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Non-indicated initiation of proton pump inhibitor and risk of adverse outcomes in patients with underlying chronic kidney disease

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Abstract

Objective: Evidence related to the risk of kidney damage by proton pump inhibitor (PPI) initiation in patients with "underlying" chronic kidney disease (CKD) remains scarce, although PPI use is generally associated with acute interstitial nephritis or incident CKD. We aimed to investigate the association between PPI initiation and the risk of adverse outcomes in patients with CKD in the absence of any deterministic indications for PPI usage.

Design: Retrospective observational study

Setting: Korea National Health Insurance Service database from 2009 to 2017

Participants: A retrospective cohort of new PPI and histamine H_2-receptor antagonists (H2RA) users among people with CKD. Patients with a history of gastrointestinal bleeding or those who had an endoscopic or image-based upper gastrointestinal tract evaluation were excluded.

Primary and secondary outcome measures: The study subjects were followed to ascertain clinical outcomes including mortality, end-stage kidney disease (ESKD), myocardial infarction, and stroke. The hazard ratios (HRs) of outcomes were measured using a Cox regression model after adjusting for multiple variables. We applied an inverse probability of treatment weighting model to control for residual confounders.

Results: We included total of 1,038 PPI and 3,090 H2RA users without deterministic indications for treatment. PPI initiation was significantly more associated with a higher ESKD risk compared to H2RA initiation (adjusted HR, 1.54 [1.04–2.25]), whereas the risks of mortality or cardiovascular outcomes were similar between the two groups. In subgroup analysis, the association between PPI use and the progression to ESKD remained significant in non-diabetic and low estimated-glomerular-filtration-rate (<60 mL/min/1.73 m^2) groups.

Conclusions: Initiation of PPI administration may not be recommended in patients with CKD without deterministic indication, as their usage was associated with a higher risk of ESKD.

Strengths and Limitations

The study utilized a nationwide, large-scale database to derive a cohort, which significantly enhances the robustness of the study. Larger samples increase the statistical power and reliability of the results and enable more confident generalizations.

The study implemented a robust multivariable adjustment and applied an Inverse Probability of Treatment Weighting (IPTW) model. This careful consideration for controlling confounding effects ensures that the effects observed are truly due to the variables of interest and not due to some uncontrolled factors.

The study specifically aimed at assessing non-indicated initiation of PPI in patients with CKD, and exclusion criteria were created to reduce indication bias. This makes the study more specific and relevant to real-world clinical scenarios where PPI may be initiated without clear indications.

Lack of certain important information due to data unavailability, such as the causes of death, quantitation of proteinuria, follow-up laboratory parameters, classes or doses of the studied medication, and usage of over-the-counter medications, might limit the depth and accuracy of the findings.

Keywords: proton pump inhibitor, chronic kidney disease, end-stage kidney disease, mortality

Introduction

Proton pump inhibitors (PPIs) are among the most common acid suppression agents used worldwide for gastrointestinal disease, such as gastroesophageal reflux disease, peptic ulcer disease, and the eradication of *Helicobacter pylori.*[1] They are also used for long-term prophylaxis of gastroduodenal injury in patients taking non-steroidal anti-inflammatory drugs or antiplatelet agents.[2 3] Since this pharmacological class has been perceived to be generally safe, it is available over-the-counter in several countries.[4 5] Furthermore, several retrospective observational studies reported frequent over-prescriptions and inappropriate long-term use of PPIs in the absence of medical indications.[6-8]

There is growing evidence from multiple observational studies that higher risks for uncommon but serious adverse outcomes such as *Clostridium difficile* infection,[9] community-acquired pneumonia,[10] and hip fracture[11] may be related to PPI use. In addition, adverse kidney outcomes associated with PPI use are well-documented in the literature, such as acute interstitial nephritis, acute kidney injury, or incident chronic kidney disease (CKD).[12-17] Despite the growing evidence of renal complications, patients with CKD are more frequently administered PPIs than patients without CKD, which might be attributed to the higher prevalence of acid-related gastrointestinal disorders and antiplatelet agent intake[18]. However, there is limited data on the effects of PPI use in patients with an already established CKD.

In the current study, we aimed to investigate whether de novo PPI use without deterministic indication (which would require an endoscopic or image-based evaluation of the upper gastrointestinal tract) is associated with a higher risk of adverse outcomes when compared to H2RA initiation. We investigated a Korean nationwide claims database and excluded patients with possible indication or prior usage of PPIs or H2RAs. We hypothesized that non-indicated initiation of PPI use may be associated with higher risks of adverse outcomes in patients with CKD.

Methods

Ethical considerations

The study was approved by the Institutional Review Board of Seoul National University Hospital (E-2112-048-1281). The use of the Korea National Health Insurance Service (NHIS) database was approved by the relevant government organization. The study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because this was a retrospective study using fully anonymous and unidentifiable data. All the research procedures followed the STROBE cohort reporting guidelines[19].

Data source

This study was performed using the NHIS claims database which contains information on demographics, healthcare services utilization, medical procedures, drug prescription, health examination data, and mortality data for all Korean nationals residing in Korea[20 21]. The NHIS which is a mandatory form of single social insurance covers about 97% of the Korean population. It provides general health screenings which are performed in annual or biennial intervals covering >10 million individuals, which is approximately >20% of the entire Korean population, each year. The coverage rate of the health screening was 68.4% in 2020 among the target population which included adults with age >40 years old or regular employees in any workplace. All insured medical services and health screening information are stored at NHIS and are available for research use (subject to approval).

Study design and population

We screened patients with CKD which was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 or dipstick-positive albuminuria of >1+ on ≥2 consecutive tests

from January 2009 to December 2017.[22] The index date was set as the last test date which meets the definition (Figure 1 and Figure 2).

Among these patients, those who had been prescribed PPI/H2RA previously or hospitalized with diagnosis of gastrointestinal bleeding or gastric ulcer within the past three years from the index date were excluded. As we intended to exclude the patients with possible indicated use of PPI/H2RA, those who had received endoscopy- or image-based (e.g., barium-swallowed X-ray series, computed tomography, or magnetic resonance imaging [MRI], not including simple X-rays) evaluation for their upper gastrointestinal tract within the previous 90 days were also excluded.

PPI or H2RA initiation

After the index date, the initiation of prescription of PPIs or H2RAs (>30-day supply within 365 days from the index date) was identified to determine the de novo drug exposure. Those who received a mixture of the drugs were excluded at this phase.

Outcomes

The assessed adverse prognostic outcomes were ESKD, mortality, myocardial infarction, and stroke. ESKD was defined as the initiation of kidney replacement therapy (NHIS covers all transplant and dialysis events in the nation). Mortality was identified from death certificates. As in a previous study,[23] myocardial infarction was recorded if an individual had International Classification of Disease 10th Revision (ICD-10) codes I21 or I22 during hospitalization. Stroke was defined as ICD-10 codes I63 or I64 during hospitalization, with claims information for brain MRI or brain computerized tomography imaging. The end of the follow-up period was December 2021.

Covariates

Baseline covariates including age, sex, body mass index, and comorbidities including hypertension, diabetes mellitus, dyslipidemia, active malignancy, and chronic lung disease were evaluated. Information on smoking and alcohol consumption, collected from self-questionnaires, levels of serum creatinine-based eGFR, fasting serum glucose, total cholesterol, and blood pressure measured at the index-date health check-up was also included as the baseline covariates. The participants were divided into four groups according to an equivalence scale of their average monthly income in the household: those who were at the lowest quartile or subsidized by the government were classified as low-income group.

