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# Impact of Potentially Inappropriate Medications on Kidney Function in Chronic Kidney Disease: Retrospective Cohort Study

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**Keywords**
Potentially inappropriate medication · CKD · Polypharmacy · Chronic renal insufficiency

**Abstract**
***Introduction:*** Chronic kidney disease (CKD) represents a major public health burden. Potential inappropriate medications (PIMs) are common in patients with CKD. However, its impact on kidney outcomes has not been adequately elucidated for middle-aged patients. This study aimed to clarify the prescription status of PIMs for middle-aged patients with CKD and its effect on kidney function decline. ***Methods:*** Using an administrative claims database in Japan, a retrospective cohort study was conducted among Japanese patients with CKD (aged 20–74) who underwent annual health checkups at least three times between April 2008 and December 2020. PIM exposure was defined as medications to be avoided in older adults as defined by the 2019 American Geriatrics Society Beers Criteria. The association between the number of prescribed PIMs and the decline in estimated glomerular filtration rate (eGFR) was examined using logistic regression models adjusted for clinical characteristics and laboratory variables. ***Results:*** A total of 43,143 patients with CKD (mean age 57 years, median eGFR: 52 mL/min/1.73 $m^2$) were analyzed, and approximately 40% of the patients were prescribed one or more PIMs. The most commonly prescribed PIMs were pain medications (18.5%), followed by gastrointestinal medications (9.8%), central nervous system medications (8.6%), and cardiovascular medications (8.6%). After adjustment, exposure to 2 or ≥3 PIMs was associated with an increased risk of 30% eGFR decline (adjusted odds ratio 1.71 [95% confidence interval, 1.24–2.37] and 1.65 [95% confidence interval, 1.08–2.52], respectively) as compared to the control group. ***Conclusion:*** This study showed that middle-aged patients with CKD who were prescribed ≥2 PIM had an increased risk of progression of CKD. Further studies are needed to analyze whether deprescribing steps contribute to reduce PIM prescriptions and prevent CKD progression.



## Introduction

The incidence of chronic kidney disease (CKD) has increased worldwide. In 2017, the global all-age prevalence of CKD was 9.1%, and it had increased to 29.3% since 1990 [1]. Besides, the number of people receiving renal replacement therapy exceeds 2.5 million and is projected to double to 5.4 million by 2030 [2]. Furthermore, CKD is associated with a higher risk of cardiovascular disease (CVD) and mortality [3]. Therefore, preventing CKD progression is an urgent issue for public health.

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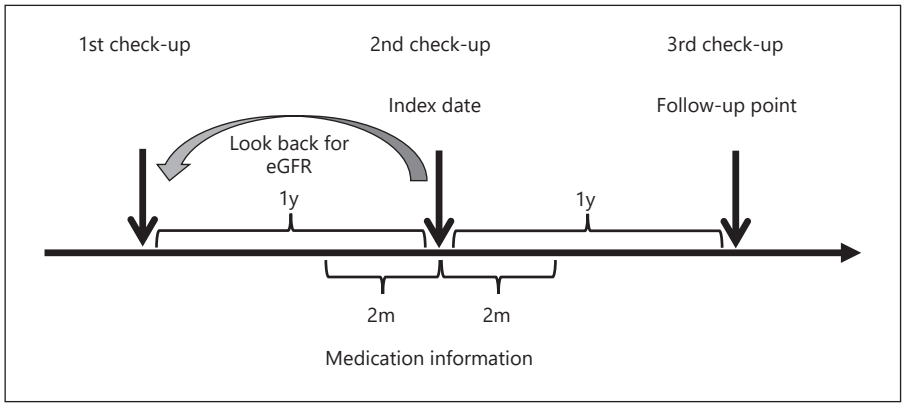


**Fig. 1.** Study timeline.

Polypharmacy, which is often defined as the concomitant use of ≥5 medications [4], is highly prevalent among patients with CKD [5, 6]. Several studies revealed that polypharmacy was linked to a higher risk of frailty, cognitive impairment, frequent hospitalizations, morbidity, and mortality among older adults [7]. Recently, even in younger patients with CKD, polypharmacy has been reported to be associated with renal dysfunction, CVD, and mortality [5, 8, 9]. Meanwhile, an appropriate prescription for optimal control of blood pressure, blood glucose, cholesterol, and uric acid levels prevents CKD progression and CVDs among patients with CKD [10].

