Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(4) 1–8

DOI: 10.1177/03000605211006653
journals.sagepub.com/home/imr
SAGE

Association between a low dose of proton pump inhibitors and kidney function decline in elderly hypertensive patients: a retrospective observational study

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Abstract

Objectives: Proton pump inhibitors (PPIs) are widely used for acid suppression therapy. Recently, PPI use was reported to be associated with chronic kidney disease (CKD); however, whether a low dose of PPIs is associated with CKD remains unknown.

Methods: This retrospective observational study included hypertensive patients who visited Kenwakai Hospital between 2017 and 2019. Renal parameters, such as the estimated glomerular filtration rate (eGFR) and serum creatinine (Scr), were extracted from medical records and compared between three years before treatment and the baseline. PPI use was assessed as cumulative exposure for three years.

Results: The study population included 152 patients (57.9% men; mean age, 74.5 years). Of those, 35.5% were PPI users (low dose, 17.1%; high dose, 18.4%). A significant decrease in eGFR and an increase in Scr were observed between three years before treatment and the baseline in the high-dose PPI group but not the non-use or low-dose PPI groups.

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Conclusions: Our results suggest that a low dose of PPIs may be safe in clinical settings, but further prospective studies are needed to clarify our findings.

Keywords
Proton pump inhibitor, low dose, chronic kidney disease, elderly patient, acid suppression therapy, hypertension

Date received: 5 March 2021; accepted: 9 March 2021

Introduction

Proton pump inhibitors (PPIs) are some of the most commonly prescribed medications worldwide. PPIs have high efficacy and an excellent safety profile.[1] Recently, several observational studies reported an association between PPI use and uncommon but serious adverse events, including hip fractures,[2] community-acquired pneumonia,[3] *Clostridium difficile* infections,[4] acute interstitial nephritis,[5–7] and acute kidney injury.[8] In addition, several population-based studies have demonstrated a relationship between PPI use and chronic kidney disease (CKD).[9–11] Specifically, the association of PPI use with CKD risk is greater in patients receiving high doses of PPIs.[11] However, whether CKD occurs in patients treated with a low dose of PPIs remains unknown.

Significantly, the prevalence of CKD has been increasing in older and aging populations.[12] In many cases, elderly patients exhibit hypertension. In this retrospective observational study, we investigated whether a low dose of PPIs is associated with CKD in elderly hypertensive patients.

Materials and methods

Study population

This retrospective observational study was approved by the Ethics Committee of Osaka University of Pharmaceutical Sciences (Takatsuki, Japan; 26 June 2017) and conducted in accordance with the Declaration of Helsinki. Adult hypertensive patients were recruited from Kenwakai Hospital (Nagano, Japan) between 2017 and 2019. The primary endpoint was a >50% increase in serum creatinine (Scr) or progression into end-stage renal disease (ESRD). Eligible participants had a blood pressure (BP) of at least 140 mmHg systolic or 90 mmHg diastolic or used antihypertensive drugs, and they were all over 60 years old. The major exclusion criteria included diabetes mellitus, a history of congestive heart failure, arterial fibrillation, angina, cardiovascular events in the past 6 months, polycystic kidney disease, IgA nephropathy, and an estimated glomerular filtration rate (eGFR) below 15 (mL/minutes per 1.73 m^2) or dialysis. We also excluded patients who had undergone kidney transplantation. All participating patients provided written informed consent.

PPI exposure and grouping

The use of PPIs 3 years before participation was determined retrospectively by analyzing the prescription history in the medical records. To assess exposure to PPIs, we determined the total duration of PPI administration, which was calculated by adding the duration of PPI prescriptions

from each outpatient visit during the study period. Therefore, the exposure time to PPIs was the total number of days but not necessarily continued over time. PPIs available in Japan were omeprazole (10 or 20 mg), esomeprazole (10 or 20 mg), lansoprazole (15 or 30 mg), and rabeprazole (5, 10, or 20 mg). Based on previous reports,[13,14] we categorized the PPI dose as either low (10 mg for omeprazole, 10 mg for esomeprazole, 15 mg for lansoprazole, and 5 or 10 mg for rabeprazole) or high (20 mg for omeprazole, 20 mg for esomeprazole, 30 mg for lansoprazole, and 20 mg for rabeprazole), which are daily doses in Japan. Patients were then classified into a low-dose PPI group and a high-dose PPI group.

