Cardiovascular Risk Factor Burden and Treatment Control in Patients with Chronic Kidney Disease: A Cross-Sectional Study

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Cardiovascular Risk Factor Burden and Treatment Control in Patients with Chronic Kidney Disease: A Cross-Sectional Study

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Aim: Cardiovascular disease is a life-threatening chronic kidney disease (CKD) complication. Although cardiovascular risk factor management is significant in patients with CKD, there are few reports that detail the frequency of complications and the treatment of cardiovascular risk factors at different stages of CKD in clinical practice.

Methods: There were a total of 3,407 patients with non-dialysis-dependent CKD who participated in the Fukuoka Kidney disease Registry Study, and they were cross-sectionally analyzed. The patients were classified into five groups based on their estimated glomerular filtration rate and urinary albumin to creatinine ratio according to Kidney Disease: Improving Global Outcomes 2012 guidelines, which recommend low, moderate, high, very high, and extremely high risk groups. The primary outcomes were the cardiovascular risk factor burden and the treatment status of cardiovascular risk factors. Using a logistic regression model, the association between the CKD groups and the treatment status of each risk factor was examined.

Results: The proportion of patients with hypertension, diabetes mellitus, and dyslipidemia significantly increased as CKD progressed, whereas the proportion of patients who achieved cardiovascular risk factor treatment targets significantly decreased. In the multivariable analysis, the odds ratios (ORs) of uncontrolled treatment targets were significantly higher for hypertension (OR 3.68) in the extremely high risk group than in the low risk group.

Conclusions: Patients with non-dialysis-dependent CKD demonstrate an increased cardiovascular risk factor burden with greater severity of CKD. Extremely high risk CKD is associated with difficulty in managing hypertension.

Key words: Cardiovascular disease, Chronic kidney disease, Estimated glomerular filtration rate, Treatment control, Urinary albumin to creatinine ratio

Introduction/Aim

Cardiovascular disease (CVD) is a critical prognostic complication in the general population, but it is of greater importance in patients with chronic kidney disease (CKD)[1-4]. It has been reported that patients with CKD have an almost twice higher risk of death from CVD than those without CKD in Japan[5-7]. CKD is itself an independent risk factor for CVD along with traditional risk factors, such as hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking[7-9]. Furthermore, anemia[10, 11], inflammation[12-14], hyperuricemia[15, 16], and dyskalemia[17, 18] in patients with CKD have also been

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recognized as risk factors for CVD. Patients with CKD have multiple risk factors for CVD, and there is a need to understand the burden of these risk factors[19, 20].

The Kidney Disease: Improving Global Outcomes (KDIGO) and Japanese Society of Nephrology guidelines aim to lessen the incidence of CVD, extend life expectancy, and reduce the progression of end-stage kidney diseases in patients with CKD[21, 22]. KDIGO guidelines include targets for the management of cardiovascular risk factors (e.g., hypertension, diabetes mellitus, and dyslipidemia) in patients with CKD[21]. Previous reports have shown that clinical guidelines for CVD management reduce the risk of renal complications in high-risk patients[23]. However, other studies have reported that patients with CKD have more difficulty in achieving therapeutic control than the general population[19, 24]. A civilian noninstitutionalized population-based survey in the United States, the National Health and Nutrition Examination Survey, revealed that only approximately 40% of patients with stages 3–5 CKD achieved adequate blood pressure control during treatment[19]. A better understanding of the cardiovascular risk factor burden of patients with CKD would be useful to improve treatment strategies, but limited studies have examined the extent to which therapeutic management of these cardiovascular risk factors is achieved in clinical practice.

We, thus, conducted this study using baseline data from the Fukuoka Kidney disease Registry (FKR) Study, which is an ongoing multicenter, prospective, observational cohort study of Japanese patients with non-dialysis-dependent CKD, to cross-sectionally examine the cardiovascular risk factor burden and the therapeutic management according to CKD severity, to reduce the risk factor burden and achieve treatment targets[25].