Beers [11] or STOPP/START [12] criteria were widely used to evaluate the appropriateness of prescribed medication. It has been reported that patients with polypharmacy or multimorbidity have an increased risk of being prescribed potentially inappropriate medications (PIMs) [13]. The use of PIM can lead to adverse drug events and is the cause of major health concerns in patients with CKD [5, 8, 14]. However, few studies have investigated the associations between PIM and CKD progression. The aim of this study was to clarify the prescription status of PIM for patients with CKD and its effect on kidney function decline using administrative claims data.

## Materials and Methods

*Study Design and Data Source*

We conducted a retrospective cohort study using the administrative claims database obtained from JMDC Inc. (JMDC), Japan [15]. The JMDC collects data from >200 employee-based health insurance plans. The number of cumulative enrollees from 2005 to 2020 was 12.8 million. This database mainly includes the working-age population due to the nature of employee-based insurance. The database includes claims data (diagnoses, procedures, and prescriptions), demographic data, laboratory and measurement data from health check-ups, and facility information. Two types of health check-ups were involved in this database: specific health check-ups for all citizens ages 40–74 years and workplace check-ups for employees provided by their companies. The diagnostic information was coded according to the International Classification of Diseases, 10th revision, and the prescribed medications are coded according to the Anatomical Therapeutic Chemical (ATC) Classification System. Information on over-the-counter (OTC) medications was not available due to not being included in this database.

*Study Subjects and Definition*

We included CKD patients aged ≥20 years who underwent annual health check-ups at least three times in a row between January 2008 and December 2020 in the database. We defined CKD as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 $m^2$, using the equation for the Japanese [16]. To exclude patients with acute kidney injury, we defined the date of the second health check-up as the index date, and we used eGFR at the first check-up to confirm the diagnosis of CKD in a patient. Then, we checked the medication information before and after 2 months of the index date (i.e., a total of 4 months). The follow-up point was at the date of the third check-up (Fig. 1). We excluded patients who had missing serum creatinine or medication information or who had received kidney replacement therapy before participating in the study. In addition, we also excluded patients with a health check-up period of less than 6 months or longer than 18 months.

Body mass index (BMI) was calculated as the ratio of body weight (kilogram) to height squared (square meter). Hypertension was defined as ≥140/90 mm Hg or the use of antihypertensive medications. Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dL, a glycated hemoglobin ≥6.5%, or the use of insulin or oral diabetic medications. Dyslipidemia was defined as a triglyceride level of ≥150 mg/dL, a low-density lipoprotein cholesterol level of ≥140 mg/dL, a high-density lipoprotein cholesterol level of <40 mg/dL, or the use of antihyperlipidemic medications. Proteinuria was defined as ≥+1 on urinary dipstick.

*Exposure and Outcomes*

Exposure to PIM was defined as prescription of medications that are to be avoided in older adults as designated by the 2019 American Geriatrics Society Beers Criteria [11]. We selected these medications because the majority of them were not primarily cleared renally, and there is limited evidence of adverse outcomes of these medications in patients with CKD. We identified PIM using ATC codes and kidney

function (online suppl. Tables S1, S2; see www.karger.com/doi/10.1159/000526326 for all online suppl. material). We included the following therapeutic categories: anticholinergics, antithrombotics, anti-infectives, cardiovascular medications, cardiovascular or hemostasis medications, central nervous system medications, central nervous system and analgesic medications, endocrine, gastrointestinal, genitourinary, hyperuricemia, and pain medications. The primary outcome of this study was a 30% decline in eGFR between the second and third health check-ups. The secondary outcome was the eGFR slope, which demonstrated eGFR changes per year.