Statistical analysis

Data are presented as the mean ± SD or median (interquartile range) for continuous variables and n (%) for categorical variables. The differences in parametric and nonparametric values between two groups were analyzed with the unpaired *t*-test and the Mann–Whitney *U*-test, respectively. A paired *t*-test was used for the comparison of variables three years before treatment and at baseline. The differences in parametric and nonparametric values between three groups were analyzed with ANOVA and Kruskal–Wallis tests. Categorical variables were compared using chi-squared tests. $P<0.05$ was considered significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA).

Results

We identified 152 consecutive elderly patients who visited our hospital (Supplementary Figure 1).

The patients in this study included those that received esomeprazole (10 mg, n = 1; 20 mg, n = 25), lansoprazole (15 mg, n = 23; 30 mg, n = 2), and rabeprazole (10 mg, n = 14; 20 mg, n = 3). These numbers also included patients who received treatment with different PPIs (Table 1). None of the patients included in this study received omeprazole. Of 54 PPI users, 40 patients were treated with only one dose of PPIs, and the remaining patients were treated with at least two different doses [both at a high dose (n = 2), one low and one high dose (n = 10), or both low doses (n = 2)]. Patients were classified into a low-dose PPI group (n = 26) and a high-dose PPI group (n = 28). Patients who received both a low and high dose of PPIs were allocated to the high-dose PPI group. The remaining 98 patients did not receive any PPIs and were classified into the non-user group. The baseline demographic characteristics are given in Table 2. The mean age was 74.5 ± 5.4 years, and 88 were men (57.9%). The baseline data in different PPI groups are illustrated in Figure 1. There were no significant differences in Scr, blood urea nitrogen (BUN), eGFR, or urine albumin-to-creatinine ratio (UACR) between PPI non-users and users.

Next, we compared the renal parameters (eGFR and Scr) between three years before treatment and baseline in PPI users and non-users. As shown in Figure 2, the eGFR was significantly decreased in the high-dose PPI group ($P = 0.009$) but not in the low-dose PPI or non-user groups. Similarly, no significant differences were observed in Scr between 3 years before treatment and baseline in the low-dose PPI and non-user groups, whereas a significant increase in Scr was found in the high-dose PPI group ($P = 0.0009$). PPI users and non-users did not achieve the primary endpoint of a >50% increase in Scr or progression into ESRD.

In addition, the greatest reduction in eGFR was observed in the high-dose PPI

Table 1. Duration of PPI exposure and doses among PPI users (68 treatments in 54 patients).

PPI	Dose of PPI (mg)	Patients treated with PPIs, n	Median cumulative exposure, days
Esomeprazole	10	1	911
	20	25	412 (66–923.5)
Lansoprazole	15	23	557 (107.5–861)
	30	2	24 (14–34)
Rabeprazole	10	14	497 (342.8–847.8)
	20	3	658.5 (266–1051)

Data are shown as the median (interquartile range).
PPI, proton pump inhibitor.

Table 2. Patient characteristics and baseline data.