Statistical analyses

Categorical and continuous variables are expressed as proportions and means±standard deviations. The risks of adverse outcomes were initially plotted by Kaplan–Meier curves. The risk of adverse outcomes of PPI vs. H2RA initiation was further analyzed by a Cox proportional hazard model. In addition to a univariable model, a multivariable model adjusted for age, sex, baseline body mass index, eGFR, dipstick albuminuria, being a current-smoker, alcohol consumer, whether on regular physical activity, low-income state, region of residence (urban or rural), history of diabetes mellitus, dyslipidemia, cancer, and chronic lung disease was constructed. To control the residual confounding effects more robustly, a propensity score method was used for the comparison between the groups. The propensity score was calculated including all variables of the multivariable model with the additional inclusion of baseline waist circumference, levels of serum glucose, high density lipoprotein, low density lipoprotein cholesterol, and triglycerides. Based on the calculated propensity score, the inverse probability of treatment weighting (IPTW) was applied to the cohort, which results in a new pseudo-cohort

where treatment assignment is independent of the measured confounders.

Results

Baseline characteristics

After applying the exclusion criteria, among the 537,607 screened individuals, we finally included 1,038 and 3,090 of new PPI and H2RA users, respectively, without a history of medication usage or a record of endoscopic or image-based evaluation of the upper gastrointestinal tract (Figure 2). Their baseline characteristics are presented in Table 1. After PS weighting, the two treatment groups were well balanced in all variables (all absolute standardized differences were <0.1).

Clinical outcomes according to PPI vs. H2RA

During the median follow-up of 2.8 years, 28,551 (5.3%) mortality, 8,296 (1.5%) ESKD, 9,298 (1.7%) myocardial infarction, and 11,967 (2.2%) stroke events were identified. Figure 3 shows the cumulative incidence curves of clinical outcomes according to the treatment groups. Compared to H2RA users, PPI users had a higher rate of progression to ESKD (16.64 vs. 7.14 per 1000 person-years) and all-cause mortality (72.36 vs. 54.08 per 1000 person-years). Similarly, in the univariable Cox regression model (Table 2), the risks of progression to ESKD (hazard ratio [HR] 2.11 [1.46, 3.05]) or all-cause mortality (HR 1.28 [1.09, 1.50]) were significantly higher in those who initiated PPI. On the other hand, for myocardial infarction and stroke risks, there were no significant differences between the two groups. After stringent adjustment by multivariable Cox regression, the risk of ESKD remained significantly higher in de novo PPI users (adjusted HR 1.68 [1.15, 2.45]), although the difference in mortality risk was nonsignificant (adjusted HR 1.14 [0.97, 1.35]).

Subgroups stratified by age, sex, diabetes, and eGFR

The regression analyses results for clinical outcomes in various subgroups are presented in Supplement Table 1. Although the findings were generally similar regardless of the divided subgroups, the risk of progression to ESKD was significantly higher in those who initiated PPI than in H2RA users only in patients without diabetes and not in those with underlying diabetes. When stratified by eGFR, the risk of ESKD with PPI initiation was significantly higher only in the patients with eGFR of <60 mL/min/1.73 m^2 and not in those with unaltered eGFR.

IPTW weighted clinical outcomes

Given the difference of baseline covariates between the PPI and H2RA groups, we further performed an IPTW weighted analysis in this cohort to control for residual confounders. The IPTW Cox regression analysis is presented in Supplement Table 2, which again demonstrated that the risk of progression to ESKD was significantly higher in those who had initiated PPI than those who had started H2RA (incidence rate 13.32 vs. 7.87, HR 1.54 [1.04, 2.25]). On the other hand, the risks of other adverse outcomes were similar between the two groups, including the risk of all-cause mortality (incidence rate 66.26 vs. 55.74 per 1000 person-years, HR 1.14 [0.96, 1.34]).

Discussion

This observational study compared the risk of adverse outcomes between the de novo initiation of PPI and H2RA use in patients with CKD without indications based on endoscopic or image-based upper gastrointestinal tract findings. With robust consideration for residual confounding effects, the risk of progression to ESKD was consistently higher in those who initiated PPI

administration than in the active controls, while cardiovascular or mortality risk was similar between the two groups. Our study suggests that non-indicated initiation of PPI in patients with CKD may be discouraged considering that their usage may elevate the risk of progression to kidney dysfunction.

Despite the strong benefit of PPI use for acid-reflux disorders and their gastroprotective effect, the medication has been reported to have certain adverse effects.[24] Evidence from multiple observational studies suggests that PPI use is associated with an increased risk of cardiovascular disease, gastric cancer, dementia, pneumonia, osteoporotic fractures, and *Clostridium difficile* infections.[25-29] Regarding the kidneys, PPI use has been suspected to cause hypomagnesemia,[30 31] interstitial nephritis,[32 33] acute kidney injury,[15] new-onset CKD,[16 17] or the progression of kidney dysfunction.[34 35] Thus, considering the highly prevalent use of PPIs in the general population, the nephrology society has warned for the possibility of PPIs causing nephrotoxicity. However, evidence from assessing specifically the clinical consequences related to new initiation of PPI administration in patients with CKD without certain indications has been rare. In this study, we sought to derive a CKD cohort without previous usage of PPI/H2RA or a history of gastrointestinal bleeding or active evaluation of the upper gastrointestinal tract, which would be amenable to the assessment of the risk of non-indicated initiation of PPI administration in CKD. Taking advantage of a nationwide large-scale database, we successfully constructed such a cohort with relatively large numbers of new PPI and H2RA users and confirmed it by laboratory findings. In addition, to reduce the indication bias, we also made efforts to control confounding effects by implementing a robust multivariable adjustment and applying an IPTW model. As the result, we identified that initiation of non-indicated PPI administration was consistently associated with significantly higher risk of progression to ESKD in patients with underlying CKD, supporting that clinicians should not administer PPI to patients with CKD without clear indications.

Concerning the risks of new PPI users of progression to ESKD, our results are congruent with several previous large-cohort observational studies that investigated the incidence and rate of CKD. Xie et al.[36] suggested that PPI exposure was associated with increased risk of incident CKD and CKD progression in patients without baseline eGFR reduction. A study by Grant et al.[37] was the first to assess the same issue in patients with reduced eGFR at baseline, which suggested that PPI use is associated with an increased risk of major adverse renal events. However, the baseline characteristics were different amongst the two groups tested: the PPI group bore more patients with lower eGFR, more proteinuria, and higher prevalence of myocardial infarction and diabetes, which may be attributed to indication bias. In another study, Cholin and colleagues also investigated PPI safety specifically in the patients with CKD and found that the use of PPIs was not associated with the increased mortality or progression to ESKD when compared to H2 blockers and to the absence of acid suppression therapy.[37] Given the results of our study particularly in the subgroup group with CKD stage of ≥3 (eGFR of <60 mL/min/1.73 m^2), our results contradict the findings of Cholin et al.[19] We believe that the difference might be attributed to our more rigorous study design through the addition of exclusion criteria for previous PPI/H2RA users and those with absolute indication for PPI/H2RA administration. Considering the solid evidence for adverse kidney effects of PPIs in the non-CKD group, we believe that our study, with its thorough consideration on indication and confounding bias, would be more appropriate to support the potential adverse effect of PPIs on kidney function, which can be present even in patients with underlying CKD.

There has been a discrepancy in the association between PPIs and all-cause mortality. A nationwide observational study of Xie et al.[38] showed a small excess of cause-specific mortality due to cardiovascular disease, CKD, and upper gastrointestinal cancer in de novo PPI users compared to H2RA users[38]. On the other hand, a meta-analysis comparing the safety of PPIs with the one of H2RAs in kidney transplant recipients suggested that PPIs may not be

associated with higher mortality risks, but related to higher hypomagnesemia rates and a decline of eGFR per year after transplantation.[39] Considering the observational nature of these studies as their major limitation to date, indication bias may overestimate the association of high mortality risk by PPI usage. Our study found no association between PPI use and overall mortality in patients with CKD in the absence of deterministic indication of usage.