*Statistical Analyses*

Baseline demographics and clinical characteristics were expressed as mean with standard deviations, medians with interquartile ranges, or frequency as appropriate. Differences among the groups were evaluated using a Jonckheere-Terpstra trend test or a Cochran-Armitage trend test [17–19]. A logistic regression model was used to estimate the association between the number of PIMs (one, two, and three or more vs. no PIM) and a decline in eGFR. For each analysis, an adjustment with the following models was applied: model 1 included age and gender; model 2 included all of the covariates in model 1 plus BMI, smoking, comorbidities (hypertension, diabetes, and dyslipidemia), and a history of CVD; and model 3 included all of the covariates in model 2 plus serum creatinine at baseline (i.e., at the second health check-up). As for secondary analysis, we compared the eGFR slope among PIM categories using the Jonckheere-Terpstra trend test. In addition, we conducted subgroup analyses to see the effect modification of the association between PIM exposure and 30% eGFR decline by age (<65 or ≥65 years), sex, eGFR (<45 or ≥45 mL/min/1.73 $m^2$), and proteinuria (positive or negative). For the sensitivity analysis, we conducted the logistic regression analysis using the 20% decline in eGFR as the objective variable. The frequencies of missing variables were as follows: BMI (0.1%), smoking history (3%), hypertension (3%), diabetes mellitus (3%), dyslipidemia (2%), CVD history (8%), systolic blood pressure (0.2%), diastolic blood pressure (0.2%), fasting glucose (8%), glycated hemoglobin (9%), triglyceride (0.1%), high-density lipoprotein cholesterol (0.1%), and low-density lipoprotein cholesterol (0.1%), respectively. Thus, we used the multiple imputation method with 20 datasets in all regression analyses. Values of $p < 0.05$ were considered for the determination of statistical significance. All analyses were conducted using STATA MP, version 15.1 (Stata Corp, College Station, TX, USA).

## Results

*Cohort Characteristics and PIM*

Of the 93,846 CKD patients who underwent health check-ups at least three times during the study period, 43,143 were included in the analysis (Fig. 2). In the cohort, 26,141 (60.1%), 11,789 (27.3%), 3,534 (8.2%), and 1,679 (3.9%) patients were prescribed PIM 0, 1, 2, and ≥3, respectively. The mean age was 57 years old, 74% was male, and the median eGFR was 52 mL/min/1.73 $m^2$. Approximately 50% of the patients had hypertension and dyslipidemia, and 16% of the patients had diabetes mellitus. Patients with a higher number of PIMs were older, had a higher BMI, a lower eGFR, and had worse glycemic control. The prevalence of hypertension, diabetes mellitus, smoking, and a history of CVD increased with an increase in PIMs (Table 1).

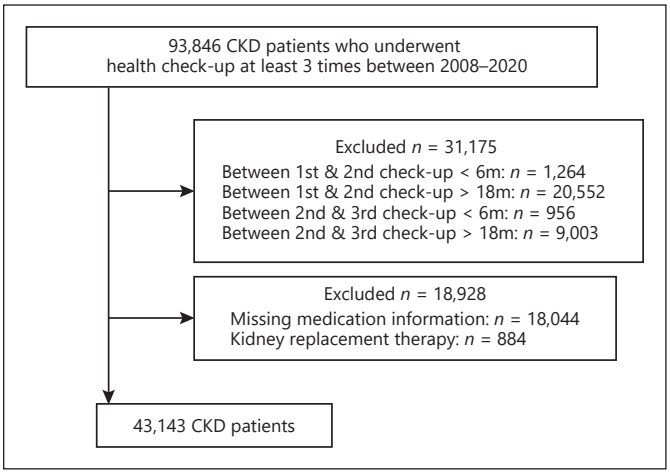


**Fig. 2.** Study patients flowchart.

Approximately 20% of the patients with CKD received pain medications, followed by gastrointestinal (9.8%), central nervous system medications (8.6%), and cardiovascular medications (8.6%). On the other hand, other PIM classes were rarely prescribed (Fig. 3).

