



Association of Polypharmacy with Kidney Disease Progression in Adults with CKD

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Abstract

Background and objective Polypharmacy is common in patients with CKD and reportedly associated with adverse outcomes. However, its effect on kidney outcomes among patients with CKD has not been adequately elucidated. Hence, this investigation was aimed at exploring the association between polypharmacy and kidney failure requiring KRT.

Design, setting, participants, and measurements We retrospectively examined 1117 participants (median age, 66 years; 56% male; median eGFR, 48 ml/min per 1.73 m²) enrolled in the Fukushima CKD Cohort Study to investigate the association between the number of prescribed medications and adverse outcomes such as kidney failure, all-cause mortality, and cardiovascular events in Japanese patients with nondialysis-dependent CKD. Polypharmacy and hyperpolypharmacy were defined as the regular use of 5–9 and ≥10 medications per day, respectively.

Results The median number of medications was eight; the prevalence of polypharmacy and hyperpolypharmacy was each 38%. During the observation period (median, 4.8 years), 120 developed kidney failure, 153 developed cardiovascular events, and 109 died. Compared with the use of fewer than five medications, adjusted hazard ratios (95% confidence intervals) associated with polypharmacy and hyperpolypharmacy were 2.28 (1.00 to 5.21) and 2.83 (1.21 to 6.66) for kidney failure, 1.60 (0.85 to 3.04) and 3.02 (1.59 to 5.74) for cardiovascular events, and 1.25 (0.62 to 2.53) and 2.80 (1.41 to 5.54) for all-cause mortality.

Conclusions The use of a high number of medications was associated with a high risk of kidney failure, cardiovascular events, and all-cause mortality in Japanese patients with nondialysis-dependent CKD under nephrology care.

CJASN 16: ●●–●●, 2021. doi: <https://doi.org/10.2215/CJN.03940321>

Introduction

The incidence of CKD has increased worldwide, and it represents a major global public burden (1). This progressive disease leads to kidney failure and is associated with a higher risk of cardiovascular disease and mortality (2). Multiple comorbid conditions, such as hypertension, diabetes mellitus, and dyslipidemia, are well-known risk factors for the incidence and progression of CKD (3,4). Multimorbidity is often defined as having two or more coexisting chronic morbidities and may lead to polypharmacy, increase the treatment burden, and negatively affect patients' quality of life (5). Polypharmacy is linked to a higher risk of medication-related problems, frequent hospitalizations, morbidity, mortality, and higher financial burden in terms of health care costs (6,7). Therefore, the appropriate management of multimorbidity to minimize polypharmacy is crucial for patients with CKD. Several studies have evaluated the kidney function decline associated with polypharmacy (8–10). However, the effect of polypharmacy on patients with

nondialysis-dependent CKD has not been adequately elucidated. Therefore, in this study, we investigated the associations between polypharmacy and kidney failure requiring KRT over 5 years with annual assessments among Japanese patients with nondialysis-dependent CKD in the Fukushima CKD cohort study.

Materials and Methods

Study Population (Fukushima CKD Cohort)

The Fukushima CKD Cohort, a subcohort of the Fukushima Cohort Study, was a prospective survey aimed at investigating the characteristics of and outcomes for patients with CKD who were not on dialysis at the Fukushima Medical University Hospital (11–14). This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (Reg. No. UMIN000040848). Participants were recruited between June 2012 and July 2014, and a total of 2724 participants registered for the Fukushima Cohort study. The inclusion criteria were as

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follows: (1) patients aged ≥ 18 years, (2) Japanese patients living in Japan, and (3) patients with CKD defined as an eGFR of < 60 ml/min per 1.73 m² or proteinuria (positive dipstick results, $\geq 1+$), with stable kidney function for ≥ 3 months before entry into the study. The eGFR was calculated using the estimation equation for Japanese patients with CKD (15). The exclusion criteria were as follows: (1) patients who received KRT in the 3 months before study entry, (2) patients with an active malignancy, (3) patients with an infectious disease, (4) pregnant patients, and (5) patients with a history of organ transplantation. We also excluded patients for whom data on serum creatinine or urine test results were missing. All participants were under the care of specialists in nephrology or diabetology. The study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee of Fukushima Medical University (Acceptance No. 1456, 2001). All participants provided written informed consent for participation.

Data Collection

Information on participants' demographic characteristics, presence of comorbidities (hypertension, diabetes mellitus, and dyslipidemia), and prescribed medications at baseline were obtained from the participants' medical records or blood examination results obtained at registration. Medications were confirmed and coded on the basis of the Japan Standard Commodity Classification by physicians. The medication information was collected only at baseline, and medications prescribed by other hospitals were obtained if they were mentioned in the medical record. Body mass index (BMI) was calculated as the ratio of body weight (kg) to height (m²). Blood pressure was measured by trained staff by using a standard sphygmomanometer or an automated device while in a seated position after the patient had rested for 5 minutes. Hypertension was defined as a systolic blood pressure of ≥ 140 mm Hg, a diastolic blood pressure of ≥ 90 mm Hg, or the use of antihypertensive drugs. Diabetes mellitus was defined as a fasting plasma glucose concentration of ≥ 126 mg/dl or a glycated hemoglobin value of $\geq 6.5\%$ (National Glycohemoglobin Standardization Program) or use of insulin or oral antidiabetic drugs. Dyslipidemia was defined as a triglyceride concentration of ≥ 150 mg/dl, LDL cholesterol concentration of ≥ 140 mg/dl, HDL cholesterol concentration of < 40 mg/dl, or the use of antihyperlipidemic drugs.