The risk of ESKD was different regarding the presence of a history of diabetes mellitus. As diabetes mellitus constitutes a prevalent cause of progression of kidney dysfunction, the potential adverse effects related to PPI initiation might have been accentuated in those without such a risk factor. Namely, the potential adverse kidney effects of PPI might not have been evident in the condition of diabetes, as diabetes itself would determine the fate of kidney prognosis of patients with CKD. On the other hand, the risk of ESKD related to PPI initiation was prominent in those with established reduction in eGFR (<60 mL/min/1.73 m^2), suggesting that clinicians should refrain from starting non-indicated PPI administration in patients with an overt kidney dysfunction.

This study bears several limitations. First, we could not include certain information due to data unavailability, including the causes of death, quantitation of proteinuria, follow-up laboratory parameters, classes or doses of the studied medication, and usage of over-the-counter medications. Second, our study specifically aimed to assess the non-indicated initiation of PPI in patients with CKD; thus, the study result would not discourage the use of PPIs even in patients with CKD and clear indications (e.g., ulcer bleeding or concomitant use with high-risk medication, such as corticosteroids). Third, the generalizability of our study is limited as we were able to investigate a single-ethnic group of East Asians. Lastly, despite our efforts to control for measured confounding effects, the retrospective nature of this study could not eliminate the possibility of effects from unmeasured confounders.

In conclusion, our study showed the higher risk of progression to ESKD in patients who

initiated PPI administration compared with de novo users of H2RA, while cardiovascular or mortality risk was similar between the two groups. The evidence that the risk of ESKD related to PPI initiation was prominent in those with eGFR of <60 mL/min/1.73 m^2 indicates the need for heightened vigilance among those with this condition. Given the high prevalence of PPI use in this population, the findings have public health implications and raise the clinical awareness related to the non-indicated use of PPI in patients with CKD.

Conflicts of interests

The authors declare that they have no competing interests.

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Availability of data and materials

The data are available from the National Health Insurance Service.

Consent for publication

Not applicable.

Author Contributions

The corresponding author attests that all of the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. SGK, KWJ, DKK and SP contributed to the conception and design of the study. SGK, JMC, SL, YK, SC, HH and SP advised on statistical aspects and interpreted the data. SP and KH performed the main statistical analysis, assisted by KWJ, SL, MK, and EK. DKK offered advice regarding the data interpretation. SP obtained funding and supervised the overall project. All of the authors participated in drafting the manuscript. All of the authors reviewed the manuscript and approved the final version to be published.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not required

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Table 1. Baseline characteristics of patients of using PPI vs. H2RA in total study population

Characteristics	Propensity Score Weighting					
	Before			After		
	PPI user (n=1038)	H2RA user (n=3090)	ASD	PPI user (n=1038)	H2RA user (n=3090)	ASD
Age, years	68.4 ± 12.1	69.6 ± 11.4	0.1	69.1±11.65	69.28±11.6	0.01
Male	506 (48.8%)	1112 (36.0%)	0.26	406.5(39.2%)	1213.4(39.2%)	0.0005
BMI, kg/m^2	24.92 ± 3.6	24.92 ± 3.6	0.002	24.89±3.58	24.92±3.61	0.008
Current smoker	144 (13.9%)	347 (11.2%)	0.08	122.7(11.8%)	366.7(11.9%)	0.002
Alcohol			0.11			0.005
Non-drinker	779 (75.1%)	2461 (79.6%)		816.1(78.8%)	2427.4(78.5%)	
Moderate(<30g/day)	216 (20.8%)	502 (16.3%)		176.9(17.1%)	539.8(17.3%)	
Heavy(≥30g/day)	43 (4.1%)	127 (4.1%)		43.4(4.2%)	127.4(4.1%)	
Regular exercise	199 (19.2%)	544 (17.6%)	0.04	187.9(18.1%)	556.8(18.0%)	0.004
Low income†	192 (18.5%)	562 (18.2%)	0.007	190.7(18.4%)	564.9(18.3%)	0.003
Urban resident	440 (42.4%)	1320 (42.7%)	0.006	448.1(43.2%)	1321.7(42.8%)	0.009
Diabetes	430(41.4%)	1145 (37.1%)	0.09	396.4(38.3%)	1175.8(38.0%)	0.005
Hypertension	795 (76.6%)	2325 (75.2%)	0.03	788.1(76.1%)	2328.4(75.3%)	0.02
Dyslipidemia	549 (52.9%)	1604 (51.9%)	0.02	542.5(52.4%)	1604.3(51.9%)	0.008
Active malignancy	85 (8.2%)	202 (6.5%)	0.063	73.4(7.1%)	215.4(7.0%)	0.004
COPD	161 (15.5%)	521 (16.9%)	0.037	171.9(16.6%)	511(16.5%)	0.001
eGFR < 60ml/min/1.73m^2	847 (81.6%)	2534 (82.1%)	0.02	854.1(82.4%)	2527.4(81.6%)	0.02
Albuminuria ≥ 1+	340 (32.8%)	857 (27.7%)	0.11	302.6(29.2%)	896.9(29.0%)	0.003
eGFR, ml/min/1.73m^2	54.4 ± 20.5	55.3 ± 19.9	0.05	55.1±20.2	55.1±20.2	0.002
Systolic BP, mmHg	130.6 ± 17.8	130.7 ± 16.7	0.004	130.6±17.7	130.6±16.7	0.0004
Diastolic BP, mmHg	77.5 ± 11.21	77.8 ± 10.5	0.032	77.8±11.1	77.7±10.5	0.003
Glucose, mg/dL	118.1 ± 52.4	115.4 ± 44.8	0.055	116.1±49.2	116.1±46.0	0.0002
Total cholesterol, mg/dL	185.2 ± 46.2	191.8 ± 43.7	0.123	190.1±47.2	190.1±43.6	0.0007

PPI, proton pump inhibitor; H2RA, histamine type 2 receptor antagonist; ASD, absolute standardized difference; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; BP, blood pressure.
†Lowest quartile of income or under government aid

Table 2. Hazard ratios for clinical outcomes according to use of PPI compared to H2Ra

Outcomes	Group	N	Event	Follow-up Person-Years	Incidence Rate (per 1000PY)	Model 1		Model 2		Model 3	
						HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
ESKD	PPI	1038	46	2765	16.64	2.11 (1.46 to 3.04)	< 0.001	1.72 (1.19 to 2.48)	0.004	1.82 (1.26 to 2.62)	0.001
	H2RA	3090	76	10647	7.14	1 (Reference)		1 (Reference)		1 (Reference)	
Mortality	PPI	1038	205	2833	72.36	1.34(1.14 to 1.57)	< 0.001	1.29 (1.10 to 1.51)	0.002	1.28 (1.09 to 1.50)	0.002
	H2RA	3090	582	10762	54.08	1 (Reference)		1 (Reference)		1 (Reference)	
MI	PPI	1038	23	2818	8.16	0.75 (0.48 to 1.17)	0.20	0.72 (0.46 to 1.13)	0.15	0.74 (0.47 to 1.15)	0.18
	H2RA	3090	113	10571	10.69	1 (Reference)		1 (Reference)		1 (Reference)	
Stroke	PPI	1038	41	2770	14.80	1.05 (0.74 to 1.48)	0.81	1.04 (0.74 to 1.48)	0.81	1.06 (0.75 to 1.50)	0.75
	H2RA	3090	142	10481	13.55	1 (Reference)		1 (Reference)		1 (Reference)	

Model 1: univariable
Model 2: adjusted for age, sex, BMI, hypertension, diabetes, eGFR and albuminuria.
Model 3: adjusted for age, sex, BMI, hypertension, diabetes, eGFR, albuminuria, dyslipidemia, COPD, current smoker, alcohol, regular exercise, low income, and region of residence (urban)
PY, person-year; HR, hazard ratio; MI, myocardial infarct; PPI, proton pump inhibitor; H2RA, histamine type 2 receptor antagonist; ESKD, end-stage kidney disease.

Figure legends

Figure 1. Graphical depiction of the time windows used to determine the studied variables. S indicates the national health screenings that were mostly performed at annual or biennial intervals.