*PIM and Kidney Function Decline*

During the observation period, 408 patients with CKD reached an eGFR decline of 30%. In an unadjusted model, PIM exposure of 1, 2, and ≥3 PIMs had a graded association with a 30% eGFR decline versus no PIM. These associations were attenuated after an additional adjustment in model 1 to 3 but remained significant with exposure to 2 and ≥3 PIMs (Table 2). In model 3, the adjusted odds ratios were 1.25 (95% confidence interval [CI]: 0.97–1.60), 1.71 (95% CI: 1.24–2.37), and 1.65 (95% CI: 1.08–2.52) for exposure to 1, 2, ≥3 PIM, respectively. When we used the 20% decline in eGFR as the objective variable for sensitivity analysis, consistent trends were observed between the number of PIM and kidney function decline (Table 3).

PIM exposure showed an adjusted odds ratio of 1.40 (95% CI: 1.13–1.74) for a 30% eGFR decline in overall patients. In subgroup analyses, this association was not modified by baseline age (<65 or ≥65 years), sex, eGFR (<45 or ≥45 mL/min/1.73 $m^2$), and proteinuria (positive or negative; $P$ interaction >0.30 for all) (Fig. 4). Patients with a higher PIM exposure tended to have a larger eGFR slope in secondary analysis; however, this was not statistically significant (Table 4).

**Table 1.** Baseline characteristics of 43,143 CKD patients stratified by PIMs

| | Total<br>*n* = 43,143 | PIM = 0<br>*n* = 26,141 | PIM = 1<br>*n* = 11,789 | PIM = 2<br>*n* = 3,534 | PIM ≥ 3<br>*n* = 1,679 |
|---|---|---|---|---|---|
| Age, years | 57.0±7.9 | 56.9±7.8 | 56.9±8.1 | 57.7±8.2 | 57.2±8.1 |
| Men, % | 74 | 74 | 75 | 75 | 72 |
| BMI, kg/m$^2$ | 24.6±3.8 | 24.5±3.7 | 24.7±3.9 | 24.9±4.1 | 25.3±4.3 |
| Smoke, % | 17 | 16 | 17 | 19 | 20 |
| Hypertension, % | 56 | 55 | 56 | 61 | 61 |
| Diabetes, % | 16 | 15 | 16 | 19 | 19 |
| Dyslipidemia, % | 54 | 54 | 53 | 53 | 54 |
| History of CVD, % | 6 | 5 | 8 | 9 | 10 |
| Serum creatinine, mg/dL | 1.12±0.40 | 1.10±0.35 | 1.14±0.42 | 1.17±0.45 | 1.23±0.68 |
| eGFR, mL/min/1.73 m$^2$ | 52.1±7.3 | 52.6±6.7 | 51.9±7.7 | 50.9±8.5 | 49.8±9.8 |
| Proteinuria, % | 20 | 19 | 21 | 23 | 25 |
| Systolic blood pressure, mm Hg | 125.6±16.8 | 125.6±16.8 | 125.7±16.8 | 126.0±16.9 | 124.6±16.9 |
| Diastolic blood pressure, mm Hg | 78.7±11.7 | 78.9±11.7 | 78.7±11.7 | 78.4±11.7 | 77.6±11.5 |
| Fasting blood glucose, mg/dL | 102.0±21.3 | 101.6±20.4 | 102.2±21.9 | 103.6±23.4 | 103.9±25.3 |
| HbA1c, % | 5.8±0.7 | 5.8±0.7 | 5.8±0.7 | 5.8±0.8 | 5.9±0.9 |
| Triglyceride, mg/dL | 109 (77–157) | 109 (76–155) | 109 (78–159) | 113 (79–165) | 115 (82–167) |
| HDL cholesterol, mg/dL | 56 (47–69) | 57 (48–69) | 56 (47–69) | 56 (46–68) | 55 (46–66) |
| LDL cholesterol, mg/dL | 123 (104–144) | 124 (105–144) | 123 (103–144) | 121 (100–141) | 120 (100–140) |

Values are expressed as mean±SD, medians (IQR range), or number and percentage as appropriate. Differences among groups were evaluated by nonparametric trend tests (Jonckheere-Terpstra trend test or Cochran-Armitage trend test). CKD, chronic kidney disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PIM, potentially inappropriate medication; HbA1c, glycated hemoglobin.

