Original Article

Kidney Res Clin Pract 37:59-68, 2018
pISSN: 2211-9132 • eISSN: 2211-9140
https://doi.org/10.23876/j.krcp.2018.37.1.59

KIDNEY RESEARCH AND CLINICAL PRACTICE

Association of proton pump inhibitor use with renal outcomes in patients with coronary artery disease

Nam-Jun Cho, Chi-Young Choi, Samel Park, Sang-Ho Park, Eun Young Lee, Hyo-Wook Gil

Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Korea

Background: Several studies have suggested that proton pump inhibitor (PPI) use is associated with adverse renal outcomes, but obvious evidence for this association is lacking. We investigated the association between PPI use and adverse renal outcomes in patients who had undergone percutaneous coronary intervention.

Methods: Of the 1,284 patients hospitalized for percutaneous coronary intervention between January 2007 and May 2012, 934 patients with baseline estimated glomerular filtration rate greater than 60 mL/min/1.73 m^2 were enrolled. Multivariable Cox models were used to examine whether PPI use was associated with acute and chronic adverse renal outcomes.

Results: In adjusted time-dependent Cox models, PPI use was associated with acute kidney injury (hazard ratio [HR], 1.46; 95% confidence interval [95% CI], 1.05–2.02), especially in patients aged 65 years or younger (HR, 2.08; 95% CI, 1.09–3.96) or in patients with diabetes (HR, 2.00; 95% CI, 1.23–3.25). In multivariable Cox models, the association between duration of PPI use and chronic kidney disease development was not statistically significant (HR of heavy users, 1.50; 95% CI, 0.61–3.67), but a longer duration of PPI use was associated with mild renal progression in patients younger than 65 years (HR of heavy users, 2.24; 95% CI, 1.09–4.60).

Conclusion: Our results suggest that PPI use increases the risk of AKI development, and that PPI use is more significantly associated with acute and chronic renal injuries in younger patients.

Keywords: Acute kidney injury, Chronic kidney failure, Proton pump inhibitors, Risk factors

Introduction

Proton pump inhibitors (PPIs) are one of the most widely used classes of drugs and are prescribed primarily for gastric acid-related diseases, eradication of *Helicobacter pylori*, and prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathy; however, they are often used without any clear indication [1]. Although PPIs have an excellent overall safety profile, some severe adverse effects, which include bone fracture, dementia, myocardial infarction, infections, micronutrient deficiencies, and kidney diseases, have been proposed with little evidence [2,3].

An adverse renal outcome was first reported in 1992 in a case report of PPI-associated acute interstitial nephritis (AIN) [4]. Since then, several studies have reported that PPI use is related to AIN and acute kidney injury (AKI) [5–7]. Recently, large population studies have suggested that chronic kidney disease (CKD) might also be an important complication arising from PPI use [8–10]. Although an immunologic reaction is the proposed mechanism of PPI-associated renal injury [11], the exact mechanism has not yet been clearly identified.

Received October 17, 2017; **Revised** January 31, 2018;
Accepted February 10, 2018
Correspondence: Hyo-Wook Gil
Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, 31 Soonchunhyang 6-gil, Cheonan 31151, Korea. E-mail: hwgil@schmc.ac.kr
ORCID: http://orcid.org/0000-0003-2550-2739

Because PPI-associated renal injury is often asymptomatic and requires a longer duration of drug exposure to be detected [12], the results of current studies can be influenced by many confounding factors, such as concomitant medication use, bleeding, and comorbid conditions. Furthermore, it is difficult to quantify PPI use due to widespread prescribing habits and over-the-counter (OTC) sales in many countries. This can also lead to misclassification bias. Because OTC sale of PPIs is not available in Korea, and because prescription of drugs are strictly controlled in patients who have undergone percutaneous coronary intervention (PCI), our previous retrospective PCI cohort [13] is an ideal population for PPI studies. With this well-controlled cohort, we investigated the relationship of PPI use and the development of CKD and AKI.

Methods

Study population

The study population consisted of 1,284 patients who underwent PCI from January 2007 to May 2012 at Soonchunhyang University Cheonan Hospital, Korea, and who had taken part in our previous study [13]. Baseline estimated glomerular filtration rate (eGFR) and baseline creatinine were the median values measured between 6 and 12 months after PCI, as PCI with contrast use could affect creatinine levels. Participants were excluded if they were missing baseline eGFR measurements, had a baseline eGFR less than 60 mL/min/1.73 m^2, or were already on hemodialysis. Participants who completed follow-up in less than 365 days were also excluded from the analysis of CKD outcomes because the cumulative number of days of PPI use in the first year after PCI was used as the primary predictive variable. Finally, 934 participants were included in the analysis for AKI outcomes, and 916 participants were included in the analysis for CKD outcomes (Fig. 1).

In the analysis for both CKD and AKI outcomes, all participants were followed up for five years after PCI. Participants were considered lost to follow-up if there was no further creatinine value within an observation period, and they were censored in survival analyses at the date of the last documented serum creatinine measurement.

The present study was approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (2017-09-021-002).