Figure 2. Study population. eGFR = estimated glomerular filtration rate, MI = myocardial infarction, ESKD = end-stage kidney disease, PPI = proton pump inhibitor, H2RA = histamine H_2-receptor antagonists

Figure 3. Kaplan-Meier survival curves showing the cumulative risks of clinical outcomes. The y-axes indicate cumulative adjusted incidence probability, and the x-axes indicate the time (years). The survival tables are presented below the adjusted survival curves. (A) ESKD (B) Mortality (C) MI (D) Stroke. ESKD = end-stage kidney disease, MI = myocardial infarction.

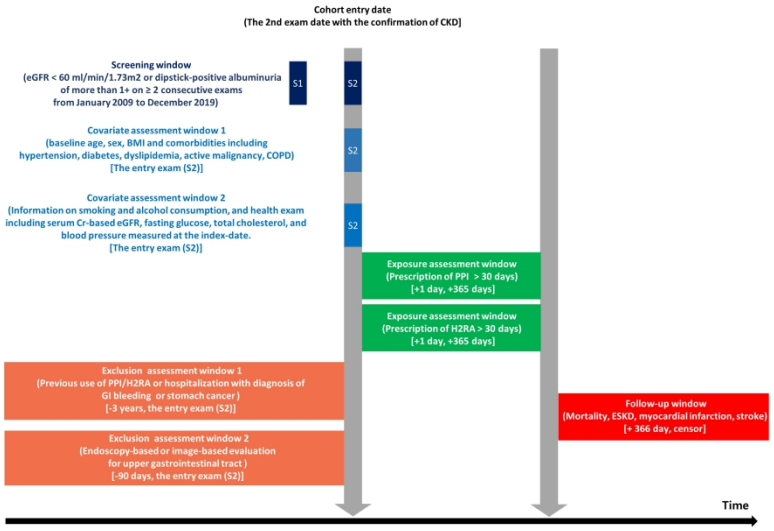

Figure 1. Graphical depiction of the time windows used to determine the studied variables. S indicates the national health screenings that were mostly performed at annual or biennial intervals.

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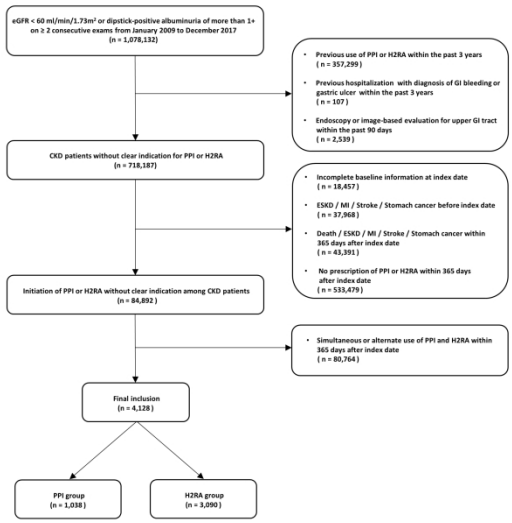

Figure 2. Study population. eGFR = estimated glomerular filtration rate, MI = myocardial infarction, ESKD = end-stage kidney disease, PPI = proton pump inhibitor, H2RA = histamine H2-receptor antagonists

338x190mm (300 x 300 DPI)

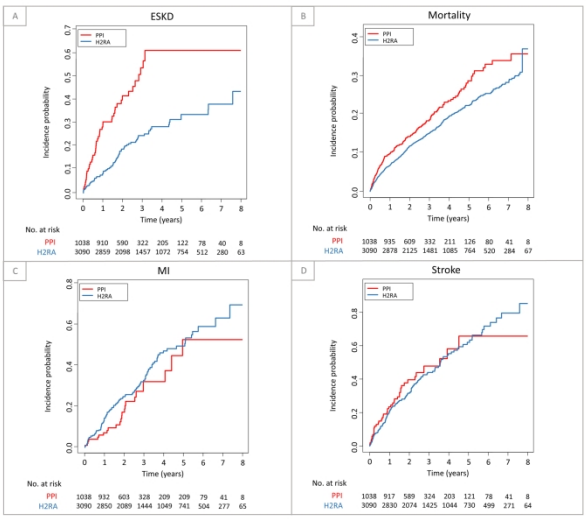

Figure 3. Kaplan-Meier survival curves showing the cumulative risks of clinical outcomes. The y-axes indicate cumulative adjusted incidence probability, and the x-axes indicate the time (years). The survival tables are presented below the adjusted survival curves. (A) ESKD (B) Mortality (C) MI (D) Stroke. ESKD = end-stage kidney disease, MI = myocardial infarction.

338x190mm (300 x 300 DPI)

Supplement Table 1. Cox regression analysis in subgroups according to diabetes and low eGFR

Subgroup		ESKD		Mortality		MI		Stroke	
		Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Diabetes									
Yes	PPI	1.21 (0.74 to 1.96)	0.45	1.09 (0.86 to 1.39)	0.48	0.69 (0.35 to 1.35)	0.27	0.87 (0.52 to 1.48)	0.61
	H2RA	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
No	PPI	3.07 (1.64 to 5.74)	< 0.001	1.17 (0.93 to 1.46)	0.18	0.71 (0.38 to 1.33)	0.29	1.20 (0.74 to 1.94)	0.46
	H2RA	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
eGFR									
≥ 60	PPI	2.59 (0.79 to 8.42)	0.55	1.14 (0.74 to 1.76)	0.58	0.94 (0.30 to 2.90)	0.91	0.99 (0.42 to 2.31)	0.98
	H2RA	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
< 60	PPI	1.63 (1.09 to 2.43)	0.02	1.14 (0.96 to 1.36)	0.15	0.68 (0.41 to 1.12)	0.13	0.98 (0.66 to 1.45)	0.91
	H2RA	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; MI, myocardial infarction; PPI, proton pump inhibitor; H2RA, histamine type 2 receptor antagonist

Adjusted for age, sex, BMI, hypertension, diabetes, eGFR, albuminuria, dyslipidemia, COPD, current smoker, alcohol, regular exercise, low income, and region of residence (urban or rural)

Supplement Table 2. IPTW weighted Cox regression analysis of clinical outcomes

Outcome	Group	Weighted Incidence Rate (per 1000 PY)	Weighted HR (95% CI)	*P*
ESKD	PPI	13.31	1.72 (1.19 to 2.48)	0.03
	H2RA	7.86	1 (Reference)	
Mortality	PPI	66.26	1.14 (0.96 to 1.34)	0.12
	H2RA	55.74	1 (Reference)	
MI	PPI	7.60	0.72 (0.46 to 1.13)	0.1
	H2RA	10.73	1 (Reference)	
Stroke	PPI	14.48	1.04 (0.74 to 1.48)	0.9
	H2RA	13.52	1 (Reference)	

IPTW, inverse probability of treatment weight; PY, person-year; HR, hazard ratio; ESKD, end-stage kidney disease; MI, myocardial infarction

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*10,11*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10,11
		(*b*) Report category boundaries when continuous variables were categorized	10,11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10,11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Non-indicated initiation of proton pump inhibitor and risk of adverse outcomes in patients with underlying chronic kidney disease: A nationwide, retrospective, cohort study

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Non-indicated initiation of proton pump inhibitor and risk of adverse outcomes in patients with underlying chronic kidney disease: A nationwide, retrospective, cohort study

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Abstract

Objective: Evidence related to the risk of kidney damage by proton pump inhibitor (PPI) initiation in patients with "underlying" chronic kidney disease (CKD) remains scarce, although PPI use is generally associated with acute interstitial nephritis or incident CKD. We aimed to investigate the association between PPI initiation and the risk of adverse outcomes in patients with CKD in the absence of any deterministic indications for PPI usage.

Design: Retrospective observational study

Setting: Korea National Health Insurance Service database from 2009 to 2017

Participants: A retrospective cohort of new PPI and histamine H_2-receptor antagonists (H2RA) users among people with CKD. Patients with a history of gastrointestinal bleeding or those who had an endoscopic or image-based upper gastrointestinal tract evaluation were excluded.