			PPI users		
Variables	Total (n=152)	PPI non-users (n = 98)	Low dose (n = 26)	High dose (n = 28)	P-value
Men, n (%)	88 (57.9)	58 (38.2)	16 (10.6)	14 (9.2)	0.029
Age, years	74.5 ± 5.4	74.1 ± 5.6	74.6 ± 5.0	75.9 ± 5.3	0.30
BMI, kg/m^2	24.2 ± 3.6	24.4 ± 3.8	24.0 ±3.6	23.5 ± 2.9	0.47
Systolic BP, mmHg	132.9 ± 13.6	133.7 ± 12.8	128.2 ± 11.3	134.6 ± 17.6	0.14
Diastolic BP, mmHg	73.7 ± 9.7	74.8 ± 10.1	71.3 ± 9.3	72.0 ± 8.5	0.16
Ever smoker, %	48 (31.6)	27 (17.8)	14 (9.2)	7 (4.6)	0.001
Ever drinker, %	73 (48)	53 (34.9)	9 (5.9)	11 (7.2)	0.005
Duration of hypertension, years	11 (6–20)	11 (8–20)	7.5 (4–11.3)	9.5 (4.3–18.8)	0.08
Serum albumin, g/dL	4.1 ± 0.3	4.1 ± 0.3	4.1 ± 0.5	4.1 ± 0.3	0.81
Hemoglobin, g/dL	13.2 ± 1.5	13.3 ± 1.5	13.1 ± 1.4	13.0 ± 1.7	0.64
HbA1c, %	6.0 ± 0.6	6.0 ± 0.5	6.1 ± 0.7	6.0 ± 0.6	0.59
Triglyceride, mg/dL	123 (89.5–190.8)	128.5 (90.5–197.3)	131 (90.5–192.3)	105 (89–133.8)	0.17
LDL, mg/dL	104.3 ± 22.9	107.3 ± 23.2	100.4 ± 21.3	96.6 ± 21.6	0.08
HDL, mg/dL	61.4 ± 16.4	62.4 ± 16.2	56.1 ± 14.5	63.0 ± 18.4	0.19
CPK, IU/L	98 (73–134.5)	104 (74–132.5)	106 (78–141)	95 (70–135)	0.74
Uric acid, mg/dL	6.0 ± 1.4	6.1 ± 1.4	5.9 ± 1.6	5.9 ± 1.4	0.72
Serum creatinine, mg/dL	1.0 ± 0.4	1.0 ± 0.4	0.95 ± 0.4	1.1 ± 0.5	0.57
BUN, mg/dL	19.9 ± 8.4	20.4 ± 7.1	18.7 ± 8.3	19.1 ± 11.9	0.56
UACR, mg/g Cr	22.3 (10–84.3)	24.3 (11.3–85.5)	15.9 (8.1–33.2)	22.3 (12.8–114.5)	0.53
eGFR, mL/minutes per 1.73 m^2	57.5 (42.3–69.8)	57.5 (42.2–69.1)	62.7 (51.5–78.6)	49.6 (38.8–69.9)	0.18
NSAIDs user, n (%)	55 (36.2)	29 (19.1)	12 (7.9)	14 (9.2)	0.003

Data are presented as the mean ± SD or median (interquartile range) for continuous variables and n (%) for categorical variables.
BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; HbA1c, glycated hemoglobin; UACR, urinary albumin-to-creatinine ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CPK, creatinine phosphokinase; eGFR, estimated glomerular filtration ratio; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

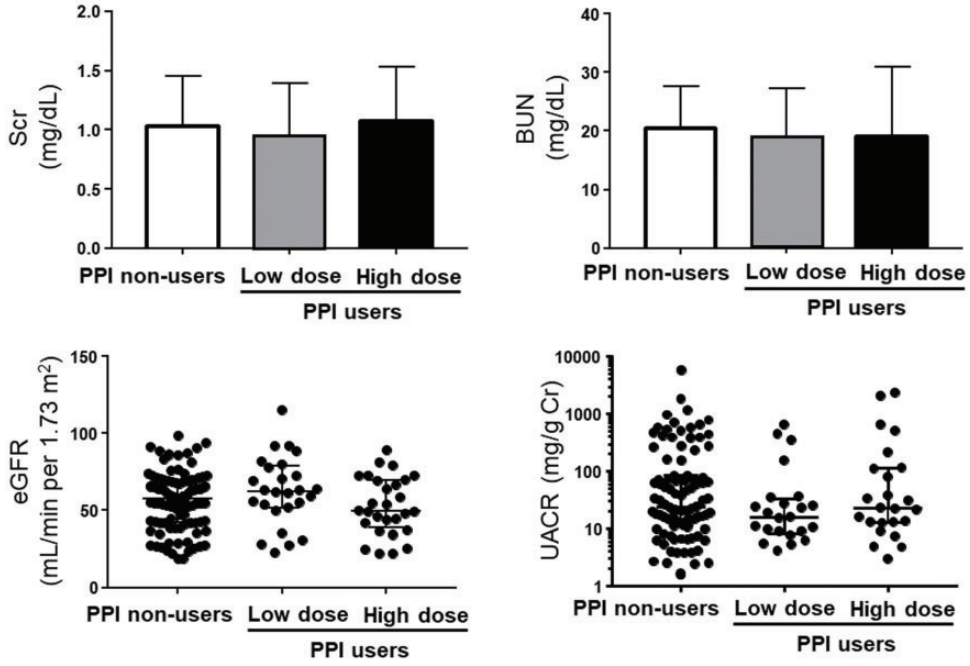

Figure 1. The baseline Scr, BUN, eGFR, and UACR values in the high-dose, low-dose, and non-use PPI groups. Results are presented as the mean ± SD (Scr and BUN) and median and interquartile range (eGFR and UACR). The *bars* show the median values.
BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; PPI, proton pump inhibitor; Scr, serum creatinine; UACR, urinary albumin-to-creatinine ratio.

group, although this result was not statistically significant (Figure 3).