CKD and AKI outcomes

We used the term 'CKD outcomes' to combine three independent outcomes: incident CKD, incident CKD with progression, and mild renal progression. 'Incident CKD' was defined as the first sustained drop in eGFR below 60 mL/min/1.73 m^2 for at least 90 days [9]. 'Incident CKD with progression' was defined as the first drop in eGFR below 60 mL/min/1.73 m^2 with a subsequent decrease in eGFR of at least 25% [14], and 'mild renal progression' was defined as a sustained decrease in eGFR of at least 10%.

We also used the term 'AKI outcomes' to combine two

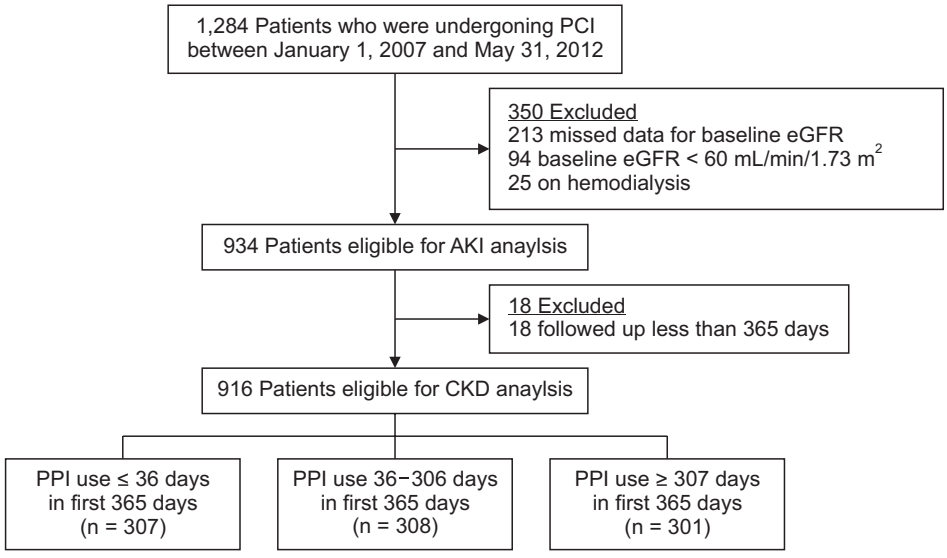

Figure 1. Flow chart of patient enrollment.
AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.

independent outcomes: 'AKI-creatinine,' which was defined as at least 0.3 mg/dL or 50% increase in serum creatinine within 30 days [9], and 'AKI-eGFR,' which was defined as a decrease in eGFR of at least 25% within 30 days of PCI. If multiple AKIs occurred within 120 days, only the first was considered as the event occurrence, and all other AKIs were ignored. If an event occurred 120 days after the first event, it was considered a second AKI. In this manner, each patient could have multiple AKI outcomes.

Measurement of PPI use

PPI dosing and duration of use were investigated using the electronic medical record system of Soonchunhyang University Cheonan Hospital. In the analysis for CKD outcomes, 'duration of PPI use' was defined as cumulative number of days of PPI use in the first 365 days after PCI. Those patients prescribed PPIs were categorized as light users (≤ 36 days), moderate users (37–306 days), or heavy users (≥ 307 days) based on tertile, where light user was set as the reference category. In the analysis for AKI outcomes, 'PPI use' was assessed as a time-varying covariate that was composed of time intervals and binary values (PPI use or not). If there were more than 30 dose-free days, two different intervals were generated.

Covariates

Demographic characteristics of the participants were recorded at the time of admission for PCI. These were age, gender, weight, height, body mass index (BMI), diabetes mellitus (DM), hypertension (HTN), dyslipidemia, and cancer. The laboratory variables assessed on admission included serum urea nitrogen, creatinine, calcium, phosphorus, albumin, hemoglobin, platelets, routine urinalysis, and echocardiographic findings, such as left ventricular ejection fraction (LVEF). NSAID use in the first year after PCI was also measured in the same way as PPI use.

Plasma creatinine level was measured by a modified kinetic Jaffé method, and eGFR was computed based on age, sex, race, and serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation [15].

Statistical analysis

Statistical analyses were performed using R version 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were expressed percentages. Normally distributed continuous variables were expressed as means ± standard deviations, and non-normally distributed continuous variables were expressed as medians (interquartile ranges).

The difference in baseline characteristics between the three groups for the duration of PPI use was assessed using chi-square and ANOVA tests for categorical and continuous variables, respectively. Using a Spearman's correlation coefficient, we analyzed whether the duration of PPI use in the first 365 days was associated with the duration of PPI use in the first 730 days and 1,095 days.

Kaplan-Meier curves with log-rank tests were used for assessing associations between duration of PPI use and CKD outcomes. We used multivariable Cox proportional hazards models to assess the associations between duration of PPI use and CKD outcomes after adjusting for other covariates. Nonlinear associations were examined using restricted cubic splines to relax linearity assumptions for continuous variables, especially for duration of PPI use.

Associations between PPI use and AKI outcomes were evaluated using time-dependent Cox models with the Andersen-Gill extension, which was used to capture the impact of temporal changes in PPI use and to deal with multiple events. Furthermore, in some time-dependent Cox models, 7, 14, 28, and 42 days of time lag to time-dependent PPI use was taken into account for a delayed effect of PPI exposure on AKI occurrence. Subgroup analyses of both CKD and AKI outcomes were performed for participants partitioned by demographic and comorbid conditions and by significant laboratory markers.