Exposure and Outcomes

The primary exposure of interest for this study was the total number of prescribed medications without including over-the-counter (OTC) medications. The participants were categorized into three groups on the basis of the number of medications used: nonpolypharmacy, zero to four medications; polypharmacy, five to nine medications, and hyperpolypharmacy, ≥ 10 medications. Participants received regular follow-up care of specialists in nephrology or diabetology in the outpatient ward and were followed up until study withdrawal, loss to follow-up (*i.e.*, transferred to other medical institutions or started maintenance dialysis therapy), or end of the study period (June 30, 2019). The primary outcome was kidney failure requiring KRT. The

secondary outcomes were cardiovascular events, including fatal or nonfatal myocardial infarction, angina pectoris, congestive or acute heart failure, arrhythmias, cerebrovascular disorder, chronic arteriosclerosis obliterans, aortic disease, and sudden death, and all-cause mortality. Information on dialysis, kidney transplant, and cardiovascular events was captured from the medical record.

Statistical Analyses

All variables were expressed as mean \pm SD, medians with interquartile ranges, or frequency as appropriate. Differences in baseline characteristics among the groups were evaluated by a nonparametric trend test (Cuzick's test) (16) or Cochran-Armitage trend test (17–19). The Cox proportional hazard model was used to examine the association between polypharmacy and incidences of kidney failure, cardiovascular events, and all-cause mortality in patients with CKD. The proportional hazards assumptions were tested using Schoenfeld residuals. For each analysis, hierarchical adjustment with the following models was applied: (1) Model 1, which included age, sex, BMI, comorbidities (hypertension, diabetes, and dyslipidemia), a history of cardiovascular disease, and smoking history; and (2) Model 2, which included all of the covariates in Model 1 plus eGFR, serum albumin, hemoglobin, and proteinuria. Model 2 was defined as the primary model of interest. To evaluate for nonlinear associations between the number of medications (continuous) and each of the outcomes, we used Model 2–adjusted restricted cubic spline functions with four knots at the fifth, 35th, 65th, and 95th percentiles of each index. As a secondary analysis, we assessed which type of medication led to excess risk for kidney failure, cardiovascular events, and all-cause mortality using Cox proportional hazard model. We adjusted with the number of medications as a continuous variable and all of the variables on Model 2. The frequencies of missing variables, namely, hemoglobin, dyslipidemia, BMI, smoking history, and serum albumin level were 2%, 2%, 3%, 6%, and 10%, respectively. To account for missing variables, a multiple imputation method with 10 datasets was used in all analyses. All analyses were conducted using STATA MP, version 15.1 (Stata Corp, College Station, TX).

Results

Participants Characteristics and Medications

Among 2724 participants enrolled in the Fukushima Cohort Study, 1117 participants who met our inclusion criteria were enrolled in our analysis (Figure 1). The median participant age was 66 years, 56% of the participants were male, the median eGFR was 48 ml/min per 1.73 m², 87% of the participants had hypertension, and 49% had diabetes. The median number of medications was eight, and polypharmacy and hyperpolypharmacy were noted in 429 (38%) and 427 (38%) participants, respectively. Participants with a higher number of medications were older, had a higher BMI, a lower eGFR, a lower serum albumin level, and a lower hemoglobin level. The prevalence of hypertension and diabetes, smoking history, and a history of cardiovascular disease was more frequent in people with a higher number of medications ($P_{\text{trend}} < 0.001$ for all), whereas the

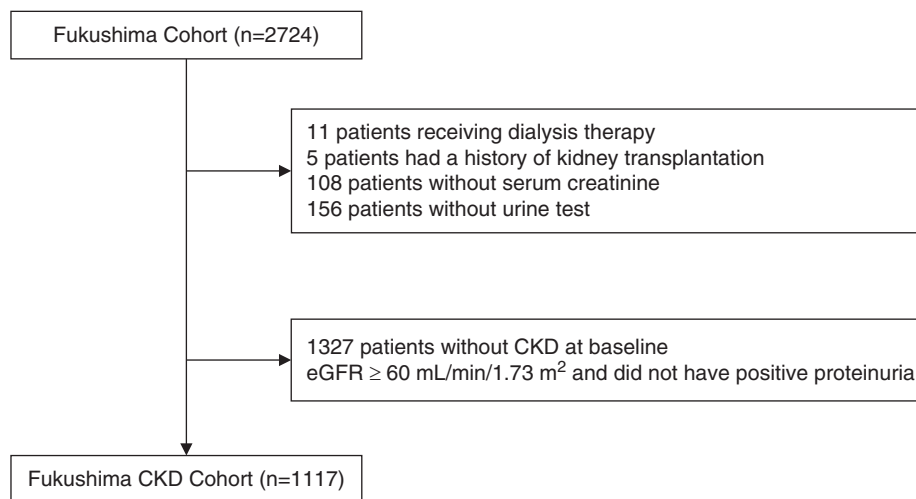


Figure 1. | Study flow diagram.

prevalence of proteinuria did not differ among the groups (Table 1).