Methods

Study Population

This study analyzed the baseline data of patients from the FKR Study[25]. As reported previously, a total of 4,476 outpatients were enrolled in the FKR Study[26, 27]. Of the 4,476 patients, 1,065 were excluded because of a lack of data on baseline characteristics, including height (22 patients), weight (26 patients), smoking habit (539 patients), systolic blood pressure (46 patients), diastolic blood pressure (51 patients), medications (104 patients), and laboratory data (330 patients). In addition, four participants who were aged 16 or 17 were excluded because the same treatment target as patients aged 18 would be inappropriate. Finally, the remaining 3,407 patients were analyzed in this study. The study protocol was approved by our institution's clinical research ethics committee (approval No. 469-09) and the ethics committees of all other participating institutions. This study followed the principles of the Declaration of Helsinki. The protocol is registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN000007988).

Clinical Parameters

The demographic and clinical data were collected from all patients at the time of study enrollment. Blood pressure values were obtained from the patients' medical records at each institution. The physicians or medical staff in the office measured the blood pressure of patients in a sitting position once in the upper arm using an appropriately sized cuff. Serum and urine biochemical parameters, including serum concentrations of cystatin C, creatinine, albumin, calcium, phosphorus, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, iron, ferritin, and high-sensitivity C-reactive protein (hs-CRP), as well as urine albumin and creatinine, were measured at a central laboratory in the nonfasting state. Low-density lipoprotein (LDL) cholesterol was determined using the Friedewald formula or the direct measurement method for patients with triglyceride concentrations of <400 mg/dL and ≥ 400 mg/dL, respectively. The estimated glomerular filtration rate (eGFR) was calculated using the appropriate equation for Japanese patients with CKD aged ≥ 18 years as follows: eGFR (mL/min/1.73 m^2) $= 194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$ in females)[28]. The urinary albumin to creatinine ratio (ACR) was adapted as a surrogate marker of daily urinary albumin excretion. Other biochemical parameters, such as hemoglobin A1c (HbA1c), were collected from the patients' medical records. The body mass index (BMI) was calculated as follows: BMI (kg/m^2) = weight (kg) $\div$ (height (m))^2. Smoking and drinking habits were obtained from the information in the questionnaires. Information on medications, including antihypertensive agents, oral antidiabetic agents, insulin, and lipid-lowering agents, was also collected from the patients' medical records.

Definition of Cardiovascular Risk Factors

Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg or the use of antihypertensive drugs[29]. Diabetes mellitus was identified in subjects in whom HbA1c was $\geq 6.5\%$, who had diabetic nephropathy or who used insulin or oral antihyperglycemic agents[30]. Dyslipidemia was defined as a serum LDL-cholesterol concentration of ≥ 140 mg/dL, a serum triglyceride

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Table 1. Cardiovascular risk factor treatment targets

Risk factor		Treatment target
Hypertension	Systolic blood pressure (mmHg)	age ≥ 75 years: <140
		age <75 years: <130 if proteinuria (+) or diabetes mellitus (+), <140 if not
	Diastolic blood pressure (mmHg)	age ≥ 75 years: <90
		age <75 years: <80 if proteinuria (+) or diabetes mellitus (+), <90 if not
Diabetes mellitus	Hemoglobin A1c (%)	<7.0
Dyslipidemia	Low-density lipoprotein-cholesterol (mg/dL)	<120 if not the below
		<100 if diabetes mellitus (+) and history of peripheral artery disease (+)
		<100 if diabetes mellitus (+) and diabetic nephropathy (+)
		<100 if diabetes mellitus (+) and current smoking (+)
		<100 if diabetes mellitus (-) and history of ischemic heart disease (+)
		<70 if diabetes mellitus (+) and history of ischemic heart disease (+)
	Triglycerides (mg/dL)	<175
	High-density lipoprotein-cholesterol (mg/dL)	≥ 40
Overweight	Body mass index (kg/m^2)	<25
Smoking		Never smoking or former smoking