**Table 2.** Logistic regression models for the association between PIMs and 30% eGFR decline

| | Events, *n* | Incident rate ratio | Unadjusted | Adjusted ORs | | |
|---|---|---|---|---|---|---|
| | | | | Model 1 | Model 2 | Model 3 |
| PIM = 0 | 180 | 0.69 | Reference | | | |
| PIM = 1 | 117 | 0.99 | 1.45 (1.14–1.83) | 1.44 (1.14–1.82) | 1.38 (1.09–1.76) | 1.25 (0.97–1.60) |
| PIM = 2 | 57 | 1.61 | 2.36 (1.75–3.19) | 2.45 (1.81–3.30) | 2.04 (1.50–2.78) | 1.71 (1.24–2.37) |
| PIM ≥ 3 | 35 | 2.08 | 3.07 (2.13–4.43) | 3.19 (2.21–4.60) | 2.62 (1.80–3.82) | 1.65 (1.08–2.52) |

Model 1: adjusted for age, sex. Model 2: adjusted for model 1 covariates and BMI, smoking, hypertension, diabetes, dyslipidemia, CVD history. Model 3: adjusted for model 2 covariates and serum creatinine. eGFR, estimated glomerular filtration rate; BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; PIM, potentially inappropriate medication.

## Discussion

By analyzing the administrative claims data of 43,143 Japanese patients with CKD who did not depend on dialysis and underwent health check-ups, we clarified the actual utilization of PIM prescriptions and the relationship between PIM and kidney function decline in this study. Approximately 40% of the CKD patients used one or more PIMs without considering OTC medications. For patients in the present study, pain medications were most frequently used, followed by gastrointestinal, central nervous system, and cardiovascular medications. Furthermore, ≥2 PIMs were associated with a higher risk of eGFR decline compared with less than two PIMs. Our findings emphasize the value of routine assessment of medication use, which may be a useful approach for in-

**Table 3.** Logistic regression models for the association between PIMs and 20% eGFR decline

| | Events, *n* | Incident rate ratio | Unadjusted | Adjusted ORs | | |
|---|---|---|---|---|---|---|
| | | | | Model 1 | Model 2 | Model 3 |
| PIM = 0 | 514 | 1.97 | Reference | | | |
| PIM = 1 | 311 | 2.64 | 1.35 (1.17–1.56) | 1.35 (1.17–1.56) | 1.30 (1.12–1.50) | 1.19 (1.02–1.38) |
| PIM = 2 | 148 | 4.19 | 2.18 (1.81–2.63) | 2.22 (1.84–2.68) | 1.94 (1.60–2.34) | 1.68 (1.38–2.05) |
| PIM ≥ 3 | 91 | 5.42 | 2.86 (2.27–3.59) | 2.93 (2.33–3.68) | 2.51 (1.98–3.18) | 1.84 (1.42–2.38) |

Model 1: adjusted for age, sex. Model 2: adjusted for model 1 covariates and BMI, smoking, hypertension, diabetes, dyslipidemia, CVD history. Model 3: adjusted for model 2 covariates and serum creatinine. eGFR, estimated glomerular filtration rate; BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; PIM, potentially inappropriate medication.

