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Proton pump inhibitor (PPI) use is associated with an increased risk of acute kidney injury (AKI), incident chronic kidney disease (CKD), and progression to end-stage renal disease (ESRD). PPI-associated CKD is presumed to be mediated by intervening AKI. However, whether PPI use is associated with an increased risk of chronic renal outcomes in the absence of intervening AKI is unknown. To evaluate this we used the Department of Veterans Affairs national databases to build a cohort of 144,032 incident users of acid suppression therapy that included 125,596 PPI and 18,436 Histamine H2 receptor antagonist (H2 blockers) consumers. Over 5 years of follow-up in survival models, cohort participants were censored at the time of AKI occurrence. Compared with incident users of H2 blockers, incident users of PPIs had an increased risk of an estimated glomerular filtration rate (eGFR) under 60 ml/min/1.73m^2 (hazard ratio 1.19; 95% confidence interval 1.15-1.24), incident CKD (1.26; 1.20-1.33), eGFR decline over 30% (1.22; 1.16-1.28), and ESRD or eGFR decline over 50% (1.30; 1.15-1.48). Results were consistent in models that excluded participants with AKI either before chronic renal outcomes, during the time in the cohort, or before cohort entry. The proportion of PPI effect mediated by AKI was 44.7%, 45.47%, 46.00%, and 46.72% for incident eGFR under 60 ml/min/1.73m^2, incident CKD, eGFR decline over 30%, and ESRD or over 50% decline in eGFR, respectively. Thus, PPI use is associated with increased risk of chronic renal outcomes in the absence of intervening AKI. Hence, reliance on antecedent AKI as warning sign to guard against the risk of CKD among PPI users is not sufficient as a sole mitigation strategy.

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Proton pump inhibitors (PPI) are widely used for acid suppression therapy. Results of the National Health and Nutrition Examination Survey estimate that 7.8% of US adults had used prescription PPIs in the previous 30 days.[1] These figures likely underestimate the real prevalence of PPI use as several PPIs are also widely available for sale over the counter without prescription in the United States.[2,3] Several observational studies suggest that PPI use is associated with an increased risk of a number of adverse health outcomes.[2] PPI use is also associated with an increased risk of acute kidney injury (AKI), incident chronic kidney disease (CKD), CKD progression, and end-stage renal disease (ESRD).[3–7]

AKI is a significant risk factor for the development of CKD, CKD progression, and ESRD.[8,9] CKD increases the propensity for the development of AKI where a bidirectional nexus exists between AKI and CKD and progression to ESRD.[8–12] The association between PPI exposure and risk of AKI and acute interstitial nephritis is well documented.[4–6,13–16] Studies that established the relationship of PPI use and CKD have postulated that the association is likely mediated by the occurrence of intervening AKI, from which some patients recover, but others do not or experience incomplete recovery and CKD might develop and progress to ESRD.[3,14,16,17] It has also been suggested that PPI use may lead to subclinical AKI, AKI that is not clinically diagnosed, or chronic indolent renal damage.[3,7,18] Previous studies have not addressed whether PPI-associated CKD is mediated by the occurrence of intervening AKI or via other pathways. Whether the use of PPI is associated with untoward long-term kidney outcomes including the development of CKD and progression to ESRD in the absence of intervening AKI is not known.[13,19]

In this work, we aimed to examine the association of PPI use and the risk of long-term renal outcomes in those without intervening AKI. We therefore used the US Department of Veterans Affairs (VA) databases to build a national cohort of new users of acid suppression therapy (either PPI or

histamine H2 receptor antagonists [H2 blockers]) without kidney disease at baseline (baseline estimated glomerular filtration rate [eGFR] >60 ml/min per 1.73 m^2) and followed them for 5 years to characterize the association of PPI use with the risk of incident CKD, the risk of CKD progression, and the risk of ESRD in the absence of intervening AKI.

RESULTS

There were 144,032 new users of acid suppression therapy; 18,436 and 125,596 were new users of H2 blockers and PPIs, respectively. There were 118,793 cohort participants with no AKI during the time in the cohort (from time 0 [T0] at cohort entry until the end of follow-up or ESRD or death); 16,101 and 102,692 were incident users of H2 blockers and PPIs, respectively. The demographic and health characteristics are given in Table 1. Overall, new users of PPIs and H2 blockers had comparable demographic characteristics, but PPI users were more likely to have diabetes, chronic lung disease, hyperlipidemia, and cardiovascular disease (Table 1). New users of PPIs were more likely to have gastrointestinal conditions (Table 1). Survival probability for chronic kidney outcomes including an incident eGFR <60 ml/min per 1.73 m^2, incident CKD, an eGFR decrease >30%, and ESRD or eGFR decrease >50% by type of acid suppressant is shown in Figure 1a–d.

PPI exposure and risk of chronic renal outcomes in the absence of intervening AKI

We examined the association of PPI use and the risk of chronic renal outcomes in the absence of intervening AKI using the analytic strategies outlined in Figure 2. In order to evaluate the association between PPI use and the risk of chronic renal outcomes in the absence of intervening AKI, we built survival models in which cohort participants were censored at the time of AKI occurrence (Figure 2, analytic approach A). In a cohort of 144,032 incident users of acid suppression therapy and over a median follow-up period of 5 years (interquartile range, 5–5), compared with new users of H2 blockers, new users of PPIs had a significantly increased risk of an eGFR <60 ml/min per 1.73 m^2 (hazard ratio [HR]1.19, 95% confidence interval [CI] 1.15–1.24), incident CKD (HR 1.26, 95% CI 1.20–1.33), an eGFR decrease >30% (HR 1.22, 95% CI 1.16–1.28), and an ESRD or eGFR decrease >50% (HR 1.30, 95% CI 1.15–1.48) (Table 2). To ascertain that associations observed in the previous models were not reversible and remained until end of cohort follow-up, we built multivariate analyses in which we used the last eGFR before censorship (time of first occurrence of AKI, ESRD, death, or end of follow-up) to define chronic renal outcomes; new users of PPIs had an increased odds of an eGFR <60 ml/min per 1.73 m^2 (odds ratio 1.26, 95% CI 1.19–1.32); an eGFR decrease >30% (odds ratio 1.24, 95% CI 1.17–1.31), and an eGFR decrease >50% (odds ratio 1.34, 95% CI 1.19–1.52) (ESRD is, by definition, a terminal event and was not included as an outcome in this analysis) (Table 3).

To evaluate the relationship of PPI use and the risk of chronic renal outcomes in participants who do not experience AKI before the onset of chronic renal outcome, we excluded cohort participants who experienced AKI before chronic renal outcomes (any AKI between the time of cohort entry (T0) and before chronic renal outcome) (Figure 2, analytic approach B); compared with new users of H2 blockers, incident users of PPIs had an increased risk of an eGFR <60 ml/min per 1.73 m^2 (HR 1.22, 95% CI 1.17–1.27), incident CKD (HR 1.29, 95% CI 1.22–1.36), an eGFR decrease >30% (HR 1.26, 95% CI 1.19–1.32), and an ESRD or eGFR decrease >50% (HR 1.35, 95% CI 1.19–1.53) (Table 4). In order to evaluate the association of PPI use and the risk of chronic renal outcomes in those who do not experience AKI after exposure to acid suppression, we excluded cohort participants in whom AKI developed during the time in the cohort (from T0 until the end of follow-up, either before or after the occurrence of chronic renal outcomes) (Figure 2, analytic approach C). The analyses yielded consistent results in that PPI users had an increased risk of an eGFR <60 ml/min per 1.73 m^2 (HR 1.17, 95% CI 1.12–1.22), incident CKD (HR 1.23; 95% CI 1.16–1.30), an eGFR decrease >30% (HR 1.19; 95% CI 1.13–1.26), and an ESRD or eGFR decrease >50% (HR 1.21, 95% CI 1.04–1.40) (Table 5).

