (3.75)	16,063 (9.27)
	HR (95% CI)	1	1.79 (1.10 to 2.89)
ESRD or >50% decline in eGFR	Number of patients with AKI during exposure to acid-suppression therapy (%)	748 (3.69)	14,293 (8.25)
	HR (95% CI)	1	1.38 (1.29 to 1.47)

HRs were obtained from Cox models adjusted for AKI during exposure to acid-suppression therapy, baseline eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *H. pylori* infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma.

considerable care to test the robustness of the associations in different cohort designs and numerous models in sensitivity analyses.

CONCISE METHODS

Patients

Cohort for primary analyses

Using administrative data from the United States Department of Veterans Affairs, we identified users of the VA healthcare system who had no PPI prescription between October 1, 1999 and September 30, 2006. Patients were then further selected into PPI-treatment and H_2-blockers groups. The PPI-treatment group selected patients who had at least one PPI prescription between October 1, 2006 and September 30, 2008. Patients in the PPI-treatment group were further restricted to those with a baseline eGFR>60 ml/min per 1.73 m^2 within 90 days before their first PPI prescription and at least one other eGFR measurement after their first PPI prescription (n=173,321). The H_2-blockers group included those who did not have a PPI prescription from October 1, 1999 until the end of follow-up on September 30, 2013, and had no H_2 blocker prescription between October 1, 1999 and September 30, 2006. The H_2-blocker group was restricted to those with a new prescription of H_2 blockers between October 1, 2006 and September 30, 2008. They were also restricted to those with a baseline eGFR>60 ml/min per 1.73 m^2 within 90 days before the first H_2 blocker prescription and at least one other eGFR measurement after their first H_2 blocker prescription (n=20,270) (Figure 1). Patients in cohort were followed for 5 years from their baseline eGFR measurement or until death. The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System, Saint Louis, MO.

Data Sources

We used Department of Veterans Affairs databases including inpatient and outpatient medical SAS datasets (that include utilization data related to all inpatient and outpatient encounters within the VA system) to ascertain detailed patient demographic characteristics and comorbidity information based on Current Procedural Terminology codes, and ICD-9-CM diagnostic and procedure codes associated with inpatient and outpatient encounters.[39–42] The VA Managerial Cost Accounting System Laboratory Results (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) provided information on outpatient and inpatient laboratory results. The VA Corporate Data Warehouse Production Outpatient Pharmacy domain provided information on prescriptions. The VA Vital Status and Beneficiary Identification Records Locator Subsystem files provided demographic characteristics and death follow-up through September 30, 2013.[39,40] United States Renal Database System data provided information about occurrence of ESRD and date of first ESRD services.

Primary Predictor Variable

The primary predictor variable is outpatient use of PPI. Medications that contain esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole were counted as PPI. Medications including ranitidine, cimetidine, and famotidine were counted as H_2 blockers. Distribution of PPI and H_2 blocker use is provided in Supplemental Table 9.

Outcomes

The primary outcomes in survival analyses were eGFR<60 ml/min per 1.73 m^2, with CKD defined as two eGFRs<60 ml/min per 1.73 m^2 at

least 90 days apart, where the first eGFR measurement date was considered the date of CKD occurrence. Outcomes to capture kidney disease progression included >30% decline in eGFR, doubling of serum creatinine, ESRD,[43–45] and ESRD or >50% decline in eGFR.[45,46] All outcomes except ESRD were based on outpatient serum creatinine. Outcomes were ascertained for 5-year duration from time of cohort entry (where baseline eGFR was captured).

Covariates

Baseline covariates were ascertained from October 1, 1999 until baseline eGFR measure (T_0), where baseline eGFR was defined as the eGFR within 90 days before first PPI or H_2 blocker prescription between October 1, 2006, and September 30, 2008. Covariates included baseline eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, and diseases associated with PPI use. eGFR was calculated using the abbreviated four-variable Chronic Kidney Disease Epidemiology Collaboration equation on the basis of age, sex, race, and outpatient serum creatinine.[47] Race/ethnicity was categorized as white, black, or other (Latino, Asian, Native American, or other racial/ethnic minority groups). Diseases associated with PPI use included gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *Helicobacter pylori* infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma.[48] Comorbidities, except for hepatitis C and HIV, were assigned on the basis of relevant ICD-9-CM diagnostic and procedures codes and Current Procedural Terminology codes in the VA Medical SAS datasets.[38,45,49,50] Hepatitis C and HIV were assigned based on laboratory results.