When selecting covariates for adjustment, univariate Cox models were performed, and covariates whose *P* value was less than 0.05 were considered to be potential confounders. Proportional hazards assumptions were tested using Schoenfeld residuals. In Cox regression models, a 95% confidence interval (CI) of a hazard ratio (HR) that did not include 1.0 was considered statistically significant. In other analyses, a *P* value less than 0.05 was considered statistically significant.

Results

Participant characteristics

There were 934 participants in the analysis for AKI outcomes and 916 participants in the analysis for CKD outcomes. Their median follow up period was 3.6 years and 3.5 years from baseline, respectively. The median frequency of serum creatinine measurements in each patient was six (interquartile range, 4–11) during the follow-up period. Participant characteristics according to the duration of PPI use are presented in Table 1. The light user group had more male participants than the other groups, and the other characteristics did not show significant differences between the groups.

Characteristics of PPI use

The distribution of duration of PPI use was bimodal, and the median value was 250 days (interquartile range, 15–319 days), and 139 participants did not take a PPI at all in the first 365 days. The duration of PPI use in the first 365 days was relatively consistent with the duration of PPI use in the first 730 days (Spearman's rho = 0.884, $P < 0.001$) and 1,095 days (Spearman's rho = 0.853, $P < 0.001$). This was analyzed in participants who were followed for longer than 730 days (n = 867) and 1,095 days (n = 802). During the whole observation period, 46 patients (4.9%) did not take a PPI, 309 (33.1%) took only one type of PPI, and 579 (62.0%) took two or more types of PPI. The types and frequencies of PPI medications were as follows: pantoprazole, 382; lansoprazole, 866; esomeprazole, 462; rabeprazole, 62; S-pantoprazole, 12; dexlansoprazole, 10; and ilaprazole, 6.

Association between PPI use and CKD outcomes

Among the 916 participants, there were 31 with inci-

Table 1. Participant characteristics according to duration of proton pump inhibitor (PPI) use

Variable	Duration of PPI use in the first 365 days			*P* value
	Light users (≤ 36 days) (n = 307)	Moderate users (37–306 days) (n = 308)	Heavy users (≥ 307 days) (n = 301)	
Age (yr)	61.8 ± 10.4	62.8 ± 11.6	62.0 ± 10.7	0.475
Sex, male	217 (70.7)	184 (59.7)	199 (66.1)	0.016
Hypertension, present	176 (57.3)	167 (54.2)	161 (53.5)	0.599
Diabetes, present	96 (31.3)	92 (29.9)	95 (31.6)	0.889
Dyslipidemia, present	22 (7.2)	23 (7.5)	22 (7.3)	0.990
Cancer, present	11 (3.6)	11 (3.6)	13 (4.3)	0.860
Body mass index (kg/m^2)	24.9 ± 3.3	24.8 ± 3.2	24.4 ± 3.6	0.159
Albumin (g/dL)	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	0.194
Urea nitrogen (mg/dL)	14.8 (12.5–18.2)	15.0 (11.8–19.0)	14.8 (12.0–17.5)	0.425
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.5	0.8 ± 0.3	0.700
Calcium (mg/dL)	9.1 ± 0.5	9.0 ± 0.5	9.0 ± 0.6	0.116
Phosphorus (mg/dL)	3.3 ± 0.8	3.3 ± 0.7	3.4 ± 0.9	0.430
Hemoglobin (g/dL)	13.9 ± 1.8	13.7 ± 1.7	13.8 ± 1.8	0.324
Platelet count (×10^3/μL)	234.5 ± 65.7	235.7 ± 62.2	235.5 ± 65.4	0.965
eGFR (mL/min/1.73 m^2)	91.7 ± 13.3	92.3 ± 13.5	92.3 ± 13.5	0.804
Urine dipstick protein				0.191
Negative	233 (75.9)	227 (73.7)	214 (71.1)	
Trace	61 (19.9)	65 (21.1)	61 (20.3)	
1+	9 (2.9)	9 (2.9)	11 (3.7)	
2+ or over	4 (1.3)	7 (2.3)	15 (5.0)	
LVEF	62.0 (50.0–65.0)	60.0 (50.0–65.0)	60.0 (48.0–65.0)	0.534
NSAID use, yes	29 (9.4)	40 (13.0)	40 (13.3)	0.264

Data are presented as mean ± standard deviation, median (interquartile range), or count (%), as appropriate. Comparisons are made by ANOVA or chi-square test.
eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NSAID, nonsteroidal anti-inflammatory drug.