Approximately 80% of the participants received antihypertensive medications, with angiotensin II receptor blockers (ARBs) the most common antihypertensive class. Calcium channel blockers, lipid-lowering, and diabetes medications were also commonly used by this population (Figure 2).

Polypharmacy and Kidney Failure

During the median observation period of 4.8 years, 120 of the 1117 participants developed kidney failure. Analysis using the Cox regression model revealed that participants with polypharmacy and hyperpolypharmacy were at significantly higher risks for kidney failure than the participants who received fewer than five medications (Table 2). These relationships were attenuated after an additional adjustment but remained significant with hyperpolypharmacy in Model 2. The adjusted hazard ratios (HRs) were 2.28 (95% confidence interval [95% CI], 1.00 to 5.21) and

2.83 (95% CI, 1.21 to 6.66) for polypharmacy and hyperpolypharmacy, respectively (reference: the number of medications was fewer than five). Using restricted cubic spline functions, there was a nonlinear relationship between total number of medications and the risk of kidney failure (Figure 3A).

When we assessed the relationship between each medication type and kidney failure, we found that a combination of renin-angiotensin-aldosterone system inhibitors (ARB, angiotensin-converting enzyme inhibitor, and direct renin inhibitor) and diuretics, ARB, hyperuricemia medication, and aspirin showed significant association with kidney failure (Supplemental Table 1).

Polypharmacy and Cardiovascular Event and All-Cause Mortality

During the follow-up periods, 153 of the 1117 participants developed cardiovascular events and 109 died. Assessment of the relationship using cubic spline function between the number of medications and cardiovascular

Table 1. Baseline characteristics of 1117 participants in the Fukushima Cohort Study with nondialysis-dependent CKD

Characteristics	Total	Nonpolypharmacy	Polypharmacy	Hyperpolypharmacy
<i>n</i>	1117	261	429	427
Medication	8 (5–12)	3 (2–4)	7 (6–8)	13 (11–16)
Age, yr	66 (58–75)	62 (51–70)	66 (59–74)	70 (62–77)
Men	631 (56)	149 (57)	244 (57)	238 (56)
BMI, kg/m ²	24.1 (21.8–27.0)	23.5 (21.4–25.5)	24.3 (22.0–27.3)	24.6 (21.6–27.6)
Hypertension	972 (87)	186 (71)	391 (91)	395 (93)
Diabetes mellitus	544 (49)	61 (23)	207 (48)	276 (65)
Dyslipidemia	759 (70)	123 (49)	303 (73)	333 (78)
Cardiovascular disease history	150 (13)	10 (4)	31 (7)	109 (26)
Smoking (current and/or ex)	395 (38)	73 (30)	142 (35)	180 (45)
eGFR, ml/min per 1.73 m ²	48 (35–57)	55 (46–63)	49 (36–58)	43 (30–54)
Albumin, g/dl	3.9±0.5	4.0±0.4	3.9±0.4	3.7±0.5
Hemoglobin, g/dl	12.8±1.8	13.4±1.6	13.0±1.8	12.2±1.8
Proteinuria	513 (46)	123 (47)	197 (46)	193 (45)

Values are expressed as mean±SD, medians (interquartile range), or number and percentage as appropriate. Differences among groups were evaluated by nonparametric trend tests (Cuzick's test) or Cochran-Armitage trend test. BMI, body mass index.