Statistical Analysis

t-test was used to detect mean difference for parametric continuous variables; Kruskal–Wallis test was used to detect difference for nonparametric continuous variables and chi-squared test was used to detect proportions difference between H_2 blockers and PPI treatment. Incident rates per 100,000 person-years were computed for outcomes and confidence intervals were estimated based on normal distribution. Attributable risk and number needed to harm were calculated from incident rates. Cox proportional hazard regression models were used in the assessment of the association between PPI exposure and risk of renal outcomes. Multiple models were built to assess the relationship while controlling for different covariates.

We evaluated the association between duration of exposure and risk of renal outcomes among new users of PPI. Duration was defined in cumulative days of use and categorized as ≤30, 31–90, 91–180, 181–360, 361–720, or ≥721 days, where ≤30 days was used as the referent category. Time of cohort entry was defined as the date of last use of PPI before occurrence of renal event.[32,51] Duration of PPI use was computed from the date of first PPI use until beginning of follow up.[32,51] In regression analyses, a 95% CI of an HR that does not include unity was considered statistically significant. In all analyses a *P* value of 0.05 or less was considered statistically significant. All analyses were performed using SAS Enterprise Guide version 6.1 and 7.1.

Sensitivity Analyses

To further explore the possibility of hidden bias we undertook additional analyses examine the risk of renal outcomes in a 1:1 propensity score-matched cohorts of new users of H_2 blockers who initiated a first prescription of H_2 blockers between October 1, 2006, and September 30, 2008 (*n*=20,270) and new users of PPI who initiated a first prescription of PPI between October 1, 2006, and September 30, 2008 (*n*=20,270) (Supplemental Figure 1), and also between new users of PPI (*n*=173,321) who initiated a first prescription of PPI between October 1, 2006, and September 30, 2008, and a control group without PPI prescription between October 1, 2006, and September 30, 2008 (*n*=173,321) (Supplemental Figure 2). Propensity scores were calculated using a nonparsimonious logistic regression model with PPI exposure as the dependent variable, with predictor variables of baseline eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *H. pylori* infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma. Nearest-neighbor matching without replacement was used, with a caliper distance set as 0.1, after the order of the treatment and control group was randomized.[52,53]

After 1:1 propensity score-matched cohorts of new users of PPI (*n*=20,270) and H2 blockers (*n*=20,270) (Supplemental Figure 1, Supplemental Table 2), and 1:1 propensity matched cohort of new PPI users (*n*=173,321) and a control group (*n*=173,321) (Supplemental Figure 2, Supplemental Table 3) were obtained, standardized differences were used to evaluate balance in distribution of baseline variables between PPI and control groups in matched cohorts, where a difference <0.1 was taken to indicate sufficient balance. Multivariate conditional Cox proportional hazards regression that stratified by matched pairs were conducted to examine the association between PPI and outcomes.

As a test of calibration, we evaluated the association between PPI exposure and the outcome of AKI during exposure to acid-suppression therapy and where AKI was defined as 0.3 mg/dl or 50% increase in serum creatinine within 30 days.[45,49,54] To examine whether the association of PPI exposure and risk of chronic renal outcomes is mediated by occurrence of AKI, we controlled for AKI occurrence during exposure to acid-suppression therapy.

In order to further evaluate the consistency and robustness of the findings of our study, we examined the observed associations in a number of additional sensitivity analyses where we: (*1*) included the number of eGFR measurements from October 1, 1999 until time of cohort entry (T_0) for each patient as a covariate, (*2*) included use of NSAIDs, defined in separate models as exposure to NSAIDs for 30 days or more before and during time in cohort, as a covariate, (*3*) included baseline microalbumin-to-creatinine ratio as a covariate in a subcohort of patients where data were available (*n*=29,059), (*4*) included serum bicarbonate as a covariate where it was treated as a continuous variable, and (*5*) included the ACEI and ARB, defined as exposure to ACEI or ARB for 30 days or more before and during time in cohort as a covariate in separate models.

ACKNOWLEDGMENTS

Kevin Martin from the Office of Information and Technology at the US Department of Veterans Affairs (VA) contributed to the development of SAS code for propensity score matching in a large cohort.

Support for VA/Centers for Medicare and Medicaid Services (CMS) data is provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (Project Number/Data Use Agreement ID Al-Aly-01-A-1). This work was funded by a grant from the US Department of Veterans Affairs (for Z.A.A.).

The contents do not represent the views of the US Department of Veterans Affairs or the US Government.

DISCLOSURES

None.

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See related editorial, "Proton Pump Inhibitors and CKD," on pages 2926–2928.

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2015121377/-/DCSupplemental.