Because a history of AKI increases the risk of both AKI recurrence and CKD,[10,20] we evaluated the research question among cohort participants without a history of AKI within 5 years before cohort entry ($N = 132{,}699$) (Figure 2, analytic approach D), in which cohort participants were censored at the time of AKI occurrence; compared with new users of H2 blockers, new users of PPIs had an increased risk of chronic renal outcomes including an eGFR <60 ml/min per 1.73 m^2 (HR 1.19, 95% CI 1.15–1.25), incident CKD (HR 1.27, 95% CI 1.20–1.34), an eGFR decrease >30% (HR 1.22, 95% CI 1.16–1.29), and an ESRD or eGFR decrease >50% (HR 1.32, 95% CI 115–1.52) (Table 6).

Mediation analyses showed the proportion of PPI effect mediated by AKI was 44.7% for an incident eGFR <60 ml/min per 1.73 m^2, 45.47% for incident CKD, 46.00% for an eGFR decrease >30%, and 46.72% for an ESRD or >50% decrease in eGFR (Figure 3 and Supplementary Table S1).

In analyses evaluating the cumulative duration of exposure and risk of renal outcomes, there was a graded association between duration of use and risk in that a more prolonged duration of PPI exposure was associated with a greater risk of chronic renal outcomes (Figure 4 and Supplementary Table S2).

Sensitivity analyses

We evaluated the robustness of study results in a number of sensitivity analyses. As a test of calibration, we examined the relationship of PPI use and the risk of AKI and, separately, the relationship of PPI use and risk of chronic renal outcomes (without taking into account the possible occurrence of intervening AKI). The intent of this analysis was to verify the presence of an association where *a priori* knowledge suggests that an association is expected.[3–7] Results show that PPI users have an increased risk of AKI (HR 1.47, 95% CI 1.41–1.54). PPI use was associated with an increased risk of an eGFR

Table 1 | Demographic and health characteristics of overall cohort of new users of acid suppression therapy and those without intervening AKI by type of acid suppressant

Variables	Overall (*N* = 144,032)	H2 blockers (*N* = 18,436)	PPIs (*N* = 125,596)	No AKI[a] (*N* = 118,793)		
				H2 blockers (*N* = 16,101)	PPIs (*N* = 102,692)	Standardized difference
Age (SD), yr	57.82 (13.57)	56.81 (14.06)	57.97 (13.49)	56.29 (14.34)	57.47 (13.89)	0.08
First eGFR in ml/min per 1.73 m^2 (SD)	85.46 (15.63)	86.05 (15.81)	85.38 (15.60)	86.25 (15.82)	85.44 (15.49)	−0.05
Last eGFR in ml/min per 1.73 m^2 (SD)[b]	84.79 (18.13)	85.83 (17.96)	84.64 (18.14)	86.07 (17.59)	84.73 (17.56)	−0.08
No. (SD) of outpatient serum creatinine measurements	4.64 (5.57)	4.83 (5.75)	4.61 (5.54)	4.40 (5.10)	4.06 (4.80)	−0.06
No. (SD) of hospitalizations	0.38 (1.06)	0.43 (1.18)	0.38 (1.04)	0.35 (1.02)	0.28 (0.85)	−0.07
Race, no. (%)						
White	113,615 (78.88)	14,233 (77.20)	99,382 (79.13)	12,522 (77.77)	82,131 (79.98)	0.05
Black	24,508 (17.02)	3313 (17.97)	21,195 (16.88)	2783 (17.28)	16,350 (15.92)	−0.04
Other	5909 (4.10)	890 (4.83)	5019 (4.00)	796 (4.94)	4211 (4.10)	−0.04
Sex, no. (%)						
Male	134,507 (93.39)	17,211 (93.36)	117,296 (93.39)	14,943 (92.81)	95,324 (92.83)	0.001
Female	9525 (6.61)	1225 (6.64)	8300 (6.61)	1158 (7.19)	7368 (7.17)	−0.001
Smoking, no. (%)						
Never smoker	62,495 (43.39)	8340 (45.24)	54,155 (43.12)	7429 (46.14)	45,641 (44.44)	−0.03
Former smoker	30,605 (21.25)	3286 (17.82)	27,319 (21.75)	2867 (17.81)	22,546 (21.95)	0.10
Current smoker	50,932 (35.36)	6810 (36.94)	44,122 (35.13)	5805 (36.05)	34,505 (33.60)	−0.05
Systolic blood pressure, mm Hg, no. (%)						
<90	414 (0.29)	42 (0.23)	372 (0.30)	33 (0.20)	248 (0.24)	0.001
90–119.9	35,387 (24.57)	4438 (24.07)	30,949 (24.64)	3855 (23.94)	24,967 (24.31)	0.001
120–139.9	70,539 (48.97)	8945 (48.52)	61,594 (49.04)	7933 (49.27)	51,541 (50.19)	0.02
>139.9	37,692 (26.17)	5011 (27.18)	32,681 (26.02)	4280 (26.58)	25,936 (25.26)	−0.03
Diastolic blood pressure, mm Hg, no. (%)						
<60	7932 (5.51)	942 (5.11)	6990 (5.57)	790 (4.91)	5319 (5.18)	0.01
60–79.9	75,357 (52.32)	9521 (51.64)	65,836 (52.42)	8305 (51.58)	53,816 (52.41)	0.02
80–89.9	42,178 (29.28)	5431 (29.46)	36,747 (29.26)	4823 (29.95)	30,730 (29.92)	0.00
>89.9	18,565 (12.89)	2542 (13.79)	16,023 (12.76)	2183 (13.56)	12,827 (12.49)	−0.03
Body mass index, no. (%)						
Underweight	2335 (1.62)	334 (1.81)	2001 (1.59)	265 (1.65)	1386 (1.35)	−0.02
Normal weight	30,825 (21.40)	4038 (21.90)	26,787 (21.33)	3486 (21.65)	21,145 (20.59)	−0.03
Overweight	52,381 (36.37)	6688 (36.28)	45,693 (36.38)	5936 (36.87)	38,219 (37.22)	0.007
Obese	58,491 (40.61)	7376 (40.01)	51,115 (40.70)	6414 (39.84)	41,942 (40.84)	0.02
Diabetes mellitus, no. (%)	49,839 (34.60)	5856 (31.76)	43,983 (35.02)	4758 (29.55)	32,695 (31.84)	0.05
Chronic lung disease, no. (%)	45,315 (31.46)	5155 (27.96)	40,160 (31.98)	4183 (25.98)	29,527 (28.75)	0.06
Peripheral artery disease, no. (%)	8549 (5.94)	989 (5.36)	7560 (6.02)	690 (4.29)	4755 (4.63)	0.02
Cardiovascular disease, no. (%)	49,806 (34.58)	5588 (30.31)	44,218 (35.21)	4457 (27.68)	32,057 (31.22)	0.08
Cerebrovascular disease, no. (%)	1162 (0.81)	134 (0.73)	1028 (0.82)	88 (0.55)	624 (0.61)	0.008
Dementia, no. (%)	13,651 (9.48)	1622 (8.80)	12,029 (9.58)	1285 (7.98)	8474 (8.25)	0.01
Hyperlipidemia, no. (%)	107,060 (74.33)	13,251 (71.88)	93,809 (74.69)	11,518 (71.54)	76,493 (74.49)	−0.001
Hepatitis C, no. (%)	8210 (5.70)	990 (5.37)	7220 (5.75)	813 (5.05)	5042 (4.91)	−0.006
HIV, no. (%)	363 (0.25)	45 (0.24)	318 (0.25)	35 (0.22)	192 (0.19)	−0.007
Cancer, no. (%)	16,465 (11.43)	2104 (11.41)	14,361 (11.43)	1602 (9.95)	9981 (9.72)	−0.008
GERD, no. (%)	45,314 (31.46)	4808 (26.08)	40,506 (32.25)	4359 (27.07)	35,377 (34.45)	−0.06