Discussion

The present retrospective observational study revealed a significant decrease in eGFR and significant increase in Scr between 3 years before and after treatment with a high dose of PPIs but not a low dose of PPIs in elderly hypertensive patients.

Several observational studies reported that PPI use is associated with an increased risk of CKD.[9,15–17] A prospective community-based cohort study showed that PPI use is associated with a higher risk of CKD.[9] CKD patients take PPIs for a substantially longer duration compared with non-CKD patients; however, the dose of the individual PPIs has not been analyzed.[15] A retrospective cohort study revealed a higher rate of CKD progression in omeprazole users receiving 20 mg daily (categorized as a high dose), which is consistent with our results. In our study, the decline in eGFR was remarkable in the high-dose PPI group, and the renal safety of a low dose of PPIs was confirmed. To the best of our knowledge, this is the first study to demonstrate that high doses of PPIs, but not low doses, were associated with a decline in kidney function.

In elderly patients, kidney function decreases with aging. Therefore, it is particularly important to avoid potential drug-related complications in these patients. Because PPIs are more powerful acid suppressants than H_2 blockers, PPIs are used

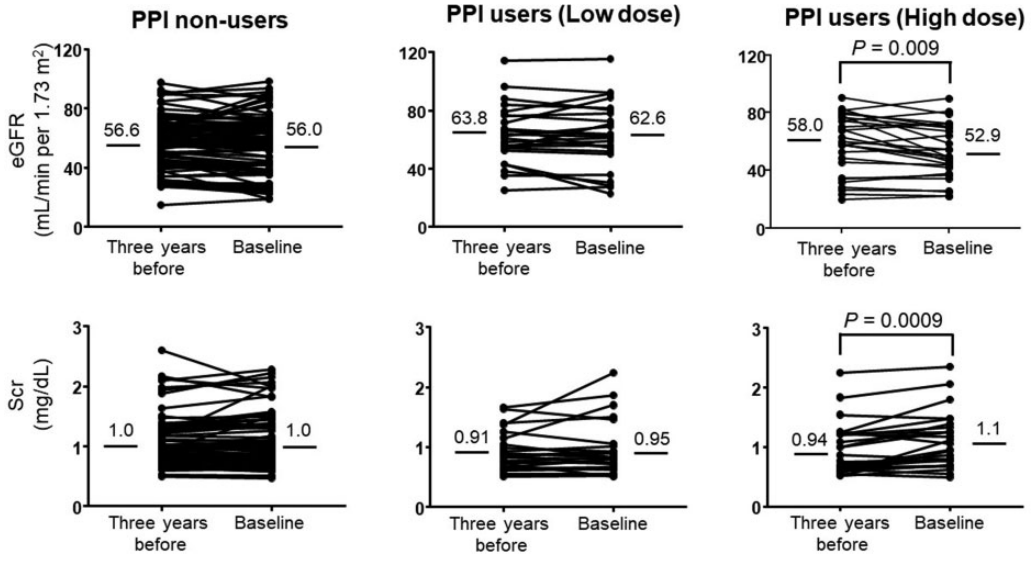

Figure 2. Comparison of eGFR and Scr between three years before treatment and baseline in the high-dose, low-dose, and non-use PPI groups. The *bars* show the mean values. A paired *t*-test was used for the comparison 3 variables three years before treatment and at baseline.
eGFR, estimated glomerular filtration rate; PPI, proton pump inhibitor; Scr, serum creatinine.

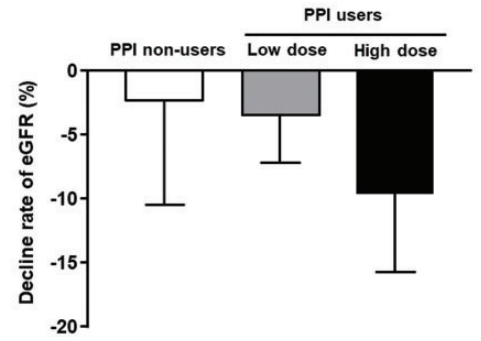

Figure 3. Decline in eGFR from the baseline value in the high-dose, low-dose, and non-use PPI groups. Results are presented as the median and interquartile range.
eGFR, estimated glomerular filtration rate; PPI, proton pump inhibitor.

more extensively in the community and prescribed more often to the elderly and patients with comorbidities. In this study, cumulative PPI exposure for 3 years at low doses was not associated with a decline in kidney function in elderly hypertensive patients, which supports the safety of this dose. However, high doses of PPIs were associated with a decline in kidney function. The associations observed in this study do not allow conclusions regarding causality. Indeed, the mechanisms by which PPI use may lead to CKD remain unknown. Previous reports indicate that omeprazole nephrotoxicity may be related to the induction of oxidative stress and renal tubular cell death.[18] In our study, PPI users mostly received lansoprazole and rabeprazole, and none were administered omeprazole. To elucidate the effects of each PPI on CKD, a prospective randomized study is needed.