Primary and secondary outcome measures: The study subjects were followed to ascertain clinical outcomes including mortality, end-stage kidney disease (ESKD), myocardial infarction, and stroke. The hazard ratios (HRs) of outcomes were measured using a Cox regression model after adjusting for multiple variables. We applied an inverse probability of treatment weighting model to control for residual confounders.

Results: We included a total of 1,038 PPI and 3,090 H2RA users without deterministic indications for treatment. IPTW-weighted Cox regression analysis showed that PPI initiation was more significantly associated with a higher ESKD risk compared to that of H2RA initiation (adjusted HR, 1.72 [1.19–2.48]), whereas the risks of mortality or cardiovascular outcomes were similar between the two groups. In the subgroup analysis, multivariable Cox regression analysis showed that the association between PPI use and the progression to ESKD remained significant in non-diabetic and low estimated-glomerular-filtration-rate (<60 mL/min/1.73 m2) groups (adjusted HR, 1.72 [1.19 to 2.48] and 1.63 [1.09 to 2.43], respectively).

Conclusions: Initiation of PPI administration may not be recommended in patients with CKD

without deterministic indication, as their usage was associated with a higher risk of ESKD.

Strengths and Limitations

The study utilized a nationwide, large-scale database to derive a cohort to include sufficient number of new PPI users with complete follow-up information that significantly enhances the robustness of the study.

The study used a comprehensive multivariable adjustment and Inverse Probability of Treatment Weighting (IPTW) to reduce confounding influences affecting the association between PPI use and patient prognosis.

The study could not include certain information due to data unavailability, including the causes of death, quantitation of proteinuria, follow-up laboratory parameters, classes or doses of the studied medication, and usage of over-the-counter medications.

Despite our best efforts to account for potential confounding variables, it's possible that some unmeasured confounding effects still influenced the outcomes owing to the retrospective nature of this study.

Keywords: proton pump inhibitor, chronic kidney disease, end-stage kidney disease, mortality

Introduction

Proton pump inhibitors (PPIs) are among the most common acid suppression agents used worldwide for gastrointestinal disease, such as gastroesophageal reflux disease, peptic ulcer disease, and the eradication of *Helicobacter pylori*.(1) They are also used for long-term prophylaxis of gastroduodenal injury in patients taking non-steroidal anti-inflammatory drugs or antiplatelet agents.(2, 3) Since this pharmacological class has been perceived to be generally safe, it is available over-the-counter in several countries.(4, 5) Furthermore, several retrospective observational studies reported frequent over-prescriptions and inappropriate long-term use of PPIs in the absence of medical indications.(6-8)

There is growing evidence from multiple observational studies that higher risks for uncommon but serious adverse outcomes such as *Clostridium difficile* infection,(9) community-acquired pneumonia,(10) and hip fracture(11) may be related to PPI use. In addition, adverse kidney outcomes associated with PPI use are well-documented in the literature, such as acute interstitial nephritis, acute kidney injury, or incident chronic kidney disease (CKD).(12-17) Despite the growing evidence of renal complications, patients with CKD are more frequently administered PPIs than patients without CKD, which might be attributed to the higher prevalence of acid-related gastrointestinal disorders and antiplatelet agent intake(18). However, there is limited data on the effects of PPI use in patients with an already established CKD.

In the current study, we aimed to investigate whether de novo PPI use without deterministic indication (which would require an endoscopic or image-based evaluation of the upper gastrointestinal tract) is associated with a higher risk of adverse outcomes when compared to H2RA initiation. We investigated a Korean nationwide claims database and excluded patients with possible indication or prior usage of PPIs or H2RAs. We hypothesized that non-indicated initiation of PPI use may be associated with higher risks of adverse outcomes

in patients with CKD.

Methods

Ethical considerations

The study was approved by the Institutional Review Board of Seoul National University Hospital (E-2112-048-1281). The use of the Korea National Health Insurance Service (NHIS) database was approved by the relevant government organization. The study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because this was a retrospective study using fully anonymous and unidentifiable data. All the research procedures followed the STROBE cohort reporting guidelines(19).

Data source

This study was performed using the NHIS claims database which contains information on demographics, healthcare services utilization, medical procedures, drug prescription, health examination data, and mortality data for all Korean nationals residing in Korea (20, 21). The NHIS which is a mandatory form of single social insurance covers about 97% of the Korean population. It provides general health screenings which are performed in annual or biennial intervals covering >10 million individuals, which is approximately >20% of the entire Korean population, each year. The coverage rate of the health screening was 68.4% in 2020 among the target population which included adults with age >40 years old or regular employees in any workplace. All insured medical services and health screening information are stored at NHIS and are available for research use (subject to approval).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Study design and population

We screened patients with CKD, defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 or dipstick-positive albuminuria of >1+ on ≥2 consecutive tests from January 2009 to December 2017(n=1,078,132).(22) The index date was set as the last test date which meets the definition. The index date was set as the last test date which meets the definition. The follow-up was initiated 1 year subsequent to the index date, marking the conclusion of the exposure period, and was censored at the date of data availability or at the occurrence of death (Figure 1).

Among these patients, those who had been prescribed PPI/H2RA previously (n=357,299) and hospitalized with diagnosis of gastrointestinal bleeding or gastric ulcer within the past 3 years from the index date (n=107) were excluded. As we intended to exclude the patients with possible indicated use of PPI/H2RA, those who had received endoscopy- or image-based (e.g., barium-swallowed X-ray series, computed tomography, or magnetic resonance imaging [MRI], not including simple X-rays) evaluation for their upper gastrointestinal tract within the previous 90 days, were also excluded (n=2,539).

After the index date, we identified the initiation of PPIs or H2RAs (a >30-day supply within 365 days from the index date) to determine de novo drug exposure. Patients who received a combination of these drugs were excluded at this phase. Finally, 1,038 individuals in the PPI group and 3,090 in the H2RA group were included in the study (Figure 2). Since PPIs are not over-the-counter medications in Korea, the possibility of its administration outside of prescription was excluded.

Outcomes

The assessed adverse prognostic outcomes were ESKD, mortality, myocardial infarction, and stroke. ESKD was defined as the initiation of kidney replacement therapy (NHIS covers all transplant and dialysis events in the nation). Mortality was identified from death certificates. As in a previous study, (23) myocardial infarction was recorded if an individual had International Classification of Disease 10th Revision (ICD-10) codes I21 or I22 during hospitalization. Stroke was defined as ICD-10 codes I63 or I64 during hospitalization, with claims information for brain MRI or brain computerized tomography imaging. The end of the follow-up period was December 2021.

Covariates

Baseline covariates including age, sex, body mass index, and comorbidities including hypertension, diabetes mellitus, dyslipidemia, active malignancy, and chronic lung disease were evaluated. Information on smoking, and alcohol consumption, and physical activity collected from self-questionnaire was included as the baseline covariates. Regular exercise was defined as engaging in moderate-intensity physical activity for≥5 days per week, or vigorous-intensity physical activity for≥3 days per week. Information on levels of serum creatinine-based eGFR, fasting serum glucose, total cholesterol, and blood pressure measured at the index-date health check-up was also included as the baseline covariates. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.(24) The participants were divided into four groups according to an equivalence scale of their average monthly income in the household: those who were at the lowest quartile or subsidized by the government were classified as low-income group. The urban region of residence included Seoul, the capital city, and the capital area and other six government-designated metropolitan cities, and other area of

the country was categorized as the rural region.