concentration of ≥ 175 mg/dL, a serum HDL-cholesterol concentration of <40 mg/dL, or current use of lipid-lowering agents[31, 32]. Overweight was defined as a BMI of ≥ 25 kg/m^2 [33, 34]. Anemia was defined as a blood hemoglobin concentration of < 11.0 g/dL or the use of erythropoiesis-stimulating agents or iron supplementation[35]. A high serum hs-CRP was defined as a serum hs-CRP concentration of ≥ 0.1 mg/dL[36]. Hyperuricemia was defined as a serum uric acid concentration of ≥ 7.0 mg/dL or the use of uric acid-lowering drugs[37]. Hypokalemia and hyperkalemia were defined as serum potassium concentrations of <4.0 mmol/L and ≥ 5.5 mmol/L, respectively, or the use of ion exchange resins[22]. Lastly, prior CVD was defined as a composite history of ischemic heart disease, congestive heart failure, stroke (ischemic and hemorrhagic), peripheral artery disease, atrial fibrillation/atrial flutter, and thoracic aortic and abdominal aortic aneurysm. In the present study, we defined the treatment targets for cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, overweight, and smoking according to published guidelines[29-34] **(Table 1)**.

Statistical Analysis

In this study, the patients were divided into five groups according to the severity of CKD based on eGFR (G1, G2, G3a, G3b, G4, and G5) and ACR (A1, A2, and A3) by KDIGO clinical practice guidelines as follows: low risk=G1A1 or G2A1; moderate risk=G1A2, G2A2, or G3aA1; high risk=G1A3, G2A3, G3aA2, or G3bA1; very high risk=G3aA3, G3bA2, G3bA3, G4A1, or G4A2; and extremely high risk=G4A3, G5A1, G5A2, or G5A3 [21] **(Fig. 1)**. The patients' baseline characteristics according to CKD severity are presented as number and percentage for categorical variables and as median and interquartile range for continuous variables. Using the Cochran–Armitage test for categorical variables and the Jonckheere–Terpstra test for continuous variables, the trends across CKD severity were examined. We assessed the frequency of five traditional cardiovascular risk factors (e.g., hypertension, diabetes mellitus, dyslipidemia, overweight, and current smoking). Nontraditional cardiovascular risk factors that were investigated in this study included anemia, high serum hs-CRP concentration, hyperuricemia, and hypokalemia/hyperkalemia.

Unadjusted, age- and sex-adjusted, and multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for uncontrolled treatment targets for the five abovementioned cardiovascular risk factors were estimated using a logistic regression model. The multivariable-adjusted model was adjusted for age; sex; history of CVD; cause of CKD (chronic glomerulonephritis, diabetic nephropathy, hypertensive nephrosclerosis, other); the presence of hypertension, diabetes mellitus, and dyslipidemia; BMI; and current smoking, except the variables relevant to the individual factors. In addition, the ORs for uncontrolled treatment targets for hypertension, diabetes mellitus, and dyslipidemia were analyzed in patients with each risk factor, using all patients as the denominator to assess the risk of being overweight or current smoking. The interaction of CKD severity and history of CVD and its association with the treatment status of cardiovascular risk factors were evaluated by adding an interaction term in the relevant statistical