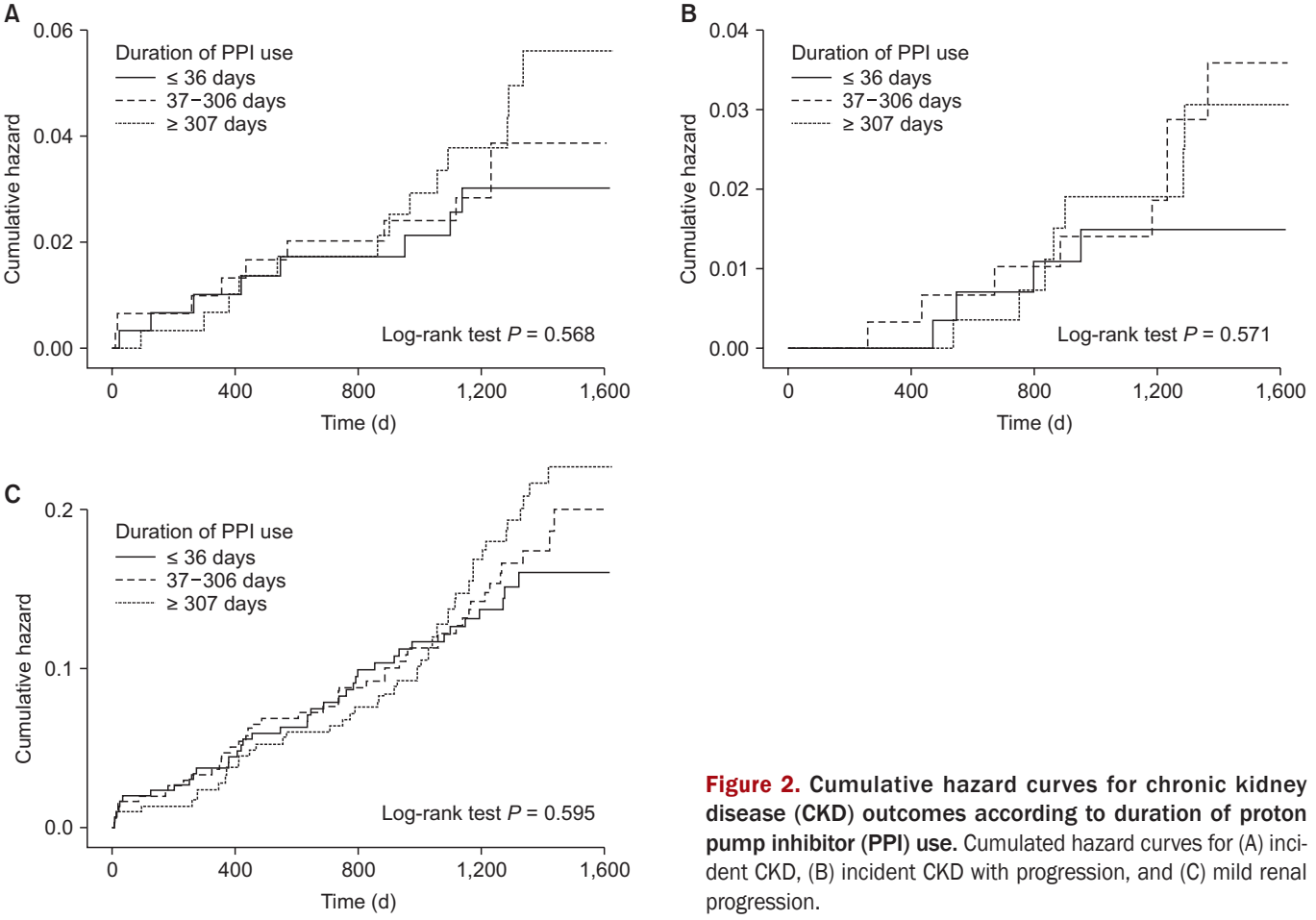

Figure 2. Cumulative hazard curves for chronic kidney disease (CKD) outcomes according to duration of proton pump inhibitor (PPI) use. Cumulated hazard curves for (A) incident CKD, (B) incident CKD with progression, and (C) mild renal progression.

Table 2. Incidence rate and hazard ratio for chronic kidney disease (CKD) outcomes according to duration of proton pump inhibitor (PPI) use

CKD outcome	Duration of PPI use in the first 365 days		
	Light users (≤ 36 days) (n = 307)	Moderate users (37–306 days) (n = 308)	Heavy users (≥ 307 days) (n = 301)
Incident CKD			
Number of events	8 (2.6)	10 (3.2)	13 (4.3)
Incidence rate	8.2 (3.9–15.4)	9.8 (5.0–17.4)	12.9 (7.2–21.5)
Hazard ratio	1 (reference)	1.29 (0.50–3.32)	1.50 (0.61–3.67)
Incident CKD with progression			
Number of events	4 (1.3)	8 (2.6)	7 (2.3)
Incidence rate	4.0 (1.4–9.6)	7.7 (3.7–14.6)	6.9 (3.1–13.5)
Hazard ratio	1 (reference)	1.61 (0.47–5.48)	1.46 (0.42–5.03)
Mild renal progression			
Number of events	38 (12.4)	44 (14.3)	49 (16.3)
Incidence rate	41.1 (29.5–55.8)	45.8 (33.7–60.9)	51.2 (38.7–54.5)
Hazard ratio	1 (reference)	1.07 (0.69–1.66)	1.22 (0.79–1.87)

Data are presented as number (%) or value (95% confidence interval [CI]).