Statistical analyses

Categorical and continuous variables are expressed as proportions and means±standard deviations. The risks of adverse outcomes were initially plotted by Kaplan–Meier curves. The risk of adverse outcomes of PPI vs. H2RA initiation was further analyzed by a Cox proportional hazard model. In addition to a univariable model, a multivariable model adjusted for age, sex, baseline body mass index, eGFR, dipstick albuminuria, being a current-smoker, alcohol consumer, whether on regular physical activity, low-income state, region of residence (urban or rural), history of diabetes mellitus, dyslipidemia, cancer, and chronic lung disease was constructed. We also conducted a subgroup analysis based on the presence of diabetes and an eGFR of 60 mL/min/1.73 m2, and interaction term P values were calculated according to the variables. In an effort to control for potential confounding effects more effectively, we employed a propensity score method for group comparisons. This score incorporated all variables from the multivariable model, along with baseline waist circumference, levels of serum glucose, high density lipoprotein, low density lipoprotein cholesterol, and triglycerides. Upon calculating the propensity score, the inverse probability of treatment weighting (IPTW) was applied to the cohort. This application of IPTW aimed to balance the distribution of these measured variables across the treatment groups, facilitating a more equitable comparison.

Results

Baseline characteristics

After applying the exclusion criteria, among the 537,607 screened individuals, we finally

included 1,038 and 3,090 of new PPI and H2RA users, respectively, without a history of medication usage or a record of endoscopic or image-based evaluation of the upper gastrointestinal tract (Figure 2). Their baseline characteristics are presented in Table 1. After PS weighting, the two treatment groups were well balanced in all variables (all absolute standardized differences were <0.1).

Clinical outcomes according to PPI vs. H2RA

During the median follow-up of 2.8 years, 787 (19.1%) mortality, 122 (3.0%) ESKD, 136 (3.3%) myocardial infarction, and 183 (4.4%) stroke events were identified. Figure 3 shows the cumulative incidence curves of clinical outcomes according to the treatment groups. Compared to H2RA users, PPI users had a higher rate of progression to ESKD (16.64 vs. 7.14 per 1000 person-years) and all-cause mortality (72.36 vs. 54.08 per 1000 person-years). Similarly, in the univariable Cox regression model (Table 2), the risks of progression to ESKD (hazard ratio [HR] 2.11 [1.46, 3.05]) or all-cause mortality (HR 1.28 [1.09, 1.50]) were significantly higher in those who initiated PPI. On the other hand, for myocardial infarction and stroke risks, there were no significant differences between the two groups. After stringent adjustment by multivariable Cox regression, the risk of ESKD remained significantly higher in de novo PPI users (adjusted HR 1.68 [1.15, 2.45]), although the difference in mortality risk was nonsignificant (adjusted HR 1.14 [0.97, 1.35]).

Subgroups stratified by diabetes, and eGFR

The regression analyses results for clinical outcomes in various subgroups are presented in Supplement Table 1. Although the findings were generally similar regardless of the divided subgroups, the risk of progression to ESKD was significantly higher in those who initiated PPI than in H2RA users only in patients without diabetes and not in those with underlying diabetes.

When stratified by eGFR, the risk of ESKD with PPI initiation was significantly higher only in the patients with eGFR of <60 mL/min/1.73 m^2 and not in those with unaltered eGFR.

IPTW weighted clinical outcomes

Given the difference in baseline covariates between the PPI and H2RA groups, we further performed an IPTW-weighted analysis in this cohort, aiming to address these disparities. The IPTW Cox regression analysis is presented in Supplement Table 2, which again demonstrated that the risk of progression to ESKD was significantly higher in those who had initiated PPI than those who had started H2RA (incidence rate 13.32 vs. 7.87, HR 1.54 [1.04, 2.25]). On the other hand, the risks of other adverse outcomes were similar between the two groups, including the risk of all-cause mortality (incidence rate 66.26 vs. 55.74 per 1000 person-years, HR 1.14 [0.96, 1.34]).

Discussion

This observational study compared the risk of adverse outcomes in CKD patients, without a history of endoscopic examinations or gastrointestinal imaging, who were newly initiating PPI or H2RA. With robust consideration for confounding effects, the risk of progression to ESKD was consistently higher in those who initiated PPI administration compared to that in the active controls, while the risk of cardiovascular diseases or mortality remained similar between the two groups. Our study suggests that non-indicated initiation of PPI in patients with CKD may be discouraged considering that their usage may elevate the risk of progression to kidney dysfunction.

Despite the strong benefit of PPI use for acid-reflux disorders and their gastroprotective effect, the medication has been reported to have certain adverse effects.(25) Evidence from

multiple observational studies suggests that PPI use is associated with an increased risk of cardiovascular disease, gastric cancer, dementia, pneumonia, osteoporotic fractures, and *Clostridium difficile* infections.(26-30) Regarding the kidneys, PPI use has been suspected to cause hypomagnesemia,(31, 32) interstitial nephritis,(33, 34) acute kidney injury,(15) new-onset CKD,(16, 17) or the progression of kidney dysfunction.(35, 36) Thus, considering the highly prevalent use of PPIs in the general population, the nephrology society has warned for the possibility of PPIs causing nephrotoxicity. However, evidence from assessing specifically the clinical consequences related to new initiation of PPI administration in patients with CKD without certain indications has been rare. In this study, we sought to derive a CKD cohort without previous usage of PPI/H2RA or a history of gastrointestinal bleeding or active evaluation of the upper gastrointestinal tract, which reduced the indication bias for assessing the risk of non-indicated initiation of PPI administration in CKD. Taking advantage of a nationwide large-scale database, we successfully constructed such a cohort with relatively large numbers of new PPI and H2RA users and confirmed it by laboratory findings. In addition, to reduce the indication bias, we also made efforts to control confounding effects by implementing a robust multivariable adjustment and applying an IPTW model. As a result, we identified that the initiation of non-indicated PPI administration might be associated with a higher risk of progression to ESKD in patients with underlying CKD, suggesting that clinicians should consider not administering PPI indiscriminately to patients with CKD.

Concerning the risks of new PPI users of progression to ESKD, our results are congruent with several previous large-cohort observational studies that investigated the incidence and rate of CKD. Xie et al.(37) suggested that PPI exposure was associated with increased risk of incident CKD and CKD progression in patients without baseline eGFR reduction. A study by Grant et al.(38) was the first to assess the same issue in patients with reduced eGFR at baseline, which suggested that PPI use is associated with an increased risk of major adverse renal events.

However, the baseline characteristics were different amongst the two groups tested: the PPI group bore more patients with lower eGFR, more proteinuria, and higher prevalence of myocardial infarction and diabetes, which may be attributed to indication bias. In the subsequent systematic review followed by a meta-analysis, it was indicated that there is a significant association between the use of PPIs and an increased risk of CKD and ESKD.(39) In another study, Cholin and colleagues also investigated PPI safety specifically in the patients with CKD and found that the use of PPIs was not associated with the increased mortality or progression to ESKD when compared to H2 blockers and to the absence of acid suppression therapy.(40) Given the results of our study particularly in the subgroup group with CKD stage of ≥3 (eGFR of <60 mL/min/1.73 m^2), our results contradict the findings of Cholin et al. We believe that the difference might be attributed to our more rigorous study design through the addition of exclusion criteria for previous PPI/H2RA users and those with absolute indication for PPI/H2RA administration. Considering the solid evidence for adverse kidney effects of PPIs in the non-CKD group, we believe that our study, with its thorough consideration on indication and confounding bias, would be more appropriate to support the potential adverse effect of PPIs on kidney function, which can be present even in patients with underlying CKD.

There has been a discrepancy in the association between PPIs and all-cause mortality. A nationwide observational study of Xie et al.[38] showed a small excess of cause-specific mortality due to cardiovascular disease, CKD, and upper gastrointestinal cancer in de novo PPI users compared to H2RA users(41). On the other hand, a meta-analysis comparing the safety of PPIs with the one of H2RAs in kidney transplant recipients suggested that PPIs may not be associated with higher mortality risks, but related to higher hypomagnesemia rates and a decline of eGFR per year after transplantation.(42) Considering the observational nature of these studies as their major limitation to date, indication bias may overestimate the association of high mortality risk by PPI usage. Our study sought to minimize indication bias by excluding

patients with gastrointestinal history or imaging studies. As another possible cause, the relatively stable patient cohort, mainly composed of individuals undergoing general health check-ups, likely excluded many patients with advanced CKD, which could have led to fewer observations of mortality.