Upper GI tract bleeding, no. (%)	3176 (2.21)	155 (0.84)	3021 (2.41)	119 (0.74)	2067 (2.01)	0.11
Ulcer disease, no. (%)	9894 (6.87)	785 (4.26)	9109 (7.25)	680 (4.22)	6901 (6.72)	0.11
Helicobacter pylori infection, no. (%)	1306 (0.91)	25 (0.14)	1281 (1.02)	22 (0.14)	1018 (0.99)	0.11
Barrett's esophagus, no. (%)	1112 (0.77)	12 (0.07)	1100 (0.88)	7 (0.04)	909 (0.89)	0.13
Achalasia, no. (%)	65 (0.05)	0 (0.00)	65 (0.05)	0 (0.00)	51 (0.05)	0.03
Stricture, no. (%)	856 (0.59)	30 (0.16)	826 (0.66)	21 (0.13)	664 (0.65)	0.08
Esophageal adenocarcinoma, no. (%)	75 (0.05)	1 (0.01)	74 (0.06)	0 (0.00)	46 (0.04)	0.03
NSAID use, no. (%)	37,125 (25.78)	5154 (27.96)	31,971 (25.46)	4420 (27.45)	25,479 (24.81)	−0.06
ACE/ARB use, no. (%)	43,497 (30.20)	5654 (30.67)	37,843 (30.13)	4609 (28.63)	28,242 (27.50)	−0.03
Incident AKI in 1000 person-years, (95% CI)	37.75 (37.29–38.22)	27.23 (26.14–28.36)	39.30 (38.80–39.82)	N/A	N/A	N/A
AKI, no. (%)						
Overall	25,239 (17.52)	2335 (12.67)	22,904 (18.24)	N/A	N/A	N/A
>50% increase in serum creatinine within 90 days	16,699 (11.59)	1501 (8.14)	15,198 (12.10)	N/A	N/A	N/A
>0.3 mg/dl increase in serum creatinine within 90 days	24,475 (16.99)	2258 (12.25)	22,217 (17.69)	N/A	N/A	N/A
Duration of wash-out period (IQR)[c]	5.02 (1.25–8.42)	5.49 (1.82–8.53)	4.94 (1.17–8.40)	5.36 (1.70–8.47)	4.73 (1.07–8.30)	−0.11
Follow-up, yr (IQR)[d]	5.00 (5.00–5.00)	5.00 (5.00–5.00)	5.00 (5.00–5.00)	5.00 (5.00–5.00)	5.00 (5.00–5.00)	0.009
Death, no. (%)	19,465 (13.51)	2316 (12.56)	17,149 (13.65)	1606 (9.97)	10,467 (10.19)	0.007
Incident eGFR <60 ml/min per 1.73 m^2, no. (%)	38,247 (26.55)	4021 (21.81)	34,226 (27.25)	2574 (15.99)	19,545 (19.03)	0.08
Incident chronic kidney disease, no. (%)	20,797 (14.44)	2042 (11.08)	18,755 (14.93)	1235 (7.67)	9977 (9.72)	0.07
>30% decrease in eGFR, no. (%)	27,259 (18.93)	2740 (14.86)	24,519 (19.52)	1431 (8.89)	10,973 (10.69)	0.06
ESRD or >50% decrease in eGFR, no. (%)	8899 (6.18)	809 (4.39)	8090 (6.44)	205 (1.27)	1616 (1.57)	0.03
Microalbumin/creatinine ratio, mg/g, no. (%), $N = 18,871$						
<30	15,235 (80.73)	1900 (81.06)	13,335 (80.69)	1602 (82.58)	10,446 (83.39)	0.02
30–300	3233 (17.13)	399 (17.02)	2834 (17.15)	305 (15.72)	1893 (15.11)	−0.02
>300	403 (2.14)	45 (1.92)	358 (2.17)	33 (1.70)	187 (1.49)	−0.02
Glycated hemoglobin, % (SD), $N = 74,802$	6.45 (4.00)	6.38 (2.89)	6.47 (4.14)	6.31 (2.46)	6.38 (4.19)	0.02

ACE, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GERD, gastroesophageal reflux disease; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PPIs, proton pump inhibitors.

[a]Did not experience AKI from T0 until ESRD or end of follow-up.

[b]eGFR value before and closest to AKI occurrence or ESRD or end of follow-up.

[c]Years between enrolled in Veterans Affairs and T0; 140,677 patients with data were available.

[d]From T0 until ESRD or end of follow-up.

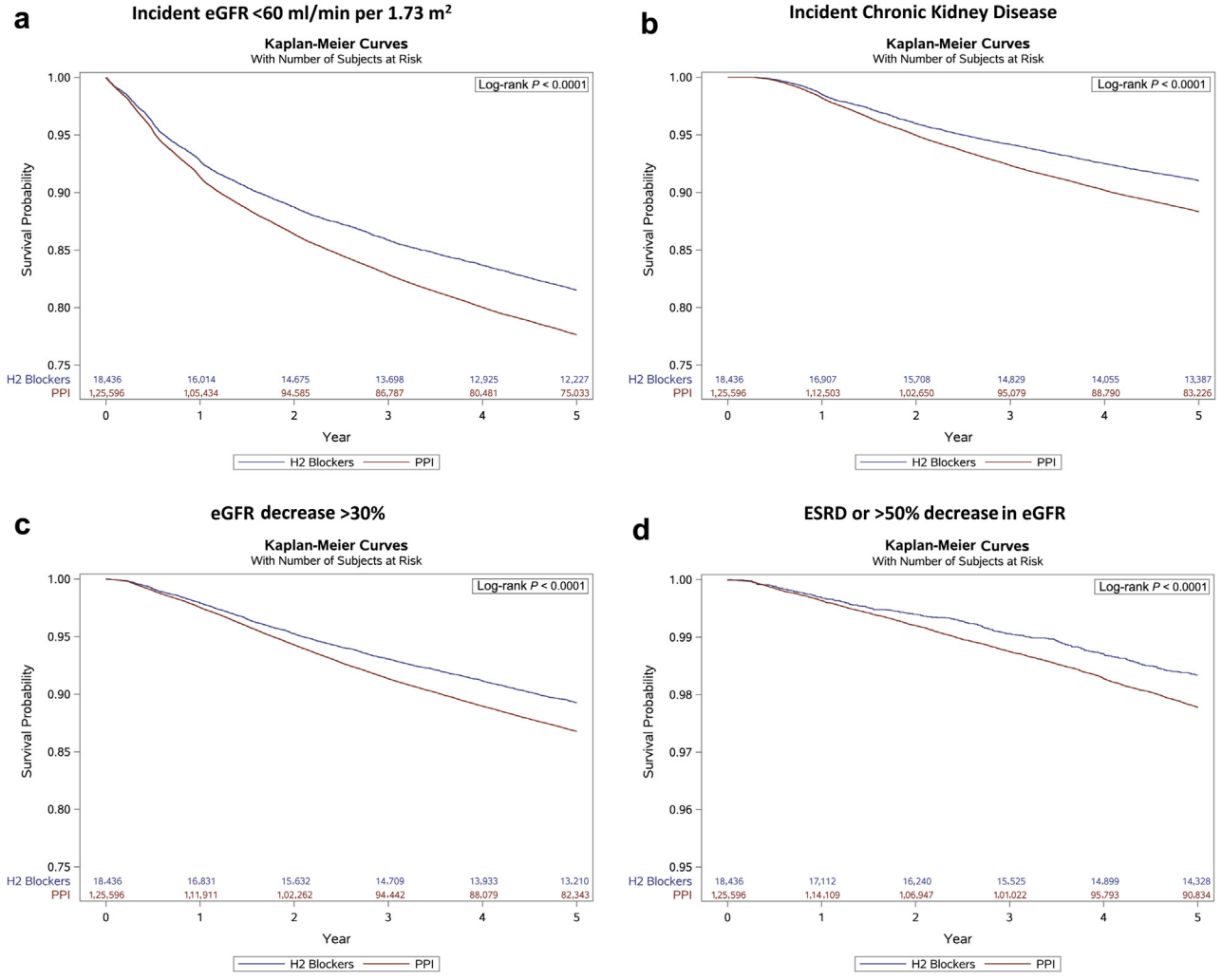
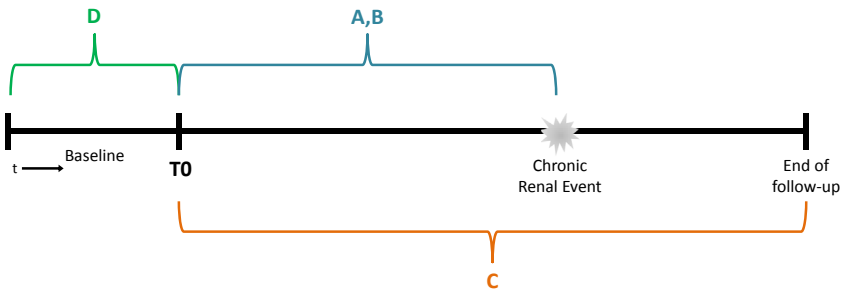


Figure 1 | Survival probability for chronic kidney outcomes by the type of acid suppressant. (**a**) Incident estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2. (**b**) Incident chronic kidney disease. (**c**) eGFR decrease >30%. (**d**) End-stage renal disease or eGFR decrease>50%.