Incidence rate is presented as a number of events per 1,000 person-years. Hazard ratios (95% CI) were attained by multivariable Cox proportional hazard models adjusted for age, gender, diabetes mellitus, hypertension, serum albumin, baseline estimated glomerular filtration rate, and urine dipstick protein.

dent CKD, 19 with incident CKD with progression, and 131 with mild renal progression. The incidence rates were 10.3 per 1,000 person-years (95% CI, 7.1–14.4), 6.3 per 1,000 person-years (95% CI, 3.9–9.6), and 46.1 per 1,000 person-years (95% CI, 36.7–54.5), respectively. The unadjusted cumulative hazard curves of CKD outcomes by duration of PPI use are shown in Fig. 2. There was no significant difference between these groups in log-rank tests.

The association between duration of PPI use and CKD outcomes was examined by multivariable Cox models with adjustment for age, gender, DM, HTN, serum albumin, baseline eGFR, and urine dipstick protein. As the duration of PPI use increased, the hazard of the CKD outcomes tended to increase as well. However, there was no statistical significance in all Cox models for CKD outcomes (Table 2). Additionally, the participants were categorized as non-PPI users (n = 139) vs. PPI users (n = 777) according to a history of PPI use in the first 365 days following PCI. The percentages of development of

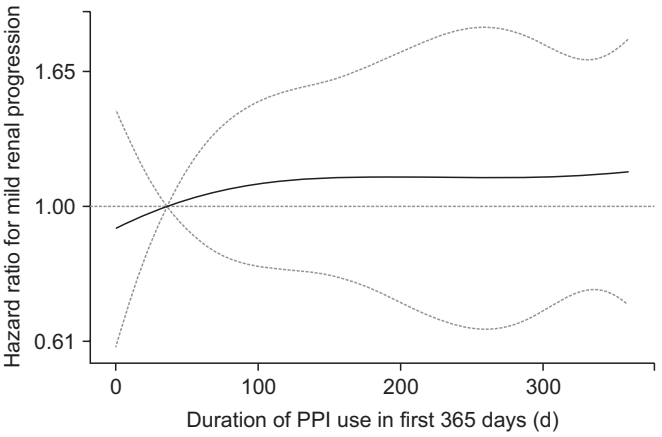

Figure 3. Hazard of mild renal progression according to duration of proton pump inhibitor (PPI) use. Restricted cubic spline regression model of the hazard of mild renal progression by duration of PPI use after adjusting for age, gender, diabetes, hypertension, serum albumin, baseline estimated glomerular filtration rate, and urine dipstick protein. The figure shows an estimated adjusted hazard ratio as a function of duration of PPI use with 95% pointwise confidence limits, using 36 days as the reference duration.

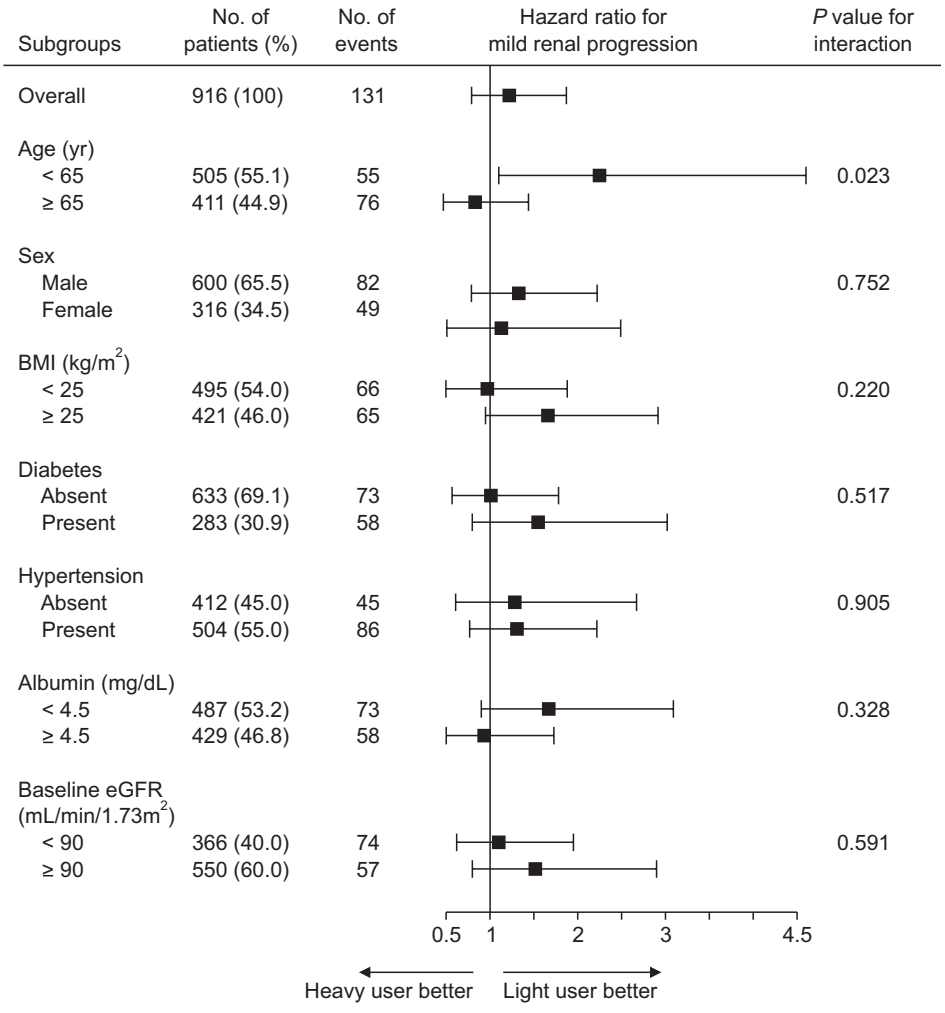

Figure 4. Multivariable-adjusted hazard ratios (95% confidence interval) of mild renal progression between the light user group and heavy user group, according to subgroup.
BMI, body mass index; eGFR, estimated glomerular filtration rate.