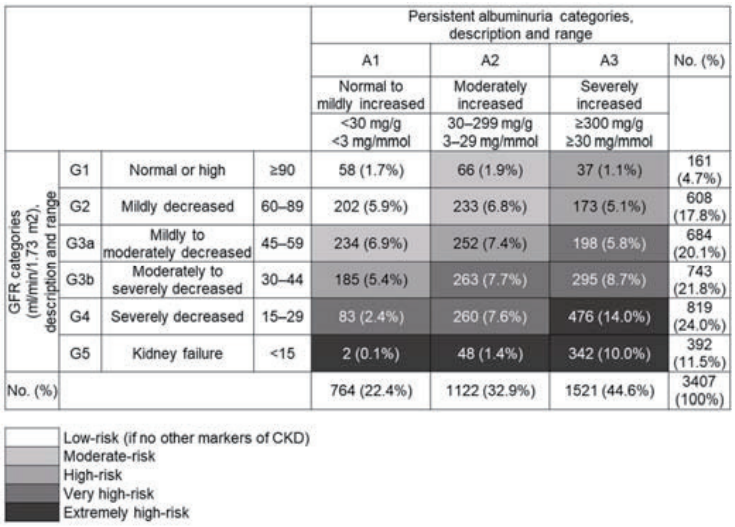

Fig. 1. Classification of CKD according to eGFR and ACR categories (KDIGO 2012)

Abbreviations: ACR, urinary albumin to creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

model. In the analysis, the exposure (CKD severity) was entered as an ordinal variable (low risk, 1; moderate risk, 2; high risk, 3; very high risk, 4; extremely high risk, 5). In addition, there were several sensitivity analyses that were conducted to confirm the consistent association between CKD severity and the treatment target for cardiovascular risk factors: 1) estimating multivariable-adjusted ORs for uncontrolled treatment targets for hypertension, diabetes mellitus, and dyslipidemia using all patients as the denominator; 2) excluding users of erythropoiesis-stimulating agents and/or iron supplementation; and 3) estimating multivariable-adjusted ORs using a logistic regression model with generalized estimating equation methods to account for facility-level clustering. We used the methods with a binomial distribution, logit function, and exchangeable working correlation matrices. Finally, we selected covariates using a logistic regression model and stepwise backward selection with a *P*-value of <0.01 for the remaining variables to determine the factors independently associated with uncontrolled risk factors. Age and sex were included as initial candidate variables. Several variables (e.g., ACR, serum hs-CRP, serum ferritin, serum triglycerides, and serum parathyroid hormone concentrations) were log transformed because these distributions were skewed. SAS software, version 9.4 (SAS Institute, Cary, NC, USA), was used for all statistical analyses. A two-tailed *P*-value of <0.05 was considered statistically significant.

Results

1. Baseline Characteristics of the Study Population

Fig. 1 shows the distribution of enrolled patients stratified by eGFR and ACR. The risk ranking for adverse outcomes based on eGFR and ACR stratified 7.6%, 15.6%, 19.0%, 32.2%, and 25.5% of the study population as low risk, moderate risk, high risk, very high risk, and extremely high risk, respectively. Table 2 shows the baseline characteristics according to the eGFR and ACR categories. Patients with advanced CKD were significantly older and more likely to be male with a significantly higher prevalence of diabetic nephropathy and hypertensive nephrosclerosis and a more frequent CVD history (all $P<0.001$). In addition, serum uric acid, hs-CRP, ferritin, potassium, phosphate, and parathyroid hormone concentrations were significantly higher in patients with advanced CKD (all $P<0.001$), while blood hemoglobin, serum albumin, and calcium concentrations were significantly lower (all $P<0.001$).

2. Prevalence of Cardiovascular Risk Factors According to CKD Category

Table 3 shows the prevalence of cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, overweight, and current smoking, according to the eGFR and ACR categories. The proportion of patients with hypertension, diabetes mellitus, and dyslipidemia increased significantly as CKD progressed. The cumulative number of traditional and nontraditional risk factors was significantly higher in patients with advanced CKD

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Table 2. Patients' baseline characteristics and cardiovascular risk factor burden according to the classification of CKD by eGFR and ACR categories