The risk of ESKD was different regarding the presence of a history of diabetes mellitus. As diabetes mellitus constitutes a prevalent cause of progression of kidney dysfunction, the potential adverse effects related to PPI initiation might have been accentuated in those without such a risk factor. Namely, the potential adverse kidney effects of PPI might not have been evident in the condition of diabetes, as diabetes itself would determine the fate of kidney prognosis of patients with CKD. On the other hand, the risk of ESKD related to PPI initiation was prominent in those with established reduction in eGFR (<60 mL/min/1.73 m^2), suggesting that clinicians should refrain from starting non-indicated PPI administration in patients with an overt kidney dysfunction.

This study bears several limitations. First, we could not include certain information due to data unavailability, including the causes of death, quantitation of proteinuria, follow-up laboratory parameters, classes or doses of the studied medication, and usage of over-the-counter medications. Second, beyond the criteria we have excluded, it is conceivable that our study may include instances where physicians administered PPIs based on clinical judgment, such as patient symptoms, or in patients who were concurrently receiving high-risk medications such as corticosteroids. Third, the generalizability of our study is limited as we were able to investigate a single-ethnic group of East Asians. Lastly, despite our efforts to control for measured confounding effects, the retrospective nature of this study could not eliminate the possibility of effects from unmeasured confounders.

In conclusion, our study showed that the higher risk of progression to ESKD in patients who initiated PPI administration without deterministic indication compared with de novo users of

H2RA, while the risk of cardiovascular diseases or mortality was similar between the two groups. The evidence that the risk of ESKD related to PPI initiation was prominent in those with eGFR of <60 mL/min/1.73 m^2 indicates the need for heightened vigilance among those with this condition. Given the high prevalence of PPI use in this population, the findings have public health implications and raise the clinical awareness related to the non-indicated use of PPI in patients with CKD.

Conflicts of interests

The authors declare that they have no competing interests.

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Availability of data and materials

The data are available from the National Health Insurance Service.

Patients consent for publication

Not applicable.

Author Contributions

The corresponding author attests that all of the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. SGK, KWJ, DKK and SP contributed to the conception and design of the study. SGK, JMC, SL, YK, SC, HH and SP advised on statistical aspects and interpreted the data. SP and KH performed the main statistical analysis, assisted by KWJ, SL, MK, and EK. DKK offered advice regarding the data interpretation. SP obtained funding and supervised the overall project. All of the authors participated in drafting the manuscript. All of the authors reviewed the manuscript and approved the final version to be published.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Table 1. Baseline characteristics of patients of using PPI vs. H2RA in total study population

Characteristics	Propensity Score Weighting					
	Before			After		
	PPI user (n=1038)	H2RA user (n=3090)	ASD	PPI user (n=1038)	H2RA user (n=3090)	ASD
Age, years	68.4 ± 12.1	69.6 ± 11.4	0.1	69.1±11.65	69.28±11.6	0.01
Male	506 (48.8%)	1112 (36.0%)	0.26	406.5(39.2%)	1213.4(39.2%)	0.0005
BMI, kg/m^2	24.92 ± 3.6	24.92 ± 3.6	0.002	24.89±3.58	24.92±3.61	0.008
Current smoker	144 (13.9%)	347 (11.2%)	0.08	122.7(11.8%)	366.7(11.9%)	0.002
Alcohol			0.11			0.005
Non-drinker	779 (75.1%)	2461 (79.6%)		816.1(78.8%)	2427.4(78.5%)	
Moderate(<30g/day)	216 (20.8%)	502 (16.3%)		176.9(17.1%)	539.8(17.3%)	
Heavy(≥30g/day)	43 (4.1%)	127 (4.1%)		43.4(4.2%)	127.4(4.1%)	
Regular exercise	199 (19.2%)	544 (17.6%)	0.04	187.9(18.1%)	556.8(18.0%)	0.004
Low income†	192 (18.5%)	562 (18.2%)	0.007	190.7(18.4%)	564.9(18.3%)	0.003
Urban resident	440 (42.4%)	1320 (42.7%)	0.006	448.1(43.2%)	1321.7(42.8%)	0.009
Diabetes	430(41.4%)	1145 (37.1%)	0.09	396.4(38.3%)	1175.8(38.0%)	0.005
Hypertension	795 (76.6%)	2325 (75.2%)	0.03	788.1(76.1%)	2328.4(75.3%)	0.02
Dyslipidemia	549 (52.9%)	1604 (51.9%)	0.02	542.5(52.4%)	1604.3(51.9%)	0.008
Active malignancy	85 (8.2%)	202 (6.5%)	0.063	73.4(7.1%)	215.4(7.0%)	0.004
COPD	161 (15.5%)	521 (16.9%)	0.037	171.9(16.6%)	511(16.5%)	0.001
eGFR < 60ml/min/1.73m^2	847 (81.6%)	2534 (82.1%)	0.02	854.1(82.4%)	2521.4(81.6%)	0.02
Albuminuria ≥ 1+	340 (32.8%)	857 (27.7%)	0.11	302.6(29.2%)	896.9(29.0%)	0.003
eGFR, ml/min/1.73m^2	54.4 ± 20.5	55.3 ± 19.9	0.05	55.1±20.2	55.1±20.2	0.002
Systolic BP, mmHg	130.6 ± 17.8	130.7 ± 16.7	0.004	130.6±17.7	130.6±16.7	0.0004
Diastolic BP, mmHg	77.5 ± 11.21	77.8 ± 10.5	0.032	77.8±11.1	77.7±10.5	0.003
Glucose, mg/dL	118.1 ± 52.4	115.4 ± 44.8	0.055	116.1±49.2	116.1±46.0	0.0002
Total cholesterol, mg/dL	185.2 ± 46.2	191.8 ± 43.7	0.123	190.1±47.2	190.1±43.6	0.0007

PPI, proton pump inhibitor; H2RA, histamine type 2 receptor antagonist; ASD, absolute standardized difference; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; BP, blood pressure.

†Lowest quartile of income or under government aid

Table 2. Hazard ratios for clinical outcomes according to use of PPI compared to H2Ra

Outcomes	Group	N	Event	Follow-up Person-Years	Incidence Rate (per 1000PY)	Model 1		Model 2		Model 3	
						HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
ESKD	PPI	1038	46	2765	16.64	2.11 (1.46 to 3.04)	< 0.001	1.72 (1.19 to 2.48)	0.004	1.82 (1.26 to 2.62)	0.001
	H2RA	3090	76	10647	7.14	1 (Reference)		1 (Reference)		1 (Reference)	
Mortality	PPI	1038	205	2833	72.36	1.34(1.14 to 1.57)	< 0.001	1.29 (1.10 to 1.51)	0.002	1.28 (1.09 to 1.50)	0.002
	H2RA	3090	582	10762	54.08	1 (Reference)		1 (Reference)		1 (Reference)	
MI	PPI	1038	23	2818	8.16	0.75 (0.48 to 1.17)	0.20	0.72 (0.46 to 1.13)	0.15	0.74 (0.47 to 1.15)	0.18
	H2RA	3090	113	10571	10.69	1 (Reference)		1 (Reference)		1 (Reference)	
Stroke	PPI	1038	41	2770	14.80	1.05 (0.74 to 1.48)	0.81	1.04 (0.74 to 1.48)	0.81	1.06 (0.75 to 1.50)	0.75
	H2RA	3090	142	10481	13.55	1 (Reference)		1 (Reference)		1 (Reference)	

Model 1: univariable
Model 2: adjusted for age, sex, BMI, hypertension, diabetes, eGFR and albuminuria.
Model 3: adjusted for age, sex, BMI, hypertension, diabetes, eGFR, albuminuria, dyslipidemia, COPD, current smoker, alcohol, regular exercise, low income, and region of residence (urban)
PY, person-year; HR, hazard ratio; MI, myocardial infarct; PPI, proton pump inhibitor; H2RA, histamine type 2 receptor antagonist; ESKD, end-stage kidney disease.