CKD outcomes were higher in PPI users than in non-PPI user, but there was no significant difference (Supplementary Table 1; available at https://doi.org/10.23876/j.krcp.2018.37.1.59).

The restricted cubic spline regression model was used to visualize intuitive relationships between the duration of PPI use and CKD outcomes after adjustment for age, gender, DM, HTN, serum albumin, baseline eGFR, and urine dipstick protein. The hazard ratios for mild renal progression gradually increased from the zero point and flattened after about 150 days of PPI use (Fig. 3).

In the subgroup that included participants younger than 65 years (n = 505), heavy PPI users were more significantly associated with mild renal progression than light users (HR of moderate users, 1.85 [95% CI, 0.87–3.92]; HR of heavy users, 2.24 [95% CI, 1.09–4.60]) (Fig. 4). In other subgroups, partitioned by sex, BMI, DM, HTN, serum albumin, and baseline eGFR, the duration of PPI

Table 3. Hazard ratio for acute kidney injury (AKI) outcomes according to time-dependent proton pump inhibitor (PPI) use

PPI use	AKI outcomes			
	Incident AKI assessed by creatinine		Incident AKI assessed by eGFR	
Model 1	1.29 (0.97–1.72)	0.078	1.39 (1.00–1.91)	0.048
Model 2	1.32 (0.99–1.77)	0.055	1.46 (1.05–2.02)	0.023
Model 3a	1.36 (1.02–1.82)	0.035	1.45 (1.04–2.01)	0.027
Model 3b	1.37 (1.02–1.83)	0.034	1.42 (1.02–1.97)	0.035
Model 3c	1.29 (0.96–1.72)	0.087	1.36 (0.98–1.89)	0.062
Model 3d	1.10 (0.83–1.46)	0.519	1.12 (0.81–1.54)	0.490

Data are presented as the hazard ratio (95% confidence interval) and *P* value attained by multivariable time-dependent Cox models with Andersen-Gill extension.

Model 1: not adjusted; Model 2: adjusted for age, body mass index, diabetes mellitus, hypertension, serum albumin, serum hemoglobin, and baseline estimated glomerular filtration rate (eGFR) and left ventricular ejection fraction; Model 3a–d: adjusted for Model 2 variables, with 7, 14, 28 and 42 days of time lag to time-dependent PPI use.