		Classification of CKD by eGFR and ACR categories					
	Total (n=3407)	Low-risk n=260	Moderate-risk n=533	High-risk n=647	Very high-risk n=1099	Extremely high-risk n=868	P for trend
Demographics and comorbidities							
Age, years	67 (56–76)	54 (40–66)	62 (46–70)	65 (53–74)	70 (61–78)	72 (63–79)	<0.001
Female sex, %	1948 (44.0)	152 (58.5)	279 (52.4)	278 (43.0)	468 (42.6)	321 (37.0)	<0.001
BMI, kg/m^2	22.9 (20.6–25.6)	21.7 (19.9–24.6)	22.7 (20.5–25.2)	23.4 (21.4–25.8)	23.0 (20.8–25.9)	22.9 (20.5–25.4)	0.25
Smoking, %							
Current	381 (11.2)	35 (13.5)	47 (8.8)	76 (11.8)	111 (10.1)	112 (12.9)	0.41
Former	1410 (41.4)	72 (27.7)	182 (34.2)	232 (35.9)	481 (43.8)	443 (51.0)	
Never	1616 (47.4)	153 (58.9)	304 (57.0)	339 (52.4)	507 (46.1)	313 (36.1)	
Current drinking, % (n=3071)	1897 (61.8)	148 (62.5)	304 (62.0)	364 (62.1)	602 (61.1)	479 (62.0)	0.81
Cause of CKD							
Chronic glomerulonephritis	1670 (49.0)	197 (75.8)	347 (65.1)	378 (58.4)	482 (43.9)	266 (30.7)	<0.001[§]
Diabetic nephropathy	364 (10.7)	1 (0.4)	14 (2.6)	17 (2.6)	102 (9.3)	230 (26.5)	
Hypertensive nephrosclerosis	751 (22.0)	7 (2.7)	74 (13.9)	130 (20.1)	302 (27.5)	238 (27.4)	
Other	622 (18.3)	55 (21.2)	98 (18.4)	122 (18.9)	213 (19.4)	134 (15.4)	
Systolic blood pressure, mmHg	130 (120–142)	121 (113–132)	126 (115–137)	128 (118–139)	131 (120–142)	135 (125–147)	<0.001
Diastolic blood pressure, mmHg	74 (67–82)	73 (65–80)	75 (68–82)	75 (69–83)	74 (67–82)	74 (66–81)	<0.001
History of CVD, %	880 (25.8)	19 (7.3)	66 (12.4)	118 (18.2)	325 (29.6)	352 (40.6)	<0.001
History of ischemic heart disease, %	384 (11.3)	10 (3.9)	23 (4.3)	51 (7.9)	141 (12.8)	159 (18.3)	<0.001
History of congestive heart failure, %	100 (2.9)	0 (0.0)	1 (0.2)	13 (2.0)	37 (3.4)	49 (5.7)	<0.001
History of cerebral infarction, %	296 (8.7)	4 (1.5)	24 (4.5)	39 (6.0)	103 (9.4)	126 (14.5)	<0.001
History of cerebral hemorrhage, %	64 (1.9)	2 (0.8)	3 (0.6)	8 (1.2)	27 (2.5)	24 (2.8)	<0.001
History of peripheral artery disease, %	111 (3.3)	4 (1.5)	5 (0.9)	16 (2.5)	39 (3.6)	47 (5.4)	<0.001
History of AF/AFL, %	189 (5.6)	3 (1.2)	21 (3.9)	25 (3.9)	78 (7.1)	62 (7.1)	<0.001
History of TAA, %	28 (0.8)	0 (0.0)	2 (0.4)	3 (0.5)	9 (0.8)	14 (1.6)	0.002
History of AAA, %	83 (2.4)	1 (0.4)	2 (0.4)	7 (1.1)	30 (2.7)	43 (5.0)	<0.001
History of bone fracture, %	218 (6.4)	8 (3.1)	26 (4.9)	40 (6.2)	81 (7.4)	63 (7.3)	0.004