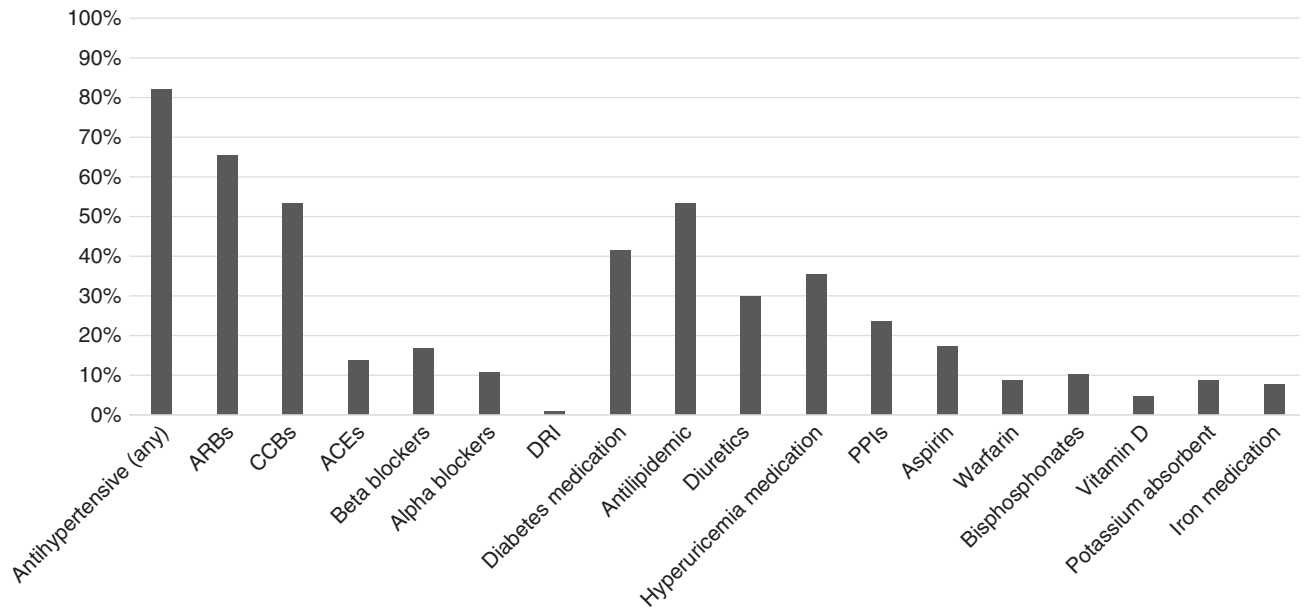


Figure 2. | Proportion of medications used at baseline among 1117 participants with nondialysis-dependent CKD. ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; DRI, direct renin inhibitor; PPI, proton pump inhibitor.

events, all-cause mortality revealed that increasing numbers of medications associated with higher risk after five medications (Figure 3, B and C). However, only hyperpolypharmacy showed a significantly higher risk for cardiovascular events and all-cause mortality. The adjusted HRs for hyperpolypharmacy-related cardiovascular events and all-cause mortality were 2.93 (95% CI, 1.55 to 5.53) and 2.54 (95% CI, 1.29 to 4.99), respectively (Table 2).

Discussion

In this observational study of Japanese patients with nondialysis-dependent CKD, approximately 75% of the participants used five or more medications without including OTC medications. We found that a higher number of

medications were associated with higher risks of kidney failure, cardiovascular events, and death, especially taking ≥ 10 medications. Furthermore, combination of renin-angiotensin-aldosterone system inhibitors and diuretics, ARB, antilipidemics, and aspirin led to excess risk for kidney failure. Our findings emphasize the value of routine assessment of medication use and suggest that minimizing unnecessary medication use may be a useful approach for inhibiting the progression to kidney failure among patients with nondialysis-dependent CKD.

The findings of our study support those of previous investigations in which an association between polypharmacy and adverse kidney outcomes was reported. A recent prospective observational study of 270 older adults (mean age, 70.3 years; eGFR, 81.6 ml/min per 1.73 m²) in

Table 2. Associations between polypharmacy and kidney failure, cardiovascular events, and all-cause mortality

Outcomes	Number of Events	Incident Rate (95% Confidence Interval) (per 100 Person-Years)	Adjusted Hazard Ratios (95% Confidence Interval)	
			Model 1	Model 2
Kidney failure	Nonpolypharmacy	7	0.53 (0.25 to 1.10)	Reference
	Polypharmacy	48	2.29 (1.72 to 3.04)	4.51 (2.01 to 10.14)
	Hyperpolypharmacy	65	3.66 (2.87 to 4.67)	8.42 (3.72 to 19.05)
Cardiovascular events	Nonpolypharmacy	13	0.98 (0.57 to 1.69)	Reference
	Polypharmacy	46	2.19 (1.64 to 2.93)	1.83 (0.97 to 3.46)
	Hyperpolypharmacy	94	2.95 (2.51 to 3.45)	3.80 (2.03 to 7.13)
All-cause death	Nonpolypharmacy	12	0.89 (0.51 to 1.57)	Reference
	Polypharmacy	27	1.23 (0.84 to 1.79)	1.34 (0.67 to 2.70)
	Hyperpolypharmacy	70	3.61 (2.86 to 4.56)	3.61 (1.86 to 7.02)

Model 1: adjusted for age, sex, BMI, comorbidities (hypertension, diabetes, and dyslipidemia), history of cardiovascular disease, and smoking history. Model 2: adjusted Model 1 plus eGFR, serum albumin, hemoglobin, and proteinuria. BMI, body mass index.