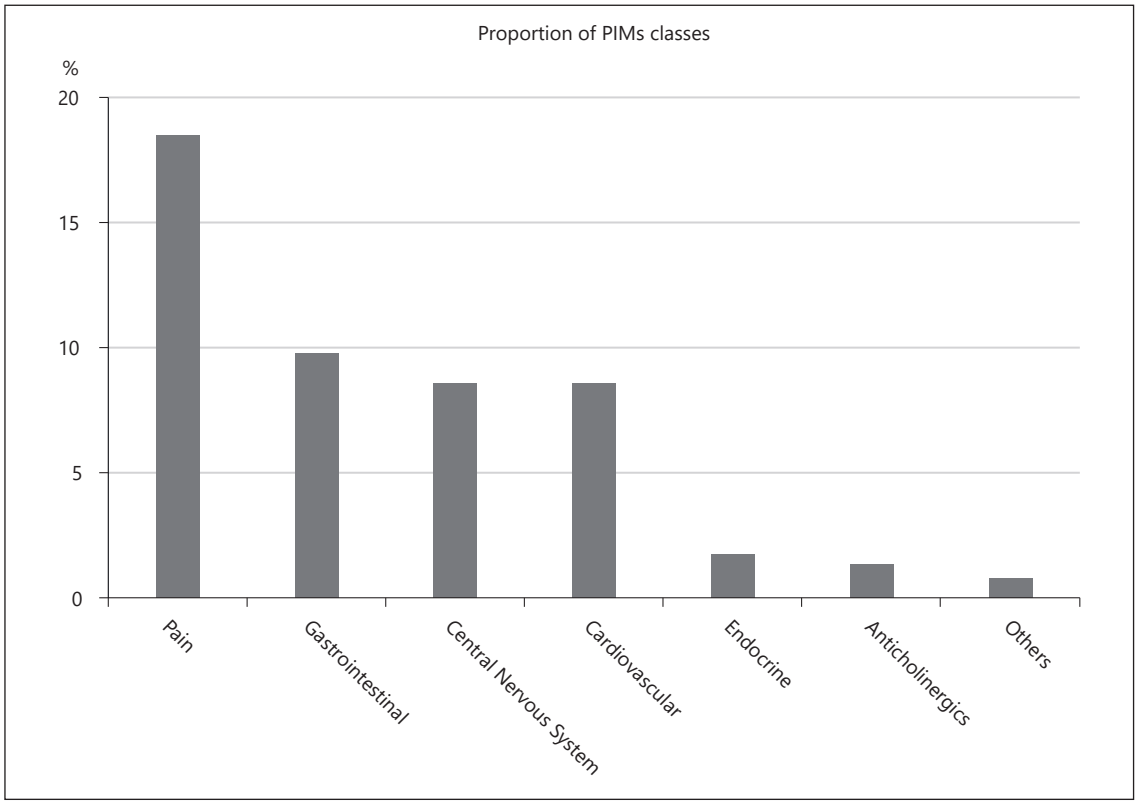


**Fig. 3.** Proportion of PIM classes among 43,143 CKD patients.

hibiting the progression to kidney failure among generalized adults with CKD.

Previous studies reported that prescription of PIMs was common for patients with CKD. The Chronic Renal Insufficiency Cohort (CRIC) study, which is a recent retrospective cohort study of 3,929 adults with CKD (mean age: 63 years, mean eGFR: 44.8 mL/min/1.73 $m^2$) in the USA, showed that 80% of CKD patients had a history of PIM use [8]. Another observational study of 6,392 older adults, including CKD patients, revealed that PIM was prescribed to 32.7% of patients with an eGFR <60 mL/min/1.73 $m^2$ [5]. In Europe, the STOPP/START criteria are widely used, and the percentage of PIM prescriptions was reported to be around 20–50% [14, 20]. In our study, PIMs were prescribed in about 40% of CKD patients, which was comparable to the number of CKD patients