Analytic Approach:

A – Censor at time of AKI (if AKI occurred between T0 and Chronic Renal Event*)

B – Exclude participants with AKI between T0 and Chronic Renal Event*

C – Exclude participants with AKI between T0 and end of follow-up

D – Exclude participants with AKI before T0

*Chronic renal event: incident eGFR <60 ml/min per 1.73 m^2, incident CKD, eGFR decrease >30%, or ESRD/eGFR decrease >50%.

Figure 2 | Analytic strategies to examine the association of proton pump inhibitor use and risk of chronic renal outcomes without intervening acute kidney injury (AKI). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

Table 2 | Survival models of the association between PPI use and risk of chronic renal outcomes among new users of acid suppression therapy (H2 blockers [referent] and PPIs) in which cohort participants were censored at the time of AKI occurrence (*N* = 144,032)

	Incident rate[a] (95% CI)		Univariate hazard ratio[b] (95% CI)	Multivariate hazard ratio[b,c] (95% CI)
	H2 blockers	PPI		
Incident eGFR <60 ml/min per 1.73 m^2	42.88 (41.38–44.41)	53.66 (53.00–54.33)	1.24 (1.19–1.28)	1.19 (1.15–1.24)
Incident chronic kidney disease	18.82 (17.86–19.81)	24.75 (24.31–25.19)	1.32 (1.25–1.39)	1.26 (1.20–1.33)
>30% decrease in eGFR	22.75 (21.70–23.84)	28.42 (27.95–28.89)	1.25 (1.19–1.31)	1.22 (1.16–1.28)
ESRD or >50% decrease in eGFR	3.32 (2.94–3.75)	4.46 (4.28–4.64)	1.34 (1.18–1.53)	1.30 (1.15–1.48)

AKI, acute kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PPIs, proton pump inhibitor.
[a]Incident rate as incident kidney outcome occurrence before AKI per 1000 person-years.
[b]Participants were censored as nonevent when they experience AKI; H2 blockers serve as the reference group.
[c]Multivariate model controlling for first eGFR, age, race, sex, smoking, body mass index, diastolic blood pressure, systolic blood pressure, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, number of outpatient serum creatinine measurements, number of hospitalizations, diabetes mellitus, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *Helicobacter pylori* infection, Barrett's esophagus, achalasia, stricture, and esophageal adenocarcinoma.

<60 ml/min per 1.73 m^2 (HR 1.25, 95% CI 1.21–1.29), incident CKD (HR 1.33, 95% CI 1.27–1.40), an eGFR decrease >30% (HR 1.31, 95% CI 1.26–1.37), and an ESRD or eGFR decrease >50% (HR 1.43, 95% CI 1.33–1.1.54).

Additional sensitivity analyses were conducted in models that censored participants at the time of AKI occurrence (Figure 2, analytic approach A). In analyses using the modified NHS England AKI algorithm, as reported by Sawhney *et al.*,[21] which has a very high sensitivity (>90%) for the detection of biochemical AKI (AKI based on actual laboratory values, not International Classification of Diseases, Ninth Revision [ICD-9] codes),[21] PPI use was associated with an increased risk of chronic renal outcomes, and the results were consistent with those shown in the primary analysis (Supplementary Table S3A). Analyses in which AKI was defined by KDIGO criteria and separately where AKI was defined by ICD-9 codes occurring during a hospital stay yielded consistent results (Supplementary Tables 3B and 3C).

In models that included incident H2 blocker users who switched to PPI use and where exposure was modeled as time dependent, compared with H2 blocker use, PPI use was associated with an increased risk of chronic renal outcomes (Supplementary Table S4). Analyses in which covariates were treated as time-dependent variables produced consistent results (Supplementary Table S5). Examination of the association in Fine and Gray models in which death and AKI were considered competing risks yielded consistent results (Supplementary Table S6).

An instrumental variable approach was used to account for the lack of random assignment of PPI and H2 blockers, and results suggest that PPI users had an increased risk of an incident eGFR <60 ml/min per 1.73 m^2 (HR 1.36, 95% CI 1.25–1.48), incident CKD (HR 1.68, 95% CI 1.48–1.91), an eGFR decrease >30% (HR 1.40, 95% CI 1.25–1.57), and an ESRD or eGFR decrease >50% (HR 1.50, 95% CI 1.13–2.00) (Supplementary Table S7).

In order to optimize control of confounding, we additionally built high-dimensional propensity score–adjusted survival models following the multistep algorithm described by Schneeweiss *et al.*[22] Among new users of acid suppression therapy, in high-dimensional propensity score–adjusted models (in which score was considered as continuous), new PPI users had an increased risk of incident eGFR <60 ml/min per 1.73 m^2 (HR 1.15, 95% CI 1.10–1.19), incident CKD (HR 1.20, 95% CI 1.13–1.27), an eGFR decrease >30% (HR 1.19, 95% CI 1.14–1.25), and an ESRD or eGFR decrease >50% (HR 1.30, 95% CI 1.15–1.48) (Supplementary Table S8). Similar results were obtained where the high-dimensional propensity score was considered in deciles (Supplementary

Table 3 | Multivariate logistic regression models of the association between PPI use and the odds of chronic renal outcomes in new users of acid suppression therapy (H2 blockers [referent] and PPIs) where the last eGFR before the first occurrence of AKI, ESRD, death, or end of follow-up was used to define outcomes (*N* = 144,032)

	No. (%) of events[a]		Univariate OR[b] (95% CI)	Multivariate OR[b,c] (95% CI)
	H2 blockers	PPIs		
eGFR <60 ml/min per 1.73 m^2	2041 (11.07)	17,463 (13.90)	1.30 (1.24–1.36)	1.26 (1.19–1.32)
>30% decrease in eGFR	1342 (7.28)	11,493 (9.15)	1.28 (1.21–1.36)	1.24 (1.17–1.31)
>50% decrease in eGFR	292 (1.58)	2272 (2.21)	1.40 (1.24–1.58)	1.34 (1.19–1.52)

AKI, acute kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; OR, odds ratio; PPIs, proton pump inhibitors.
[a]Based on a comparison of the first and last eGFRs, in which the last eGFR was the eGFR before and closest to first occurrence of AKI, ESRD, death, or end of follow-up.
[b]H2 blockers serve as the reference group.
[c]Multivariate model controlling for first eGFR, age, race, sex, smoking, body mass index, diastolic and systolic blood pressure, nonsteroidal anti-inflammatory drug; angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, number of outpatient serum creatinine measurements, number of hospitalizations, diabetes mellitus, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *Helicobacter pylori* infection, Barrett's esophagus, achalasia, stricture, and esophageal adenocarcinoma.