Laboratory tests							
Blood hemoglobin, g/dL	12.8 (11.4–14.1)	13.9 (13.0–14.7)	13.8 (12.9–14.9)	13.5 (12.5–14.7)	12.5 (11.3–13.9)	11.2 (10.3–12.3)	<0.001
Serum albumin, g/dL	4.1 (3.8–4.3)	4.3 (4.1–4.5)	4.3 (4.0–4.5)	4.2 (3.9–4.4)	4.0 (3.8–4.3)	3.9 (3.6–4.1)	<0.001
Serum uric acid, mg/dL	6.1 (5.2–7.1)	5.2 (4.2–6.1)	5.6 (4.7–6.6)	5.9 (5.1–6.9)	6.4 (5.7–7.3)	6.5 (5.6–7.5)	<0.001
Serum hs-CRP, mg/dL	0.05 (0.02–0.13)	0.03 (0.01–0.08)	0.04 (0.02–0.09)	0.05 (0.02–0.11)	0.06 (0.03–0.15)	0.07 (0.03–0.18)	<0.001
Serum ferritin, ng/mL	102 (47–188)	80 (33–148)	94 (37–170)	86 (40–166)	103 (47–189)	126 (64–220)	<0.001
Serum total cholesterol, mg/dL	192 (168–218)	200 (179–223)	197 (177–218)	198 (176–223)	193 (167–219)	180 (155–210)	<0.001
Serum LDL-cholesterol, mg/dL	105 (85–126)	109 (91–129)	108 (92–127)	109 (90–129)	105 (85–126)	98 (77–122)	<0.001
Serum triglycerides, mg/dL	122 (88–171)	104 (78–146)	112 (81–158)	120 (87–171)	126 (91–178)	129 (97–177)	<0.001
Serum HDL-cholesterol, mg/dL	57 (45–70)	64 (53–79)	61 (50–74)	59 (48–75)	55 (44–69)	51 (42–64)	<0.001
Serum urea nitrogen, mg/dL	22.6 (16.0–34.6)	14.3 (12.0–17.0)	15.5 (13.0–18.6)	17.8 (14.2–22.0)	25.0 (19.5–32.2)	43.0 (33.0–56.9)	<0.001
Serum creatinine, mg/dL	1.29 (0.89–2.05)	0.70 (0.60–0.83)	0.81 (0.69–0.98)	0.98 (0.80–1.24)	1.42 (1.18–1.77)	2.83 (2.16–3.99)	<0.001
eGFR, mL/min/1.73 m^2	40.3 (23.7–57.7)	75.9 (67.6–88.0)	63.6 (53.1–79.4)	52.3 (43.6–66.0)	35.2 (27.2–43.1)	16.3 (11.6–22.7)	<0.001
Serum potassium, mmol/L	4.4 (4.1–4.7)	4.1 (3.9–4.4)	4.2 (4.0–4.4)	4.2 (4.0–4.5)	4.5 (4.1–4.7)	4.6 (4.3–5.0)	<0.001
Serum phosphate, mg/dL	3.4 (3.0–3.9)	3.4 (3.0–3.9)	3.4 (3.0–3.7)	3.2 (2.9–3.6)	3.4 (3.0–3.8)	3.8 (3.3–4.3)	<0.001
Serum calcium, mg/dL	9.4 (9.0–9.7)	9.5 (9.3–9.7)	9.5 (9.3–9.7)	9.5 (9.2–9.7)	9.4 (9.1–9.7)	9.0 (8.7–9.4)	<0.001
Serum PTH (intact assay), pg/mL	67 (46–110)	46 (36–61)	49 (39–65)	55 (43–74)	70 (50–102)	147 (94–240)	<0.001
Hemoglobin A1c, % (n=1650)	6.0 (5.6–6.4)	5.8 (5.6–6.2)	5.9 (5.5–6.3)	5.9 (5.6–6.3)	6.0 (5.7–6.4)	6.0 (5.5–6.5)	<0.001
Urinary albumin to creatinine ratio, mg/gCr	197 (34–743)	10 (6–17)	39 (11–113)	110 (22–418)	217 (68–704)	894 (455–1882)	<0.001
Urinary protein to creatinine ratio, g/gCr	0.37 (0.11–1.25)	0.05 (0.04–0.07)	0.10 (0.06–0.21)	0.21 (0.09–0.65)	0.41 (0.19–1.12)	1.59 (0.87–3.22)	<0.001