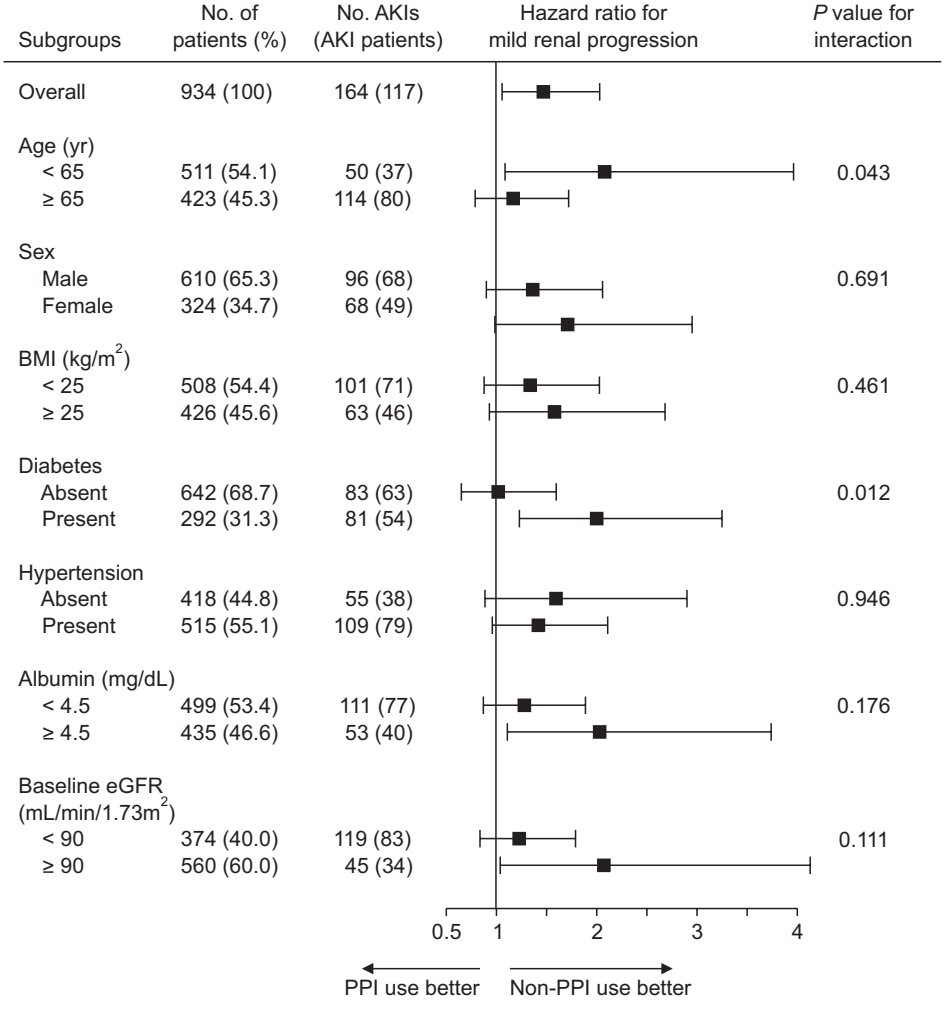

Figure 5. Multivariable-adjusted hazard ratios (95% confidence interval) of AKI-eGFR between the non-PPI use group and PPI use group, according to subgroup.

AKI, acute kidney injury; BMI, body mass index; eGFR, estimated glomerular filtration rate; PPI, proton pump inhibitor.

use was not clearly associated with any CKD outcomes.

Association between PPI use and AKI outcomes

There were 206 AKI-creatinine events (154 patients) and 164 AKI-eGFR events (117 patients) among the 934 participants. The incidence rate of AKI-creatinine was 67.2 per 1,000 person-years (95% CI, 58.5–76.9) (PPI use, 75.5 [95% CI, 63.4–89.3] per 1,000 person-years; non-PPI use, 56.3 [95% CI, 44.6–70.2] per 1,000 person-years). The incidence rate of AKI-eGFR was 53.5 per 1,000 person-years (95% CI, 45.8–62.2) (PPI use, 61.7 [95% CI, 50.8–74.2] per 1,000 person-years; non-PPI use, 42.8 [95% CI, 32.8–55.1] per 1,000 person-years).

In time-dependent Cox models adjusted for age, BMI, DM, HTN, serum albumin, serum hemoglobin, baseline eGFR, and LVEF, PPI use was significantly associated with AKI-eGFR (HR, 1.46; 95% CI, 1.05–2.02) but not with AKI-creatinine (HR, 1.32; 95% CI, 0.99–1.77). Additionally, after 7 and 14 days of time lag to time-dependent PPI use, PPI use was significantly associated with both AKI outcomes. The associations between PPI use and both AKI outcomes gradually weakened after 28 days and 42 days of time lag to time-dependent PPI use (Table 3).

In the subgroup analyses for AKI-creatinine, PPI use was significantly associated with AKI occurrence in patients younger than 65 (HR, 1.97; 95% CI, 1.18–3.28) and in those with DM (HR, 2.01; 95% CI, 1.27–3.17). In the subgroup analyses for AKI-eGFR, PPI use was also significantly associated with AKI occurrence in patients younger than 65 (HR, 2.08; 95% CI, 1.09–3.96) and DM (HR, 2.00; 95% CI, 1.23–3.25) (Fig. 5).

Discussion

In high-risk patients who underwent PCI, we found that PPI use was associated with increased risk of developing AKI, especially in younger patients with DM. A significant portion of PPI-associated AKI seemed to occur within 14 days after the initiation of PPI. Although the association between PPI use and CKD development was not statistically significant, subgroup analysis showed that a longer duration of PPI use was associated with chronic renal progression in patients younger than 65 years.

Our study showed a significant association between PPI use and AKI occurrence, especially after 7 and 14 days of time lag to the intervals of PPI use. This diminished after 28 days of time lag. From these results, we can infer that PPI use is more associated with AKI development during the first 7 to 14 days after starting a PPI than after the initial 14 days. Previous studies reported that the time interval from initiation of PPI use to AKI occurrence is quite variable, ranging from 1 week to 9 months [16], and that classic drug-associated AINs develop within 3 weeks after starting the drugs in about 80% of patients, with an average delay of about 10 days [17]. Previous reports are consistent with our results.

Recent studies suggested that PPI use was a significant risk factor for CKD development [8–10,18]; however, the association between PPI use and CKD development was not conclusive in our study. This discrepancy could result from several factors. First, the incidence rate of CKD in our study (10.3 per 1,000 person-year) was far less than that of other studies (14.2–36.8 per 1,000 person-year) [8,9]. Second, because our study was conducted with only Korean patients with coronary artery disease, the target populations differed in race and comorbidities. Last, measurements and descriptions of PPI exposure differed between studies.

Our study showed that younger individuals were more prone to develop AKI and CKD, as is consistent with previous studies [18,19]. These results are difficult to explain, considering that younger patients are less vulnerable to kidney injuries. Given that autoimmune diseases are more common in middle-aged women [20], and that PPIs might be associated with extra-renal manifestations of hypersensitivity [21], PPI-induced renal injury is suspected to result from certain immunologic processes that take place more commonly in the young. The other reason might be that in the younger population the prevalence of CKD without PPI use is quite low making the prevalence of CKD associated with PPI use more significant [18].