Table 4 | Survival models of the association of PPI use and risk of chronic renal outcomes in new users of acid suppression therapy (H2 blockers [referent] and PPIs) in which cohort participants included those with no AKI before onset of chronic renal outcome (excluded from cohort entry those participants with AKI between the time of cohort entry time 0 and before chronic renal outcome)

	Incident rate[a] (95% CI)		Univariate hazard ratio[b] (95% CI)	Multivariate hazard ratio[b,c] (95% CI)
	H2 blockers	PPIs		
Incident eGFR <60 ml/min per 1.73 m^2, $N = 124,788$	44.78 (43.22–46.39)	57.27 (56.57–57.99)	1.27 (1.22–1.32)	1.22 (1.17–1.27)
Incident chronic kidney disease, $N = 121,478$	19.76 (18.76–20.80)	26.62(26.16–27.10)	1.35 (1.28–1.42)	1.29 (1.22–1.36)
>30% decrease in eGFR, $N = 122,337$	23.82 (22.72–24.97)	30.46 (29.96–30.96)	1.28 (1.22–1.34)	1.26 (1.19–1.32)
ESRD or >50% decrease in eGFR, $N = 119,578$	3.51 (3.10–3.95)	4.83 (4.64–5.03)	1.38 (1.21–1.56)	1.35 (1.19–1.53)

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; OR, odds ratio; PPIs, proton pump inhibitors.
[a]Incident rate as incident kidney outcome occurrence per 1000 person-years.
[b]H2 blockers serve as the reference group.
[c]Multivariate model controlling for first eGFR, age, race, sex, smoking, body mass index, diastolic blood pressure, systolic blood pressure, nonsteroidal anti-inflammatory drug, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, number of outpatient serum creatinine measurements, number of hospitalizations, diabetes mellitus, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *Helicobacter pylori* infection, Barrett's esophagus, achalasia, stricture, and esophageal adenocarcinoma.

Table S8). We evaluated the association in participants without gastrointestinal conditions; the intent of this analysis was to examine the association in a lower risk cohort. Results suggest a significant relationship between PPI use and the risk of chronic renal outcomes (Supplementary Table S9). In separate analyses, we additionally controlled for glycated hemoglobin (HbA1c) and microalbumin/creatinine ratio and considered those with a microalbumin/creatinine ratio <30 mg/g; results remained consistent (Supplementary Tables S10, S11, and S12).

DISCUSSION

In this work, we show that among new users of acid suppression therapy, incident PPI users have an increased risk of chronic renal outcomes including incident CKD, CKD progression, and ESRD in the absence of intervening AKI. We built numerous models in which we censored cohort participants at the time of AKI occurrence (an analytic approach designed to ensure that events captured in the models precede the occurrence of AKI), and in alternative analytic strategies, we excluded participants in whom AKI developed before chronic renal outcomes, excluded participants in whom AKI developed during the time in the cohort, and excluded participants with AKI before cohort entry. Mediation analyses showed the proportion of PPI effect mediated by AKI was ~50% for each of the chronic renal outcomes examined in this study, endorsing the possibility of a direct effect of PPI on chronic renal outcomes. The results were consistent using various definitions of AKI (NHS England AKI algorithm definition, KDIGO definition, and a definition based on inpatient ICD-9 codes). The findings were robust to changes in other multiple sensitivity analyses including time-dependent analyses (for exposure and covariates), analyses that accounted for the competing risk of death and AKI, and analyses using an instrumental variable approach and high-dimensional propensity score–adjusted models. In all analyses, the results showed a significant association between PPI use and chronic renal outcomes including incident CKD, CKD progression, and ESRD in the absence of intervening AKI.

The relationship between PPI exposure and the risk of AKI and acute interstitial nephritis is well established,[4–6,13–16] and

Table 5 | Survival models of the association between PPI use and risk of chronic renal outcomes in new users of acid suppression therapy (H2 blockers [referent] and PPIs) in which cohort participants included those with no AKI between time of cohort entry (T0) and end of follow-up ($N = 118,793$)

	Incident rate[a] (95% CI)		Univariate hazard ratio[b] (95% CI)	Multivariate hazard ratio[b,c] (95% CI)
	H2 blockers	PPIs		
Incident eGFR <60 ml/min per 1.73 m^2	37.46 (36.03–38.94)	45.45 (44.81–46.09)	1.21 (1.16–1.26)	1.17 (1.12–1.22)
Incident chronic kidney disease	16.86 (15.94–17.83)	21.55 (21.13–21.98)	1.28 (1.21–1.36)	1.23 (1.16–1.30)
>30% decrease in eGFR	19.66 (18.66–20.71)	23.83 (23.39–24.28)	1.21 (1.15–1.28)	1.19 (1.13–1.26)
ESRD or >50% decrease in eGFR	2.71 (2.35–3.10)	3.35 (3.19–3.51)	1.24 (1.07–1.43)	1.21 (1.04–1.40)

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; PPI, proton pump inhibitor.
[a]Incident rate as incident kidney outcome occurrence per 1000 person-years.
[b]H2 blockers serve as the reference group.
[c]Multivariate model controlling for first eGFR, age, race, sex, smoking, body mass index, diastolic and systolic blood pressure, nonsteroidal anti-inflammatory drug, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, number of outpatient serum creatinine measurements, number of hospitalizations, diabetes mellitus, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *Helicobacter pylori* infection, Barrett's esophagus, achalasia, stricture, and esophageal adenocarcinoma.

Table 6 | Survival models of the association between PPI use and risk of chronic renal outcomes in new users of acid suppression therapy (H2 blockers [referent] and PPIs) in a cohort participants with no history of AKI (no AKI before cohort entry) and in which cohort participants were censored at the time of AKI occurrence (N = 132,699)

	Incident rate[a] (95% CI)		Univariate hazard ratio[b] (95% CI)	Multivariate hazard ratio[b,c] (95% CI)
	H2 blockers	PPI		
Incident eGFR <60 ml/min per 1.73 m^2	39.89 (38.41–41.42)	50.40 (49.74–51.07)	1.25 (1.20–1.30)	1.19 (1.15–1.25)
Incident chronic kidney disease	17.48 (16.54–18.47)	23.16 (22.73–23.60)	1.33 (1.25–1.41)	1.27 (1.20–1.34)
>30% decrease in eGFR	21.34 (20.29–22.44)	26.88 (26.42–27.35)	1.26 (1.20–1.33)	1.22 (1.16–1.29)
ESRD or >50% decrease in eGFR	3.00 (2.62–3.41)	4.13 (3.95–4.31)	1.38 (1.20–1.59)	1.32 (1.15–1.52)

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
[a]Incident rate as incident kidney outcome occurrence before AKI per 1000 person-years.
[b]Participants were censored as nonevent when they experienced AKI; H2 blockers serve as the reference.
[c]Multivariate model controlling for first eGFR, age, race, sex, smoking, body mass index, diastolic and systolic blood pressure, nonsteroidal anti-inflammatory drug, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, number of outpatient serum creatinine measurements, number of hospitalizations, diabetes mellitus, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, gastroesophageal reflux disease, upper GI tract bleeding, ulcer disease, *Helicobacter pylori* infection, Barrett's esophagus, achalasia, stricture, and esophageal adenocarcinoma.