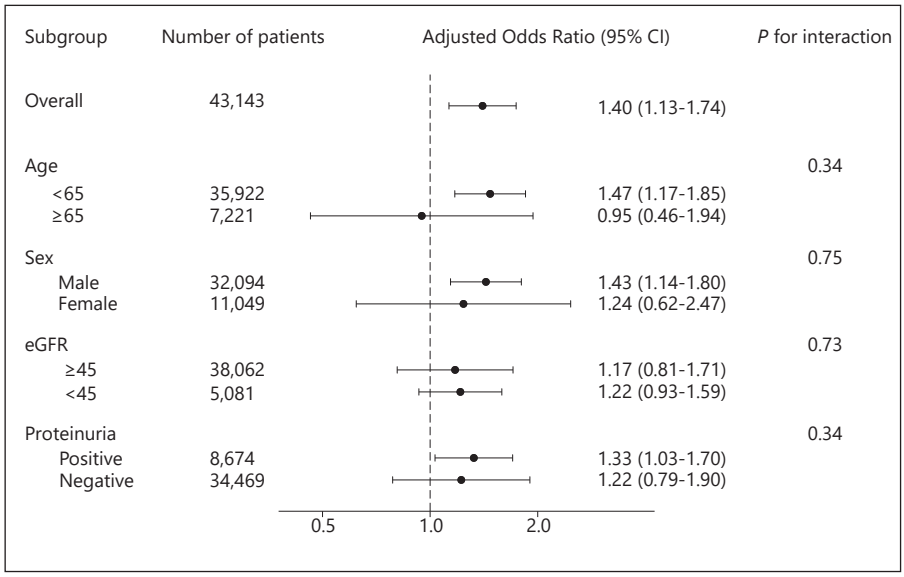


**Fig. 4.** Association of any PIM exposure and eGFR decline stratified by age, sex, eGFR, and proteinuria.

**Table 4.** Trend tests for the association between PIMs and eGFR slope

| | eGFR slope, mL/min/1.73 m$^2$ per year | *p* value for trend |
|---|---|---|
| PIM = 0 | −0.67±4.22 | 0.21 |
| PIM = 1 | −0.67±4.43 | |
| PIM = 2 | −0.77±4.80 | |
| PIM ≥ 3 | −0.72±5.03 | |

Differences among groups were evaluated by nonparametric trend test (Jonckheere-Terpstra trend test). eGFR, estimated glomerular filtration rate; PIM, potentially inappropriate medication.

with PIM prescriptions as reported in previous studies from the USA and Europe. In the CRIC study, many subjects were prescribed proton pump inhibitors (PPIs), α-blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs). When compared to patients aged ≥65, pain management medications such as NSAIDs and skeletal muscle relaxants, anticholinergic drugs, and antidepressants were prescribed relatively frequently in patients <65 years of age [8]. In the Atherosclerosis Risk in Communities (ARIC) study, first-generation antihistamines, benzodiazepines, estrogens, and zolpidem were commonly prescribed, and it was reported that the higher number of prescriptions caused the higher prescription of PIM [5]. While our study included slightly younger patients with CKD than previous studies, PIM prescriptions were similar to previous studies.

The findings of our study suggest that exposure to two or more prescriptions of PIM accelerates the progression of CKD. However, one recent retrospective cohort study in the CRIC study did not show an association between PIMs and CKD progression [8]. Presumably, this may have occurred because the CRIC study used end-stage renal disease or the composite endpoint of end-stage renal disease and a halving of eGFR in the first year of PIM exposure. Efficacy and safety in treating patients with CKD has been assessed using a doubling of serum creatinine levels or a halving of GFR as an endpoint for CKD progression. However, those endpoints require long durations of follow-up and large sample sizes in clinical trials. Therefore, as an alternative endpoint for CKD progression, a 30–40% decrease in eGFR over 2 to 3 years is being used widely [21]. Recently, it has been suggested that if the sample size is sufficient, the amount of change in eGFR per year (i.e., eGFR slope) might be a proper surrogate endpoint of CKD progression in patients with early-stage CKD [22, 23]. In our study, two or more PIM showed significantly higher odds of a 20–30% reduction in eGFR. While the eGFR slope tended to increase with the number of PIMs, it was not statistically significant. One of the reasons for this was that we calculated eGFR only at two time points, and the estimation accuracy might not be sufficient.

In this study, pain medications, including NSAIDs, were the most common, and it has been widely reported that the use of NSAIDs was a risk factor for acute kidney injury and deteriorated renal function [24]. Thus, NSAIDs should be avoided for patients with moderate-to-ad-

vanced CKD. Further, patients may have been prescribed gastrointestinal medications, including PPIs and histamine-2 receptor antagonists (H2RAs), to prevent gastrointestinal ulcers due to the side effects of NSAIDs; hence, it may not be directly related to the decrease in renal function. Patients with CKD have several problems with H2RAs, such as tolerance, developing cognitive impairment, and the necessity for dose reduction. Compared to H2RAs, PPIs have a strong efficacy profile for decreasing gastric acid secretion and are relatively easy to use in patients with CKD due to their hepatic metabolism. However, in recent years, PPI use has been demonstrated to increase the risk for hypomagnesemia, acute kidney injury, and acute interstitial nephritis [25]. Therefore, providers should limit the duration as minimal as possible and consider monitoring eGFR and serum magnesium levels.