Baseline data are expressed as median (interquartile range) or number (percentage). Conversion factors for units: hemoglobin in g/dL to g/L, ×10; albumin in g/dL to g/L, ×10; uric acid in mg/dL to μmol/L, ×59.48; CRP in mg/dL to nmol/L, ×9.524; cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129; urea nitrogen in mg/dL to mmol/L, ×0.357; creatinine in mg/dL to mmol/L, ×88.4; phosphate in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495. Abbreviations: AAA, abdominal aortic aneurysm; ACR, urinary albumin to creatinine ratio; AF/AFL, atrial fibrillation/atrial flutter; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-cholesterol, high-density lipoprotein-cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-cholesterol, low-density lipoprotein-cholesterol; PTH, parathyroid hormone; TAA, thoracic aortic aneurysm. [§]: Trend test for patients with chronic glomerulonephritis.

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Table 3. Prevalence of cardiovascular risk factors according to the classification of CKD by eGFR and ACR categories

		Classification of CKD by eGFR and ACR categories					
	Total $n=3407$	Low-risk $n=260$	Moderate-risk $n=533$	High-risk $n=647$	Very high-risk $n=1099$	Extremely high-risk $n=868$	*P* for trend
Hypertension	2929 (86.0)	136 (52.3)	384 (72.1)	543 (83.9)	1023 (93.1)	843 (97.1)	<0.001
Blood pressure ≥ 130/80 mmHg	2010 (59.0)	103 (39.6)	271 (50.8)	362 (56.0)	670 (61.0)	604 (69.6)	<0.001
Blood pressure ≥ 140/90 mmHg	1070 (31.4)	46 (17.7)	128 (24.0)	169 (26.1)	352 (32.0)	375 (43.2)	<0.001
Use of antihypertensive agents, %	2738 (80.4)	121 (46.5)	341 (64.0)	506 (78.2)	958 (87.2)	812 (93.6)	<0.001
ACE inhibitors, %	301 (8.8)	12 (4.6)	39 (7.3)	52 (8.0)	119 (10.8)	79 (9.1)	0.005
ARBs, %	2260 (66.3)	105 (40.4)	275 (51.6)	422 (65.2)	785 (71.4)	673 (77.5)	<0.001
Calcium channel blockers, %	1626 (47.7)	45 (17.3)	153 (28.7)	254 (39.3)	545 (49.6)	629 (72.5)	<0.001
β-blockers, %	516 (15.2)	15 (5.8)	31 (5.8)	68 (10.5)	181 (16.5)	221 (25.5)	<0.001
α-blockers, %	191 (5.6)	2 (0.8)	7 (1.3)	15 (2.3)	98 (11.3)	222 (25.5)	<0.001
Use of diuretics, %	688 (20.2)	9 (3.5)	30 (5.6)	71 (11.0)	263 (23.9)	315 (36.3)	<0.001
Diabetes mellitus	830 (24.3)	30 (11.5)	74 (13.8)	100 (15.5)	274 (24.9)	352 (40.6)	<0.001
Hemoglobin A1c ≥ 6.5%	381 (11.2)	9 (3.5)	48 (9.0)	53 (8.2)	135 (12.3)	136 (15.7)	<0.001
Use of insulin, %	204 (6.0)	6 (2.3)	9 (1.7)	8 (1.2)	70 (6.4)	111 (12.8)	<0.001
Use of oral antihyperglycemic drugs, %	591 (17.4)	24 (9.2)	49 (9.2)	76 (11.8)	197 (17.9)	245 (28.2)	<0.001
Sulfonylureas, %	102 (3.0)	3 (1.2)	4 (0.8)	18 (2.8)	44 (4.0)	33 (3.8)	<0.001
Biguanides, %	57 (1.7)	3 (1.2)	14 (2.6)	10 (1.6)	23 (2.1)	7 (0.8)	0.17