AKI is associated with an increased risk of CKD.[8,9] The newly reported association of PPI and the risk of the development and progression of CKD was postulated to be mediated by the occurrence of intervening AKI.[3,7,23] It was suggested that PPI-induced AKI serves as an antecedent event that may (i) offer a warning sign and induce avoidance of PPIs as acid suppressants and (ii) identify those at risk and who are susceptible to (or with a predilection for) chronic renal outcomes associated with PPI use.[18] However, whether PPI-related CKD and other chronic renal outcomes are mediated solely by the occurrence of AKI is clinically relevant but not known. Our study was designed to address this knowledge gap and answer this clinically relevant question; the results suggest that a significant association exists between PPI use and CKD outcomes without an intervening AKI. The finding that PPI use is associated with adverse chronic renal outcomes independent of the occurrence of AKI suggests that monitoring for AKI or acute interstitial nephritis among PPI users is not sufficient to guard against the development of CKD and ESRD. Although we examined the research question using 4 definitions of AKI, our design will not detect (or capture) subclinical AKI (AKI that does not meet the definition threshold), and

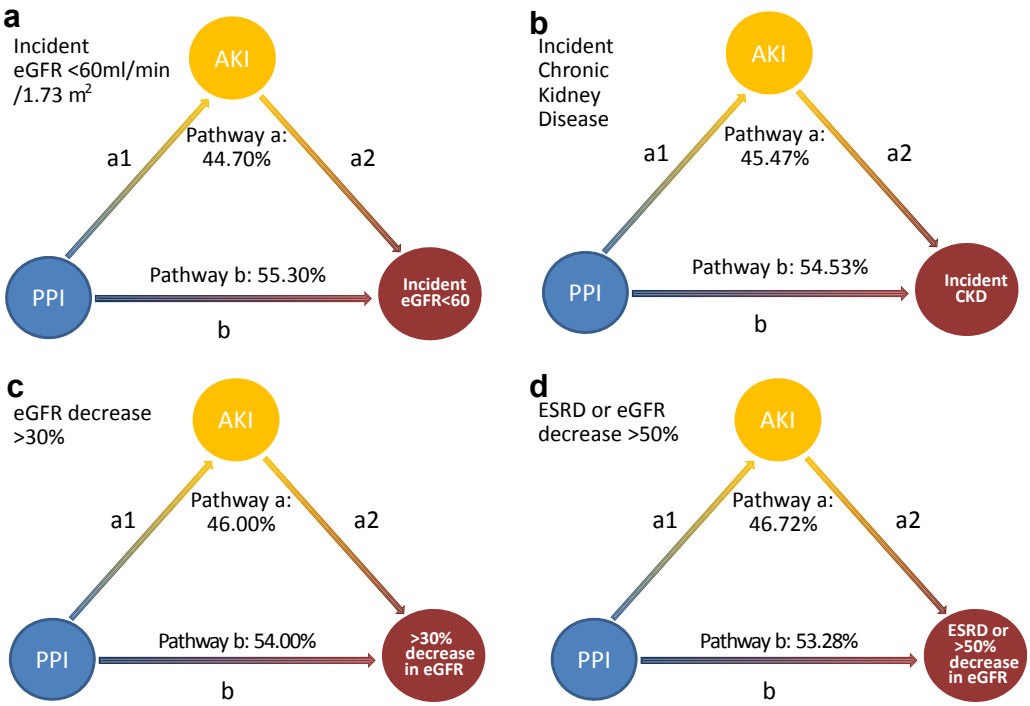


Figure 3 | Mediation analyses of the association between proton pump inhibitor (PPI) use and chronic renal outcomes where acute kidney injury (AKI) was considered a mediator. Pathway a = a1 + a2 represents the pathway mediated by AKI. Pathway b represents the pathway not mediated by AKI. (**a**) Incident estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2. (**b**) Incident chronic kidney disease (CKD). (**c**) eGFR decrease >30%. (**d**) End-stage renal disease (ESRD) or eGFR decrease >50%.

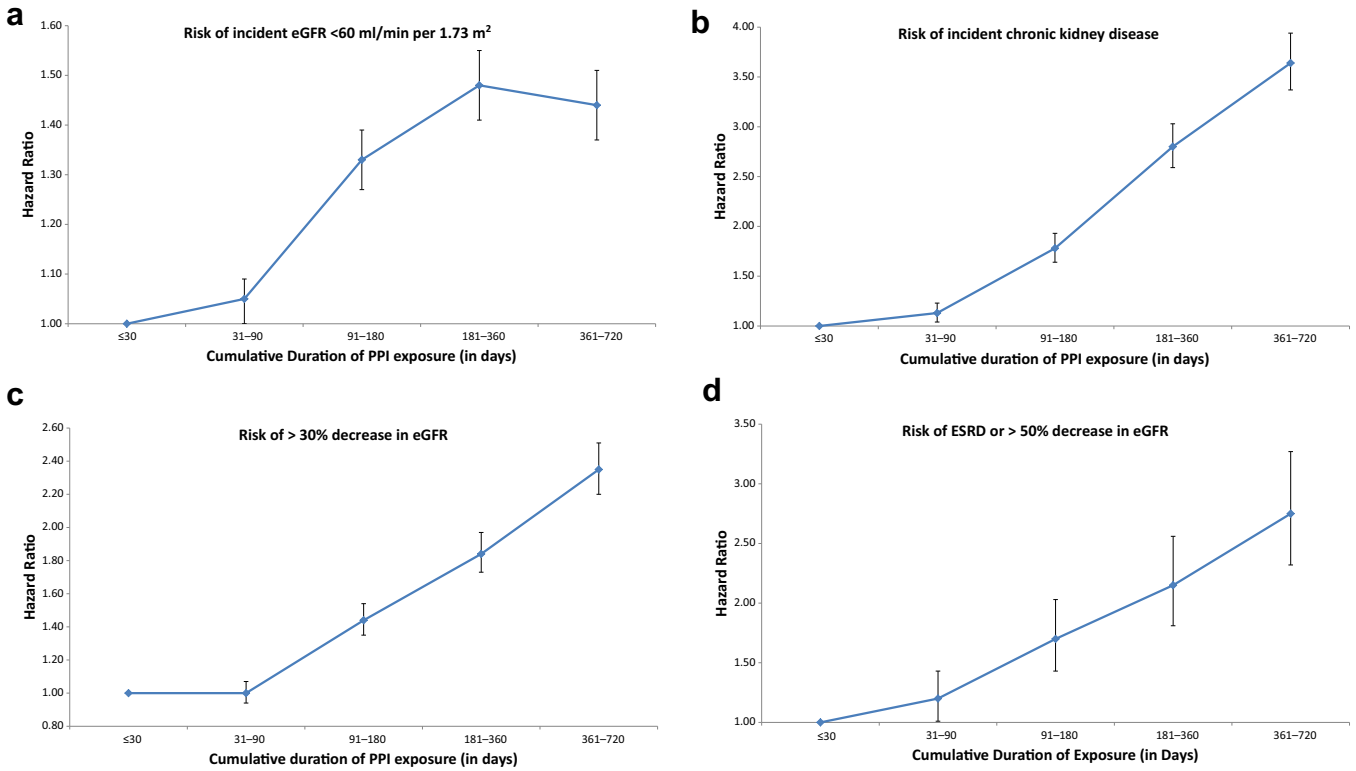


Figure 4| Cumulative duration of proton pump inhibitor (PPI) exposure and the risk of chronic renal outcomes. (**a**) Incident estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2. (**b**) Incident chronic kidney disease. (**c**) eGFR decrease >30%. (**d**) End-stage renal disease or eGFR decrease >50%.

unrecognized AKI (i.e., AKI that occurs in the outpatient setting between clinical encounters and that may have resolved by the time the laboratory parameters are obtained). In our studies, we used AKI as a surrogate measure of AKI and acute interstitial nephritis, and our analyses do not differentiate on the basis of AKI etiology. However, we designed an analytic strategy in which we examined the relationship using a number of approaches that all yielded consistent results; the constellation of findings strongly suggests a relationship between PPI use and the risk of CKD and progression to ESRD in the absence of intervening AKI.