Figure legends

Figure 1. Graphical depiction of the time windows used to determine the studied variables. S indicates the national health screenings that were mostly performed at annual or biennial intervals.

Figure 2. Study population. eGFR = estimated glomerular filtration rate, MI = myocardial infarction, ESKD = end-stage kidney disease, PPI = proton pump inhibitor, H2RA = histamine H_2-receptor antagonists

Figure 3. Kaplan-Meier survival curves showing the cumulative risks of clinical outcomes. The y-axes indicate cumulative adjusted incidence probability, and the x-axes indicate the time (years). The survival tables are presented below the adjusted survival curves. (A) ESKD (B) Mortality (C) MI (D) Stroke. ESKD = end-stage kidney disease, MI = myocardial infarction.

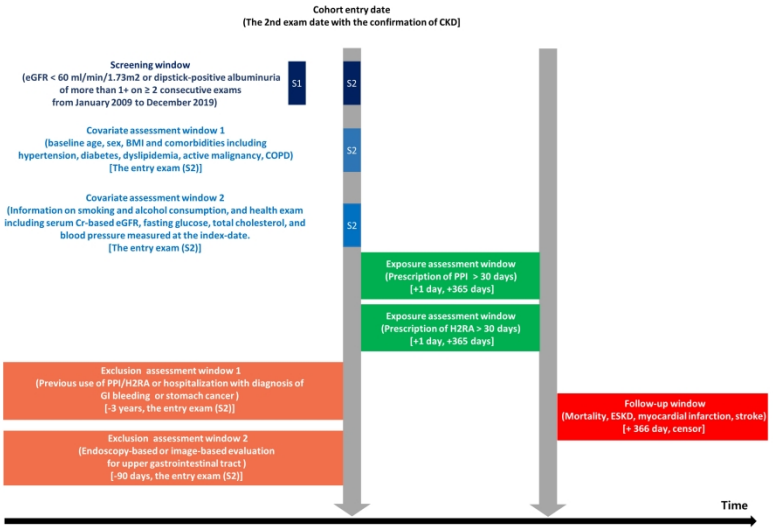

Figure 1. Graphical depiction of the time windows used to determine the studied variables. S indicates the national health screenings that were mostly performed at annual or biennial intervals.

338x190mm (300 x 300 DPI)

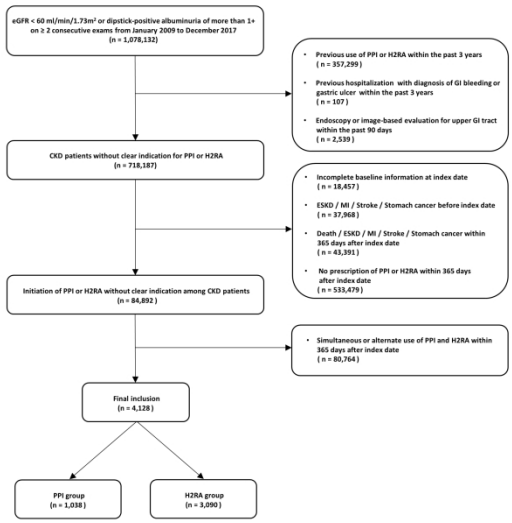

Figure 2. Study population. eGFR = estimated glomerular filtration rate, MI = myocardial infarction, ESKD = end-stage kidney disease, PPI = proton pump inhibitor, H2RA = histamine H2-receptor antagonists

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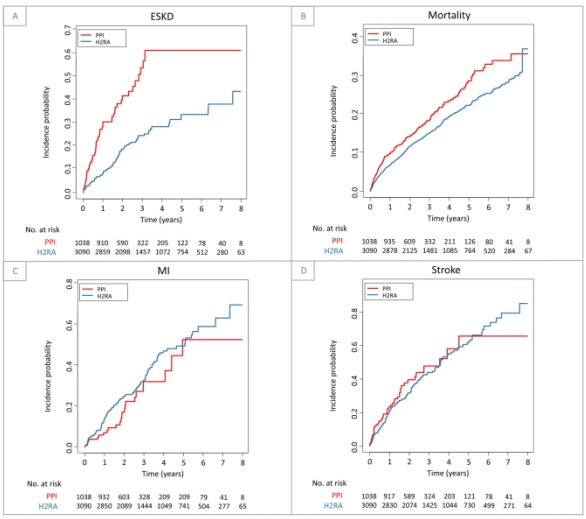

Figure 3. Kaplan-Meier survival curves showing the cumulative risks of clinical outcomes. The y-axes indicate cumulative adjusted incidence probability, and the x-axes indicate the time (years). The survival tables are presented below the adjusted survival curves. (A) ESKD (B) Mortality (C) MI (D) Stroke. ESKD = end-stage kidney disease, MI = myocardial infarction.

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Supplement Table 1. Cox regression analysis in subgroups according to diabetes and low eGFR

Subgroup		ESKD			Mortality			MI			Stroke		
		Adjusted HR (95% CI)	*P*	**Pi*	Adjusted HR (95% CI)	*P*	**Pi*	Adjusted HR (95% CI)	*P*	**Pi*	Adjusted HR (95% CI)	*P*	**Pi*
Diabetes													
Yes	PPI	1.21 (0.74 to 1.96)	0.45	0.01	1.09 (0.86 to 1.39)	0.48	0.61	0.69 (0.35 to 1.35)	0.27	0.79	0.87 (0.52 to 1.48)	0.61	0.45
	H2RA	1 (Reference)			1 (Reference)			1 (Reference)			1 (Reference)		
No	PPI	3.07 (1.64 to 5.74)	< 0.001		1.17 (0.93 to 1.46)	0.18		0.71 (0.38 to 1.33)	0.29		1.20 (0.74 to 1.94)	0.46	
	H2RA	1 (Reference)			1 (Reference)			1 (Reference)			1 (Reference)		
eGFR													
≥ 60	PPI	2.59 (0.79 to 8.42)	0.55	0.59	1.14 (0.74 to 1.76)	0.58	0.95	0.94 (0.30 to 2.90)	0.91	0.54	0.99 (0.42 to 2.31)	0.98	0.86
	H2RA	1 (Reference)			1 (Reference)			1 (Reference)			1 (Reference)		
< 60	PPI	1.63 (1.09 to 2.43)	0.02		1.14 (0.96 to 1.36)	0.15		0.68 (0.41 to 1.12)	0.13		0.98 (0.66 to 1.45)	0.91	
	H2RA	1 (Reference)			1 (Reference)			1 (Reference)			1 (Reference)		

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; MI, myocardial infarction; PPI, proton pump inhibitor; H2RA, histamine type 2 receptor antagonist

Adjusted for age, sex, BMI, hypertension, diabetes, eGFR, albuminuria, dyslipidemia, COPD, current smoker, alcohol, regular exercise, low income, and region of residence (urban or rural)

*P value for interaction

Supplement Table 2. IPTW weighted Cox regression analysis of clinical outcomes

Outcome	Group	Weighted Incidence Rate (per 1000 PY)	Weighted HR (95% CI)	*P*
ESKD	PPI	13.31	1.72 (1.19 to 2.48)	0.03
	H2RA	7.86	1 (Reference)	
Mortality	PPI	66.26	1.14 (0.96 to 1.34)	0.12
	H2RA	55.74	1 (Reference)	
MI	PPI	7.60	0.72 (0.46 to 1.13)	0.1
	H2RA	10.73	1 (Reference)	
Stroke	PPI	14.48	1.04 (0.74 to 1.48)	0.9
	H2RA	13.52	1 (Reference)	

IPTW, inverse probability of treatment weight; PY, person-year; HR, hazard ratio; ESKD, end-stage kidney disease; MI, myocardial infarction

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*10,11*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10,11
		(*b*) Report category boundaries when continuous variables were categorized	10,11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10,11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.