In recent years, the concept of "deprescribing" has been brought to public attention [26]. The process of deprescribing consists of the following five steps: (1) reconcile all medications according to indication; (2) assess the appropriateness of each medication considering the risks and benefits of use; (3) assess each medication for eligibility to be discontinued; (4) prioritize medications for discontinuation; and (5) implement and monitor medication discontinuation. Applying these steps to patients with CKD may reduce PIM prescriptions [27–29]. Furthermore, we speculate that promoting education on deprescription for the general population with or without CKD in Japan would deepen the understanding of PIMs, which may effectively prevent the progress of CKD in the future.

The strength of this study was that it used large-scale administrative claims data throughout Japan. However, several limitations of this study should be acknowledged. First, JMDC is a database based on claims received by multiple health insurance societies. Therefore, the percentage of those aged 65 and over is small, as compared to the actual demographic distribution in Japan. Originally, the Beers Criteria were proposed for the elderly aged 65 and over. However, patients with CKD have a greater risk of geriatric complications than the age-matched general population [30]. In addition, patients with CKD have decreased renal function. Thus, we must take into consideration adverse drug effects similar to those experienced by older adults when we prescribe the medications for CKD patients. Second, we were unable to assess OTC and adherence to medications. Thus, PIMs may have been underestimated or overestimated in our study. In Japan, the cost of a consultation with a physician is relatively low; hence, self-medication is not as prevalent as it is in the Western countries. Additionally, recent studies reported that adherence to medications in the Japanese population was relatively high, compared to previous reports from Western countries [31]. Therefore, these limitations would likely have a minimal impact on our study findings. Third, confounding by the reason for prescription could not be captured because we could not adjust the severity of comorbidities or responsiveness to the medications.

In summary, these analyses of PIM use and risk of kidney function decline among patients with CKD demonstrate that PIM use was highly prevalent and associated with an increased risk of CKD progression in those who were prescribed ≥2 PIMs. Further studies are needed to determine whether the deprescribing step contributes to reducing PIM prescriptions and preventing CKD progression.


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## Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Kyoto University Graduate School and the Faculty of Medicine (Acceptance No. R3076). The need to obtain patient consent was waived due to anonymized data.

## Conflict of Interest Statement

Koji Kawakami has received research funds from Eisai Co., Ltd.; Kyowa Kirin Co., Ltd.; Sumitomo Dainippon Pharma Co., Ltd.; Pfizer Inc.; Stella Pharma Corporation; CMIC Co., Ltd.; Suntory Beverage & Food Ltd.; Mitsubishi Corporation; and Real World Data Co., Ltd.; consulting fees from LEBER Inc.; JMDC Inc.; Shin Nippon Biomedical Laboratories Ltd.; Kaken Pharmaceutical Co., Ltd.; and Advanced Medical Care Inc.; executive compensation from Cancer Intelligence Care Systems, Inc.; honorarium from Mitsubishi Chemical Holdings Corporation; Mitsubishi Corporation; Pharma Business Academy; and Toppan Inc.; and holds stock in Real World Data Co., Ltd.


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## Author Contributions

Hiroshi Kimura, Satomi Yoshida, Masato Takeuchi, and Koji Kawakami conceived and designed this study, interpreted the data, and contributed to critical revision for important intellectual content. Hiroshi Kimura and Satomi Yoshida analyzed the data. Hiroshi Kimura, Satomi Yoshida, and Masato Takeuchi drafted the manuscript. Koji Kawakami gave final approval of the submitted manuscript.

## Data Availability Statement

Data sharing is not permitted under JMDC policy. If readers are interested in our dataset, please contact JMDC for data availability (https://www.jmdc.co.jp/).

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