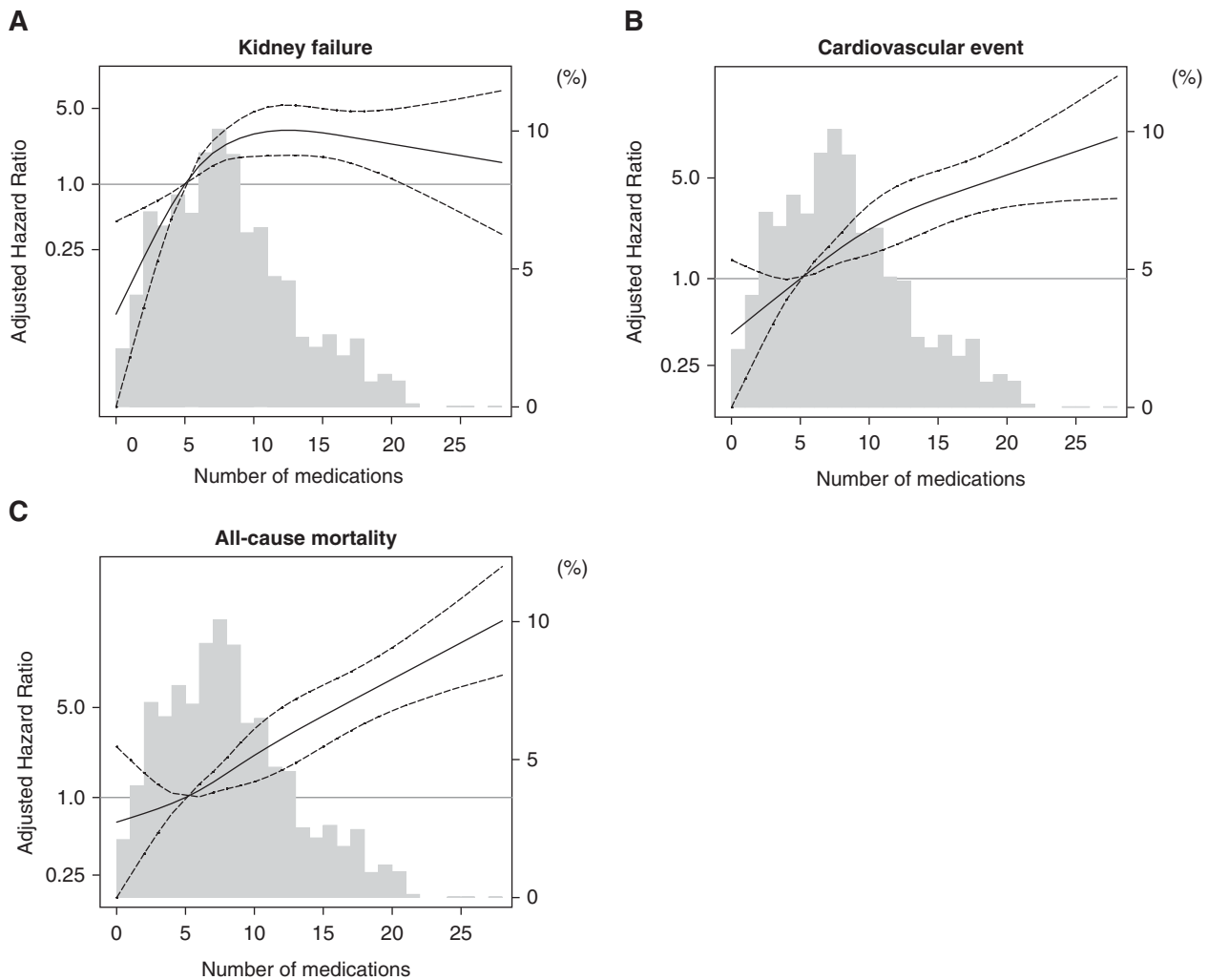


Figure 3. | Distributions and Model 2-adjusted restricted cubic splines comparing the relationship of number of medications with adverse outcomes among 1117 participants with nondialysis-dependent CKD. Solid lines represent adjusted hazard ratio estimates and dashed lines represent 95% confidence intervals (95% CIs), respectively. (A) Kidney failure, (B) cardiovascular events, and (C) all-cause mortality. Model 2: adjusted for age, sex, BMI, comorbidities (hypertension, diabetes, and dyslipidemia), history of cardiovascular disease, smoking history, eGFR, serum albumin, hemoglobin, and proteinuria. BMI, body mass index.

Switzerland revealed that every additional prescribed medication had a harmful effect on kidney function and led to a decrease in eGFR by 0.64 ml/min per 1.73 m² per drug over 24 months (10). Another longitudinal study in 406 nursing home residents (mean age, 85.0 years; eGFR, 54.0 ml/min per 1.73 m²) showed the number of medications received at baseline was an independent risk factor for a decline of >3 ml/min per 1.73 m² in kidney function in 1 year (8). A nested case-control study conducted in South Korea by using a population-based cohort showed that polypharmacy was significantly associated with a higher risk of kidney dysfunction (eGFR <60 ml/min per 1.73 m² or a decline rate of ≥10% versus the baseline value) (9). Our study not only verifies the conclusions of these previous studies but also shows a higher number of medications was associated with CKD progression to kidney failure in patients with moderate to severe CKD.

Polypharmacy is common in older adults, and several observational studies have examined the negative effects of

polypharmacy on various health outcomes, such as frailty, hospitalization, and mortality (20–25). However, not all studies have a good adjustment for comorbidities. Adjustment for comorbidity is crucial to avoid confounding by indication. In our study, associations between hyperpolypharmacy and CKD progression, cardiovascular events, and all-cause mortality remained robust against adjustment for comorbidities. However, the severity of comorbidities and responsiveness to medications could not be adjusted.

Although polypharmacy is highly prevalent in patients with CKD, most studies on polypharmacy have focused on community-dwelling older adults. Therefore, specific guidance for safe medication management in patients with CKD does not exist. According to a recent systematic review, polypharmacy is usually defined as the regular use of five or more medications; the second most common definition is the use of six or more medications daily (26). However, in most studies including CKD patients, the average number of medications was higher than five

medications. In the ARIC study, which was a prospective cohort study in 6352 older adults with and without CKD, the mean number of medications used was higher among those with CKD than in those without CKD (mean, 7.0 versus 5.7) (27). In observational studies in 3033 and 5217 patients under the routine care of nephrologists conducted in France and Germany, the median number of medications per day was eight (28,29). All these studies showed that a higher CKD stage was associated with a higher number of medications. In our study, the participants received a similar number of medications, and we observed the same association between a lower eGFR and a higher number of medications at baseline.