Our study showed that, in DM patients, PPI use was more significantly associated with AKI development, and these association have not been previously reported. High glucose concentration and activation of the renin–angiotensin aldosterone system were found to weaken the tubulointerstitium in DM patients by various mechanisms, including oxidative stress, interstitial inflammation, and induction of profibrogenic cytokines [22]. In this milieu, it is possible that PPI-induced immunologic responses in the interstitium could more severely worsen renal func-

tion. However, because exact mechanisms are not known and evidence is insufficient, additional studies are needed.

There are a few limitations to this study. First, because of its retrospective design, it was impossible to control for exposures and confounding factors. However, because the participants in this study were followed up regularly and prescriptions drugs were strictly managed, we considered the assessments of information about exposures and confounding factors to be quite reliable. Second, a history of PPI use before PCI, which could affect CKD outcomes, was not available because many participants started to regularly visit our clinic after the PCI. Third, PPIs prescribed at other hospitals were not investigated. However, considering that OTC purchase of PPIs is not possible in Korea, and that the use of drugs is strictly controlled due to the nature of these patients, the PPI history in this study is considered to be more accurate than in other studies. Fourth, participants who used NSAIDs throughout the observation period were not excluded from the study. However, most participants in this study were prescribed PPIs because of bleeding risk induced by anti-platelet agents, not NSAIDs. As such, we expect that the effect of NSAIDs on renal outcomes would not significantly differ between PPI user groups. Last, because this study was conducted on patients with coronary artery disease, we need to be cautious when expanding our results to the general population. The participants in this study were at higher risk of adverse renal outcomes because of the prevalence of comorbidities and more frequent use of PPIs than in the general population.

In conclusion, we found that PPI use increased the risk of AKI development, especially in the first 14 days of use. Also, in younger patients, PPI use was more significantly associated with adverse renal outcomes, including both acute and chronic forms. Therefore, it is necessary to prescribe PPIs with proper indications for as short a time period as possible, especially when prescribing PPIs for young or DM patients.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

This study was supported by the Young Investigator Grant from the Korean Society of Nephrology (KSN 2016) and Soonchunhyang University Research Fund.

References

[1] Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 336:2-3, 2008

[2] Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology* 152:706-715, 2017

[3] Yu LY, Sun LN, Zhang XH, et al. A Review of the novel application and potential adverse effects of proton pump inhibitors. *Adv Ther* 34:1070-1086, 2017

[4] Ruffenach SJ, Siskind MS, Lien YH. Acute interstitial nephritis due to omeprazole. *Am J Med* 93:472-473, 1992

[5] Klepser DG, Collier DS, Cochran GL. Proton pump inhibitors and acute kidney injury: a nested case-control study. *BMC Nephrol* 14:150, 2013

[6] Blank ML, Parkin L, Paul C, Herbison P. A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. *Kidney Int* 86:837-844, 2014

[7] Antoniou T, Macdonald EM, Hollands S, et al. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. *CMAJ Open* 3:E166-E171, 2015

[8] Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med* 176:238-246, 2016

[9] Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. *J Am Soc Nephrol* 27:3153-3163, 2016

[10] Klatte DCF, Gasparini A, Xu H, et al. Association between proton pump inhibitor use and risk of progression of chronic kidney disease. *Gastroenterology* 153:702-710, 2017

[11] Praga M, González E. Acute interstitial nephritis. *Kidney Int* 77:956-961, 2010

[12] Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. *Am J Kidney Dis* 64:558-566, 2014

[13] Park SH, Lee SH, Lee JS, et al. Changes in serum magnesium concentration after use of a proton pump inhibitor in patients undergoing percutaneous coronary intervention. *Kidney Res Clin Pract* 34:98-102, 2015

[14] Novak M, Mucsi I, Rhee CM, et al. Increased risk of incident

chronic kidney disease, cardiovascular disease, and mortality in patients with diabetes with comorbid depression. *Diabetes Care* 39:1940-1947, 2016

[15] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150:604-612, 2009

[16] Moledina DG, Perazella MA. PPIs and kidney disease: from AIN to CKD. *J Nephrol* 29:611-616, 2016

[17] Rossert J. Drug-induced acute interstitial nephritis. *Kidney Int* 60:804-817, 2001

[18] Arora P, Gupta A, Golzy M, et al. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. *BMC Nephrol* 17:112, 2016

[19] Yang Y, George KC, Shang WF, Zeng R, Ge SW, Xu G. Proton-pump inhibitors use, and risk of acute kidney injury: a meta-analysis of observational studies. *Drug Des Devel Ther* 11:1291-1299, 2017

[20] Marder W, Vinet É, Somers EC. Rheumatic autoimmune diseases in women and midlife health. *Womens Midlife Health* 1:11, 2015

[21] Otani IM, Banerji A. Immediate and delayed hypersensitivity reactions to proton pump inhibitors: evaluation and management. *Curr Allergy Asthma Rep* 16:17, 2016

[22] Tonolo G, Cherchi S. Tubulointerstitial disease in diabetic nephropathy. *Int J Nephrol Renovasc Dis* 7:107-115, 2014