The biological mechanisms supporting the observed association of PPI with chronic renal outcomes are unclear. Poesen *et al.*[24] proposed a hypothesis that in addition to AKI, altered gut microbial composition and metabolism may be in the causal pathway between PPIs and CKD. Experimental evidence in rats suggests that PPI administration limits the regenerative capacity of the liver after partial hepatectomy.[25] It is unclear whether PPI exposure also limits the regenerative capacity of renal tubular cells, for example. Such a mechanism, if verified, may at least partially explain the increased risk of renal outcomes in PPI users. It has also been noted that administration of PPIs upregulates the expression of mRNA and protein level and subsequent increased activity of the heme oxygenase-1 enzyme in gastric and endothelial cells.[26] Heme oxygenase-1 is generally seen as salutatory in the setting of AKI as it may decrease the sensitivity of the kidney to AKI and may reduce the propensity of AKI to CKD transition.[27] However, the salutary properties of heme oxygenase-1 are evident at lower doses and are vitiated at higher doses or in cases of sustained duration of expression.[27] It is unclear whether and to what extent PPIs upregulate heme oxygenase-1 in renal tissue and whether prolonged duration of PPI exposure leads to a high level of sustained heme oxygenase-1 where its beneficial effect is abrogated or reversed. PPIs are enriched in acidic organelles where they are activated and inhibit vacuolar H+-ATPases and acid hydrolases. A significant body of evidence suggests that PPIs impair lysosomal acidification and proteostasis, which may lead to increased oxidative stress, dysfunction, telomere shortening, and accelerated senescence in human endothelial cells.[28,29] PPIs have also been reported to induce a transepithelial leak.[30] In a high-throughput *in silico* analysis of microarray data, PPI upregulated genes in the cellular retinol metabolism pathway and downregulated genes in the complement and coagulation cascades pathway.[29] How the changes in gene expression contribute to renal manifestations is not clear as there is a substantial lack of published experimental and mechanistic evidence to facilitate a better understanding the putative off-target effects of PPIs.

We conducted a systematic PubMed search using a comprehensive list of search terms to identify animal studies of PPI-induced acute or chronic renal injury. The search results yielded no published animal studies. The conspicuous absence of published literature evaluating possible mechanisms of PPI-related renal injury suggests a significant

knowledge gap and highlights the pressing need for experimental work to further enhance our understanding of the effect of PPIs on the kidney.

Our study has a number of limitations. The analytic cohort included mostly older white male US veterans, which may limit the generalizability of study results. Our datasets did not include information on the volume of daily urine output. We cannot account for AKI that is not clinically detected, and although we used a sensitive definition to capture the occurrence of AKI, subclinical AKI (i.e., an increase in creatinine that does not meet the threshold of the AKI definition) cannot be captured but may gradually over time contribute the development of CKD and its progression to ESRD. Although we considered known covariates in the analyses, it remains possible that there may be residual confounders, either unknown or unmeasured, that may explain the observed associations. In our analyses, we defined drug exposure as having a prescription for it; because PPIs (and H2 blockers) are also available without prescription in the United States, it is possible that some participants in this cohort may have acquired PPIs without prescription. However, due to financial considerations, this possibility is not highly likely, and if it occurred in some cohort participants, it would have biased the results against the primary hypothesis and resulted in an underestimation of risk. Duration of wash out (time from VA enrollment until T0 without exposure to acid suppressants) varied among cohort participants, and it is likely that a small number of participants had a brief wash-out period (where we could ascertain the lack of exposure to acid suppressants); however, this bias would have reduced risk estimates (and biased the results toward the null hypothesis). The study has a number of strengths including the use of national large-scale data from a network of integrated health systems that were captured during routine medical care, which minimizes selection bias. We utilized a new user (incident user) design and evaluated the association between PPI use and the risk of chronic renal outcomes using a number of analytical approaches in sensitivity analyses. In sum, our results show a significant association of PPI use and the risk of CKD and progression to ESRD in the absence of intervening AKI. Reliance on antecedent AKI as warning sign to guard against the risk of the development of CKD and progression to ESRD among PPI users is not sufficient as a sole risk mitigation strategy. Exercising vigilance in PPI use, even in the absence of AKI, and careful attention to kidney function in PPI users may be a reasonable approach.

MATERIALS AND METHODS

Cohort participants

Based on the US Department of Veterans Affairs administrative database, we selected users of acid suppression therapy (PPIs or H2 blockers) between October 1, 2006 and September 30, 2008 who had no acid suppression therapy prescription from October 1, 1999, or subsequent date of VA enrollment until September 30, 2006. The first acid suppression therapy prescription date was defined as T0. We further excluded participants who were prescribed H2 blockers at T0 and received a PPI prescription during follow-up. Participants in the cohort were required to have a baseline eGFR >60 ml/min per 1.73 m^2 within 90 days before T0. In addition, participants in the cohort needed to have at least 1 eGFR between T0 and the first occurrence of one of the following: AKI, ESRD, death, or 5 years after T0 ($N = 152{,}157$). Finally, participants with missing data on covariates were excluded from the final cohort. In the final cohort of 144,032 participants, 125,596 were new PPI users, and 18,436 were new H2 blocker users. The follow-up duration was 5 years. The study was approved by the Institutional Review Board of the VA St. Louis Health Care System, St. Louis, MO.

Data sources

Veterans Health Administration Medical SAS inpatient and outpatient data sets that contain comprehensive data on national Veterans Health Administration inpatient and outpatient health care encounters were used to ascertain comorbidity information based on Current Procedural Terminology codes, and ICD-9, Clinical Modification diagnostic and procedure codes. A VA Health Factors data set provided information regarding smoking status. The VA's Managerial Cost Accounting System provided laboratory result information. The VA Corporate Data Warehouse Production Outpatient Pharmacy domain provided information on outpatient prescriptions. Vital Sign domain provided information on blood pressure and height and weight to compute body mass index. The VA Beneficiary Identification Records Locator Subsystem files, Medical SAS, and Vital Status data sets provided demographic characteristics and date of death. Information about occurrence of ESRD and date of first ESRD services were obtained from US Renal Database System.

Primary predictor variable

The primary predictor variable is acid suppression therapy. Cohort participants with their first acid suppression therapy prescription containing esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole were PPI users. Participants with first acid suppression therapy prescription containing ranitidine, cimetidine, and famotidine and had no PPI prescription during follow-up were H2 blocker users.

Outcomes

Outcomes for the study included an incident eGFR <60 ml/min per 1.73 m^2, incident CKD in which CKD was defined as 2 eGFRs <60 ml/min per 1.73 m^2 at least 90 days apart and the second eGFR measurement date was considered the date of CKD occurrence, a >30% decrease in eGFR, and >50% decrease in eGFR or ESRD.[31–34] Outcomes except for ESRD were ascertained based on outpatient serum creatinine. The date of the first ESRD services was ascertained using the USRDS databases. eGFRs were computed based on age, race, sex, and serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.[35]

AKI

Acute kidney injury in the primary analysis was defined as an increase in serum creatinine value >50% or 0.3 mg/dl within 90 days.[20] AKI was a dichotomous variable, defined as the development of AKI at least once after T0 and before ESRD or not.

Covariates

Baseline covariates were measured from 5 years before T0 until T0. Comorbidities included diabetes mellitus, cardiovascular disease,

peripheral artery disease, cerebrovascular disease, chronic lung disease, dementia, cancer, and diseases associated with use of acid suppression therapy such as gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *Helicobacter pylori* infection, Barrett's esophagus, achalasia, stricture, and esophageal adenocarcinoma. These diseases were assigned based on relevant International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic and procedure codes and Current Procedural Terminology codes.[33,36–42] Hepatitis C and HIV were assigned based on laboratory results. Body mass index was categorized into underweight, normal weight, overweight, and obese. Smoking status was categorized into never smoker, former smoker, and current smoker. Both nonsteroidal anti-inflammatory drug and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers use was defined dichotomously as use-related medication for >90 days or not. Blood pressure were represented by 4-level variables: systolic blood pressure (<90, 90–119.9, 120–139.9, >139.9) and diastolic blood pressure (<60, 60–79.9, 80–89.9, >89.9). The number of outpatient serum creatinine measurements and number of hospitalizations were calculated from laboratory and inpatient records and were used as markers of overall health. Age, race defined as white, black, and other, sex, and T0 eGFR were also included in multivariate analyses as covariates.

Statistical analyses

Counts and percentages, means and SDs, and medians and interquartile ranges were used to describe cohort participants. Because of the large sample size, standardized difference was used to test differences between PPI users and H2 blocker users in participants without AKI during follow-up as appropriate.