Our study had several limitations. First, this study was a retrospective observational study; therefore, we could not follow-up participants. Second, in terms of detection power, the number of subjects in this study was small, and we did not perform a sample

size calculation. As a result, the limited number of samples may have affected the statistical significance of our results. Further studies involving larger numbers of patients are needed to confirm our findings. Finally, our study did not include patients with other pathological backgrounds.

In conclusion, this study showed that a low dose of PPIs was not associated with kidney function decline in elderly hypertensive patients. These findings suggest that it is safe to use PPIs at least at low doses, but further studies are needed.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by JSPS KAKENHI (grant no. JP18K06768). K. Hosohata received research support from the Takeda Science Foundation.

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Supplemental material

Supplemental material for this article is available online.

References

1. Forgacs I and Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 2008; 336: 2–3.
2. Yang YX, Lewis JD, Epstein S, et al. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; 296: 2947–2953.
3. Lambert AA, Lam JO, Paik JJ, et al. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: A systematic review and meta-analysis. *PLoS One* 2015; 10: e0128004.
4. Dial S, Alrasadi K, Manoukian C, et al. Risk of clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: Cohort and case-control studies. *CMAJ* 2004; 171: 33–38.
5. Blank ML, Parkin L, Paul C, et al. A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. *Kidney Int* 2014; 86: 837–844.
6. Harmark L, Van Der Wiel HE, De Groot MC, et al. Proton pump inhibitor-induced acute interstitial nephritis. *Br J Clin Pharmacol* 2007; 64: 819–823.
7. Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: A case series. *Am J Kidney Dis* 2014; 64: 558–566.
8. Klepser DG, Collier DS and Cochran GL. Proton pump inhibitors and acute kidney injury: A nested case-control study. *BMC Nephrol* 2013; 14: 150.
9. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med* 2016; 176: 238–246.
10. Guedes JVM, Aquino JA, Castro TLB, et al. Omeprazole use and risk of chronic kidney disease evolution. *PLoS One* 2020; 15: e0229344.
11. Rodriguez-Poncelas A, Barcelo MA, Saez M, et al. Duration and dosing of proton pump inhibitors associated with high incidence of chronic kidney disease in population-based cohort. *PLoS One* 2018; 13: e0204231.
12. Breton G, Froissart M, Janus N, et al. Inappropriate drug use and mortality in community-dwelling elderly with impaired kidney function–the three-city population-based study. *Nephrol Dial Transplant* 2011; 26: 2852–2859.
13. Hendrix I, Page AT, Korhonen MJ, et al. Patterns of high-dose and long-term proton pump inhibitor use: A cross-sectional study in six south Australian residential aged care services. *Drugs Real World Outcomes* 2019; 6: 105–113.
14. Hata S, Arai M, Maruoka D, et al. Intragastric acidity during the first day

following administration of low-dose proton pump inhibitors: A randomized crossover study. *Clin Res Hepatol Gastroenterol* 2013; 37: 296–301.
15. Lee HJ, Lee H, Oh SH, et al. Chronic kidney disease (ckd) patients are exposed to more proton pump inhibitor (ppi)s compared to non-ckd patients. *PLoS One* 2018; 13: e0203878.
16. Hart E, Dunn TE, Feuerstein S, et al. Proton pump inhibitors and risk of acute and chronic kidney disease: A retrospective cohort study. *Pharmacotherapy* 2019; 39: 443–453.
17. Xie Y, Bowe B, Li T, et al. Proton pump inhibitors and risk of incident ckd and progression to esrd. *J Am Soc Nephrol* 2016; 27: 3153–3163.
18. Fontecha-Barriuso M, Martin-Sanchez D, Martinez-Moreno JM, et al. Molecular pathways driving omeprazole nephrotoxicity. *Redox Biol* 2020; 32: 101464.