Although we observed that a higher number of medications was associated with a higher risk of kidney failure, it remains unclear whether altering the number of medications could have a role in lowering the risk of kidney failure. However, our findings suggest that aiming to achieve a lower medication burden can potentially reduce the risk of kidney failure among patients with moderate to severe CKD, which could reduce the risk of other poor outcomes, such as hospitalization, cardiovascular events, and all-cause mortality. In this study, there were significant associations of only hyperpolypharmacy with kidney failure, cardiovascular events, and all-cause mortality, not in polypharmacy. Patients with CKD have multiple comorbidities and are at high risk of kidney failure and cardiovascular disease. Thus, patients with CKD tend to be prescribed medications with renoprotective and preventing cardiovascular events, such as renin-angiotensin-aldosterone system inhibitors and statin. Moreover, it is widely known that appropriate management of blood pressure, glucose, and lipids is essential for preventing CKD progression. We have speculated that well-managed patients might be included in polypharmacy group (*i.e.*, taking 5–9 medications) under the care of specialists in nephrology or diabetology.

Deprescribing, which is defined as “the systemic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits,” is gaining attention in terms of identifying and eliminating inappropriate medications (30–32). Although the guidance regarding deprescribing for patients with nondialysis-dependent CKD is scarce, several studies have reported that deprescribing or medication reconciliation improves adverse outcomes in patients on dialysis (33,34).

This study has several limitations. First, because they have been derived from an observational study, the associations described may not reflect a cause-and-effect relationship between polypharmacy and kidney failure. Second, a single determination of the number of medications used, and lack of the information on OTC medications and medications prescribed by other hospitals might have led to some misclassification of polypharmacy. Furthermore, in a previous study on adherence, it was reported that 50%–80% of patients did not take their medication as prescribed (35). We were unable to assess medication adherence in this study. Thus, polypharmacy may have been overestimated in our study. Third, information on nonsteroidal anti-inflammatory drug (NSAID) use was also lacking in our study. A subgroup analysis of an observational study conducted in Switzerland showed that a higher cumulative number of NSAIDs was associated with a three-

fold higher decline in eGFR over 24 months (10). Furthermore, the combined use of NSAIDs with diuretics and/or renin-angiotensin system inhibitors resulted in a higher incidence of AKI (36). In this study, we could not evaluate the effects of specific combinations of medications, such as NSAIDs and diuretics, NSAIDs and renin-angiotensin-aldosterone system inhibitors. However, the combination of renin-angiotensin-aldosterone system inhibitors and diuretics was associated with kidney failure in our secondary analysis.

Few participants in our cohort used NSAIDs because most nephrologists refrain from prescribing NSAIDs to patients with CKD, given their association with higher rates of AKI (37), suggesting that this limitation would likely have a minimal effect on the study findings. Fourth, polypharmacy might be associated with adverse outcomes due to often being used as a surrogate marker for comorbidities. In this study, we adjusted for several comorbidities (hypertension, diabetes, and dyslipidemia) in all analyses and found that comorbidities did not have significant associations (data not shown). Finally, we only included Japanese patients with CKD. Compared with patients with CKD in Western countries, in Japanese patients with nondialysis-dependent CKD under nephrology care, the rate of initiation of KRT was higher than the death rate due to cardiovascular events (38). Therefore, racial differences may affect the risk of kidney failure, cardiovascular events, and all-cause mortality.

In conclusion, our analysis provides longitudinal evidence of an association between a higher number of medications and a higher risk of kidney failure and cardiovascular events and all-cause mortality in Japanese patients with nondialysis-dependent CKD under nephrology care. Although further studies are needed on the association between polypharmacy and adverse outcomes among patients with CKD, polypharmacy could be used to identify patients with CKD who are high risk that could benefit from more intensive follow-up/therapies to reduce known risk factors for poor outcomes.

Disclosures

K. Asahi reports receiving research funding from Chugai Pharmaceutical, Kowa Pharmaceutical, and Ono Pharmaceutical. J.J. Kazama reports receiving research funding from Chugai, Kissei, Kyowa-Kirin, Ono, and Tanabe-Mitsubishi. All remaining authors have nothing to disclose.

Funding

None.

Acknowledgments

The authors would like to thank Ms. Ayumi Kanno for her assistance in data collection and Editage (www.editage.com) for English language editing.

Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.03940321/-/DCSupplemental>.

Supplemental Table 1. Associations between each medication and kidney failure, cardiovascular events, and all-cause mortality.