Kaplan-Meier curves were used to show the survival distributions for different outcomes and log-rank tests were applied to test the differences in the survival distributions. In addition, H2 blockers was selected as a reference group, and Cox survival models were built where the competing risk of death was noninformative and participants were censored at the time that they experienced AKI. We used participants' last eGFR before the first occurrence of AKI, ESRD, death, or end of follow-up to compare with baseline eGFR and define whether they experienced long-term kidney outcomes where appropriate. Logistic regressions were then used to evaluate the relationship between PPI use and these kidney outcomes. Three other subcohort and Cox survival models were built in which we excluded (i) cohort participants who experienced AKI before outcome; (ii) participants who experienced AKI within 5 years after T0, and (iii) participants who experienced AKI within 5 years before T0.

Mediation analyses were undertaken to evaluate the proportion of the total effect that could be explained by AKI.[43] We used accelerated failure time models with Weibull distribution for time to chronic renal outcomes and logistic regression for mediator (ever experienced AKI before outcome or not).

To examine the relationship between duration of exposure and risk of renal outcomes, we grouped PPI users based on their duration of PPI use before outcome and AKI. Cox survival models were applied to evaluate hazard differences between different duration groups where, to avoid immortal time bias, T0 was set as the last date of PPI use before outcome and AKI.[3,44,45] Participants with duration of >720 days were excluded because of a high probability of lack of follow-up time. In Cox survival models in sensitivity analyses, participants were censored at time of AKI occurrence.

In regression analyses, a 95% CI of an HR or odds ratio that does not include 1.00 was considered statistically significant. A standardized difference >0.1 was considered significant, and $P < 0.05$ was considered statistically significant. All analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC).

Sensitivity analyses

To further explore the relationship between PPI and long-term kidney outcomes and consider possible hidden bias, several sensitivity analyses were conducted. We tested several different definitions of AKI. We used the modified NHS England AKI definition as an alternative definition of AKI and repeated all the analyses.[21] Cohort participants were considered to have experienced AKI if they met any of the following criteria: (i) serum creatinine was 50% higher than the lowest creatinine value in the previous 1 to 365 days, (ii) serum creatinine had a >0.29-mg/dl increase compared with lowest creatinine value in the previous 2 days, (iii) serum creatinine was 50% higher than the lowest creatinine value in next 30 days, (iv) serum creatinine was 50% higher than the most recent creatinine in the previous 3 years.[21] We applied the KDIGO definition of AKI where cohort participants were considered to have experienced AKI if they had an increase in serum creatinine >0.3 mg/dl within 2 days or 50% within 7 days.[46] We used inpatient ICD-9 codes to define AKI as described previously.[47] Because of the widespread PPI use, cohort participants who were initially started on H2 blocker prescription were likely to use a PPI later. We included these participants and built time-dependent models, which allowed cohort participants to change from an H2 blocker to a PPI. We used a time-dependent model in which all covariates except the first eGFR, age, race, and sex were time updated. Diseases were defined as whether a related disease was experienced before time *t*. Body mass index, diastolic and systolic blood pressure, and smoking status were considered with same value as the record closest to and before time *t*. The number of outpatient serum creatinine measurements and number of hospitalizations were accumulated until time *t*. Nonsteroidal anti-inflammatory drug and angiotensin-converting enzyme/angiotensin receptor blocker use was classified into 4 levels: never used before time *t*, ever used before time *t* but not at time *t*, using at time *t*, and started within 90 days before *t* and using at time *t* and started >90 days before time *t*. We applied Fine and Gray models where both death and AKI were considered competing risks.[48] In order to account for the lack of random assignment of PPIs and H2 blockers to cohort participants, we conducted a 2-stage residual inclusion estimation based on an instrumental variable within participants.[49] The instrumental variable was defined for cohort participants as their prescribing physician's proportion of PPI users to new acid suppression therapy users during the 6 months before the participants at T0.[50] Cohort participants whose prescribing physician did not prescribe to any new users of acid suppression therapy in past 6 months were excluded. In the first stage, instrumental variables and covariables were used in a logistic regression model to predict the individual-level possibility of receiving PPI therapy. The difference between participants' real probability (equal 1 if PPI, 0 if H2 blocker) and predicted probability was considered the residual term. In the second stage, Cox survival models, which included the residual term and covariables, were conducted. In order to optimize control for confounding, we built high-dimensional propensity score–adjusted survival models following the multistep algorithm described by Schneeweiss *et al.*,[22] in which covariate selection was fully based on data and the degree of bias that they would likely cause in the relationship between exposure and outcome rather than basing covariate selection on previous knowledge.[22] Candidate

covariates were identified based on cohort participants' outpatient prescription, outpatient ICD-9 diagnosis code, outpatient Current Procedural Terminology code, inpatient ICD-9 diagnosis code, and inpatient ICD-9 procedure code within 6 months before T0. The top 500 covariates that would most likely bias the outcome were used in addition to age, race, sex, and first eGFR to obtain propensity scores. Cox survival models were built that controlled for propensity score as continuous or as deciles. We evaluated the association within cohort participants without any of the following gastrointestinal diseases: gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *H pylori* infection, Barrett's esophagus, achalasia, stricture, and esophageal adenocarcinoma. We controlled for HbA1c level before and closest to T0, where data are available. We controlled for the microalbumin/creatinine ratio before and closest to T0 where data are available. The microalbumin/creatinine ratio in mg/g was defined as 3 groups: <30, between 30 and 300, and >300. We evaluated the association in a subcohort with microalbumin/creatinine <30 mg/g.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Proportion of the association mediated by acute kidney injury ($N = 144,302$).

Table S2. Duration of proton pump inhibitor exposure and risk of chronic renal outcomes without acute kidney injury.

Table S3A. Relationship between proton pump inhibitor use and chronic renal outcomes in the absence of intervening acute kidney injury where acute kidney injury was defined according to the modified NHS England acute kidney injury algorithm (cohort participants were censored at the time of acute kidney injury occurrence [$N = 146,224$]).

Table S3B. Relationship between proton pump inhibitor use and chronic renal outcomes in the absence of intervening acute kidney injury (AKI) where AKI was defined according to the KDIGO definition (cohort participants were censored at the time of AKI occurrence [$N = 148,358$]).

Table S3C. Relationship between proton pump inhibitor use and chronic renal outcomes in the absence of intervening acute kidney injury (AKI) where AKI was defined by inpatient International Classification of Diseases, Ninth Revision diagnosis codes (cohort participants were censored at the time of AKI occurrence [$N = 148,721$]).

Table S4. Relationship between proton pump inhibitor use and chronic renal outcomes in the absence of intervening acute kidney injury (AKI) where exposure was treated as time dependent (cohort participants were censored at the time of AKI occurrence [$N = 159,647$]).

Table S5. Relationship between proton pump inhibitor use and chronic renal outcomes in the absence of intervening acute kidney injury (AKI) where variables are time dependent (cohort participants were censored at the time of AKI occurrence [$N = 144032$]).

Table S6. Association of proton pump inhibitor and risk of renal outcomes in the absence of acute kidney injury (AKI) based on the Fine and Gray model in which death and AKI were considered competing risks ($N = 144,032$).

Table S7. Association of proton pump inhibitor and risk of renal outcomes in the absence of acute kidney injury using an instrumental variable approach ($N = 132,314$).

Table S8. High-dimensional propensity score models for the association of proton pump inhibitor and risk of chronic renal outcomes in the absence of acute kidney injury ($N = 144,032$).

Table S9. Association of proton pump inhibitor and risk of renal outcomes in the absence of acute kidney injury in those without gastrointestinal conditions ($N = 87,302$).

Table S10. Association of proton pump inhibitor and risk of renal outcomes in the absence of acute kidney injury in models additionally controlling for HbA1c level ($N = 74,802$).

Table S11. Association of proton pump inhibitor and risk of renal outcomes in the absence of acute kidney injury in models additionally controlling for the microalbumin/creatinine ratio ($N = 18,871$).

Table S12. Association of proton pump inhibitor and risk of renal outcomes in the absence of acute kidney injury in a subcohort of participants with a microalbumin/creatinine ratio <30 mg/g ($N = 15,235$).

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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