References

- Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, Chen J, He J: A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 88: 950–957, 2015
- Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
- Gullion CM, Keith DS, Nichols GA, Smith DH: Impact of comorbidities on mortality in managed care patients with CKD. *Am J Kidney Dis* 48: 212–220, 2006
- Tonelli M, Wiebe N, Guthrie B, James MT, Quan H, Fortin M, Klarenbach SW, Sargious P, Straus S, Lewanczuk R, Ronksley PE, Manns BJ, Hemmelgarn BR: Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. *Kidney Int* 88: 859–866, 2015
- Fraser SDS, Roderick PJ, May CR, McIntyre N, McIntyre C, Fluck RJ, Shardlow A, Taal MW: The burden of comorbidity in people with chronic kidney disease stage 3: A cohort study. *BMC Nephrol* 16: 193, 2015
- Ernst FR, Grizzle AJ: Drug-related morbidity and mortality: Updating the cost-of-illness model. *J Am Pharm Assoc (Wash)* 41: 192–199, 2001
- Mason NA, Bakus JL: Strategies for reducing polypharmacy and other medication-related problems in chronic kidney disease. *Semin Dial* 23: 55–61, 2010
- Bolmsjö BB, Mölstad S, Gallagher M, Chalmers J, Östgren CJ, Midlöv P: Risk factors and consequences of decreased kidney function in nursing home residents: A longitudinal study. *Geriatr Gerontol Int* 17: 791–797, 2017
- Kang H, Hong SH: Risk of kidney dysfunction from polypharmacy among older patients: A nested case-control study of the South Korean senior cohort. *Sci Rep* 9: 10440, 2019
- Ernst R, Fischer K, de Godoi Rezende Costa Molino C, Orav EJ, Theiler R, Meyer U, Fischler M, Gagesch M, Ambühl PM, Freystätter G, Egli A, Bischoff-Ferrari HA: Polypharmacy and kidney function in community-dwelling adults age 60 years and older: A prospective observational study. *J Am Med Dir Assoc* 21: 254–259.e1, 2020
- Nakajima A, Tanaka K, Saito H, Iwasaki T, Oda A, Kanno M, Shimabukuro M, Asahi K, Watanabe T, Kazama JJ: Blood pressure control in chronic kidney disease according to underlying renal disease: The Fukushima CKD cohort. *Clin Exp Nephrol* 24: 427–434, 2020
- Saito H, Tanaka K, Iwasaki T, Oda A, Watanabe S, Kanno M, Kimura H, Shimabukuro M, Asahi K, Watanabe T, Kazama JJ: Xanthine oxidase inhibitors are associated with reduced risk of cardiovascular disease. *Sci Rep* 11: 1380, 2021
- Tanaka K, Saito H, Iwasaki T, Oda A, Watanabe S, Kanno M, Kimura H, Shimabukuro M, Asahi K, Watanabe T, James Kazama J: Status of anemia according to underlying renal disease in chronic kidney disease: The Fukushima CKD cohort. *Ann Clin Epidemiol* 3: 27–35, 2021
- Tanaka K, Saito H, Iwasaki T, Oda A, Watanabe S, Kanno M, Kimura H, Shimabukuro M, Asahi K, Watanabe T, Kazama JJ: Association between serum potassium levels and adverse outcomes in chronic kidney disease: The Fukushima CKD cohort study. *Clin Exp Nephrol* 25: 410–417, 2021
- Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A; Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 53: 982–992, 2009
- Cuzick J: A Wilcoxon-type test for trend. *Stat Med* 4: 87–90, 1985
- Sasieni PD: From genotypes to genes: Doubling the sample size. *Biometrics* 53: 1253–1261, 1997
- Armitage P: Tests for linear trends in proportions and frequencies. *Biometrics* 11: 375–386, 1955
- Cochran WG: Some methods for strengthening the common χ^2 tests. *Biometrics* 10: 417–451, 1954
- Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Cumming RG, Handelsman DJ, McLachlan AJ, Abernethy DR, Banks E, Le Couteur DG: High-risk prescribing and incidence of frailty among older community-dwelling men. *Clin Pharmacol Ther* 91: 521–528, 2012
- Jansen KM, Bell JS, Hilmer SN, Kirkpatrick CM, Ilomäki J, Le Couteur D, Blyth FM, Handelsman DJ, Waite L, Naganathan V, Cumming RG, Gnjidic D: Effects of changes in number of medications and drug burden index exposure on transitions between frailty states and death: The concord health and ageing in men project cohort study. *J Am Geriatr Soc* 64: 89–95, 2016
- Herr M, Robine JM, Pinot J, Arvieu JJ, Ankrj J: Polypharmacy and frailty: Prevalence, relationship, and impact on mortality in a French sample of 2350 old people. *Pharmacoepidemiol Drug Saf* 24: 637–646, 2015
- Veronese N, Stubbs B, Noale M, Solmi M, Pilotto A, Vaona A, Demurtas J, Mueller C, Huntley J, Crepaldi G, Maggi S: Polypharmacy is associated with higher frailty risk in older people: An 8-year longitudinal cohort study. *J Am Med Dir Assoc* 18: 624–628, 2017
- Yuki A, Otsuka R, Tange C, Nishita Y, Tomida M, Ando F, Shimokata H: Polypharmacy is associated with frailty in Japanese community-dwelling older adults. *Geriatr Gerontol Int* 18: 1497–1500, 2018
- Schöttker B, Saum KU, Muhlack DC, Hoppe LK, Holleczeck B, Brenner H: Polypharmacy and mortality: New insights from a large cohort of older adults by detection of effect modification by multi-morbidity and comprehensive correction of confounding by indication. *Eur J Clin Pharmacol* 73: 1041–1048, 2017
- Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE: What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 17: 230, 2017
- Secora A, Alexander GC, Ballew SH, Coresh J, Grams ME: Kidney function, polypharmacy, and potentially inappropriate medication use in a community-based cohort of older adults. *Drugs Aging* 35: 735–750, 2018
- Laville SM, Metzger M, Stengel B, Jacquelinet C, Combe C, Fouque D, Laville M, Frimat L, Ayav C, Speyer E, Robinson BM, Massy ZA, Liabeuf S; Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) Study Collaborators: Evaluation of the adequacy of drug prescriptions in patients with chronic kidney disease: Results from the CKD-REIN cohort. *Br J Clin Pharmacol* 84: 2811–2823, 2018
- Schmidt IM, Hübner S, Nadal J, Titze S, Schmid M, Bärthlein B, Schlieper G, Dienemann T, Schultheiss UT, Meiselbach H, Köttgen A, Flöge J, Busch M, Kreutz R, Kielstein JT, Eckardt KU: Patterns of medication use and the burden of polypharmacy in patients with chronic kidney disease: The German Chronic Kidney Disease study. *Clin Kidney J* 12: 663–672, 2019
- Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, Gnjidic D, Del Mar CB, Roughead EE, Page A, Jansen J, Martin JH: Reducing inappropriate polypharmacy: The process of deprescribing. *JAMA Intern Med* 175: 827–834, 2015
- Whittaker CF, Fink JC: Deprescribing in CKD: The proof is in the process. *Am J Kidney Dis* 70: 596–598, 2017
- Triantafylidis LK, Hawley CE, Perry LP, Paik JM: The role of deprescribing in older adults with chronic kidney disease. *Drugs Aging* 35: 973–984, 2018
- Pai AB, Cardone KE, Manley HJ, St Peter WL, Shaffer R, Somers M, Mehrotra R; Dialysis Advisory Group of American Society of Nephrology: Medication reconciliation and therapy management in dialysis-dependent patients: Need for a systematic approach. *Clin J Am Soc Nephrol* 8: 1988–1999, 2013
- St Peter WL: Management of polypharmacy in dialysis patients. *Semin Dial* 28: 427–432, 2015
- Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X: Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 16(2): CD000011, 2008
- Dreischulte T, Morales DR, Bell S, Guthrie B: Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or

- renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int* 88: 396–403, 2015
37. Baker M, Perazella MA: NSAIDs in CKD: Are they safe? *Am J Kidney Dis* 76: 546–557, 2020
38. Tanaka K, Watanabe T, Takeuchi A, Ohashi Y, Nitta K, Akizawa T, Matsuo S, Imai E, Makino H, Hishida A; CKD-JAC Investigators: Cardiovascular events and death in Japanese patients with chronic kidney disease. *Kidney Int* 91: 227–234, 2017

Received: March 21, 2021 **Accepted:** September 17, 2021

Published online ahead of print. Publication date available at www.cjasn.org.

Supplemental Material

Supplemental Table 1. Associations between each medication and kidney failure, cardiovascular events, and all-cause mortality

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	Adjusted Hazard Ratios (95%CI)		
	Kidney failure	Cardiovascular events	All-cause mortality
RAS + Diuretic	1.64 (1.10-2.44)	1.23 (0.86-1.75)	1.00 (0.65-1.56)
ARB	2.00 (1.08-3.73)	0.79 (0.54-1.16)	0.73 (0.47-1.13)
CCB	1.39 (0.88-2.21)	0.92 (0.64-1.32)	0.77 (0.50-1.19)
ACE	0.94 (0.58-1.52)	1.05 (0.70-1.59)	0.70 (0.40-1.23)
Beta-blockers	1.41 (0.85-2.36)	1.77 (1.22-2.60)	1.69 (1.08-2.65)
Alfa-blockers	1.14 (0.70-1.85)	1.05 (0.66-1.67)	0.80 (0.44-1.46)
DRI	0.49 (0.06-3.77)	2.21 (0.53-9.13)	2.34 (0.32-17.18)
Diabetes medication	0.94 (0.51-1.75)	0.87 (0.47-1.60)	0.83 (0.40-1.71)
Antilipidemic	1.54 (0.91-2.61)	0.92 (0.58-1.45)	0.53 (0.31-0.89)
Diuretics	1.44 (0.95-2.16)	1.43 (1.01-2.02)	1.14 (0.75-1.75)
Hyperuricemia medication	1.67 (1.08-2.57)	1.19 (0.82-1.72)	1.32 (0.85-2.06)
PPI	0.76 (0.45-1.28)	1.01 (0.70-1.45)	1.82 (1.22-2.72)
Aspirin	2.13 (1.17-3.88)	1.15 (0.74-1.80)	0.82 (0.47-1.39)
Warfarin	0.90 (0.48-1.69)	2.87 (1.95-4.22)	1.36 (0.82-2.25)
Bisphosphonate	0.60 (0.22-1.65)	0.99 (0.57-1.70)	0.91 (0.50-1.64)
Vitamin D	1.69 (0.80-3.58)	1.61 (0.80-3.24)	1.18 (0.53-2.60)
Potassium absorbent	1.20 (0.76-1.86)	2.05 (1.30-3.23)	1.69 (0.98-2.89)
Iron medication	1.27 (0.78-2.08)	1.42 (0.85-2.39)	1.41 (0.81-2.44)

Note: adjusted with the number of medications as a continuous variable and all the variables on Model 2. ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; DRI, direct renin inhibitor; PPI, proton pump inhibitor; RAS, renin-angiotensin-aldosterone system inhibitors.