α-glucosidase inhibitors, %	162 (4.8)	3 (1.2)	9 (1.7)	21 (3.3)	61 (5.6)	68 (7.8)	<0.001
Dipeptidyl peptidase-4 inhibitors, %	429 (12.6)	19 (7.3)	37 (6.9)	56 (8.7)	132 (12.0)	185 (21.3)	<0.001
Dyslipidemia	2257 (66.3)	129 (49.6)	304 (57.0)	441 (68.2)	766 (69.7)	617 (71.1)	<0.001
Serum LDL-cholesterol ≥ 140 mg/dL	496 (14.6)	39 (15.0)	74 (13.9)	104 (16.1)	163 (14.8)	116 (13.4)	<0.001
Serum triglycerides ≥ 175 mg/dL	812 (23.8)	42 (16.2)	104 (19.5)	155 (24.0)	290 (26.4)	221 (25.5)	<0.001
Serum HDL-cholesterol <40 mg/dL	429 (12.6)	6 (2.3)	24 (4.5)	57 (8.8)	176 (16.0)	166 (19.1)	<0.001
Use of statins, %	1419 (41.7)	75 (28.9)	182 (34.2)	285 (44.1)	477 (43.4)	400 (46.1)	<0.001
Use of ezetimibe, %	136 (4.0)	10 (3.9)	14 (2.6)	24 (3.7)	41 (3.7)	47 (5.4)	0.03
Use of unsaturated fatty acids, %	123 (3.6)	5 (1.9)	8 (1.5)	23 (3.6)	47 (4.3)	40 (4.6)	<0.001
Use of fibrates, %	54 (1.6)	0 (0.0)	8 (1.5)	12 (1.9)	26 (2.4)	8 (0.9)	0.53
Overweight (BMI ≥ 25 kg/m^2)	1001 (29.4)	60 (23.1)	141 (26.5)	208 (32.2)	349 (31.8)	243 (28.0)	0.13
Current smoking	381 (11.2)	35 (13.5)	47 (8.8)	76 (11.8)	111 (10.1)	112 (12.9)	0.41
Frequency (no. of conditions)							
0	180 (5.3)	55 (21.2)	60 (11.3)	37 (5.7)	19 (1.7)	9 (1.0)	<0.001[§]
1	733 (21.5)	75 (28.9)	162 (30.4)	136 (21.0)	217 (19.8)	143 (16.5)	
2	1222 (35.9)	84 (32.3)	183 (34.3)	241 (37.3)	416 (37.9)	298 (34.3)	
3	899 (26.4)	38 (14.6)	94 (17.6)	185 (28.6)	326 (29.7)	256 (29.5)	
4–5	373 (10.9)	8 (3.1)	34 (6.4)	48 (7.4)	121 (11.0)	162 (18.7)	

Baseline data are expressed as number (percentage). Frequency is the sum of the number of hypertension, diabetes mellitus, dyslipidemia, overweight, and current smoking. Conversion factors for units: cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, × 0.01129. Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ACR, urinary albumin to creatinine ratio; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol. [§]: Trend test for patients with 4 or 5 conditions.

(Supplementary Table 1, Supplementary Fig. 1).

3. Treatment Targets for Cardiovascular Risk Factors

Table 1 lists the treatment targets for cardiovascular risk factors. The number of subjects who achieved all five targets decreased significantly as eGFR and ACR categories progressed (low risk, 39.7% and extremely high risk, 16.2%) **(Fig. 2)**. When patients were stratified by eGFR or ACR categories, there was an overt association between the ACR category and the number of treatment targets **(Supplementary Fig. 2)**. **Table 4** represents the prevalence and treatment status of uncontrolled targets for cardiovascular risk factors among patients with each risk factor, while **Table 5** demonstrates the association between CKD severity and each treatment

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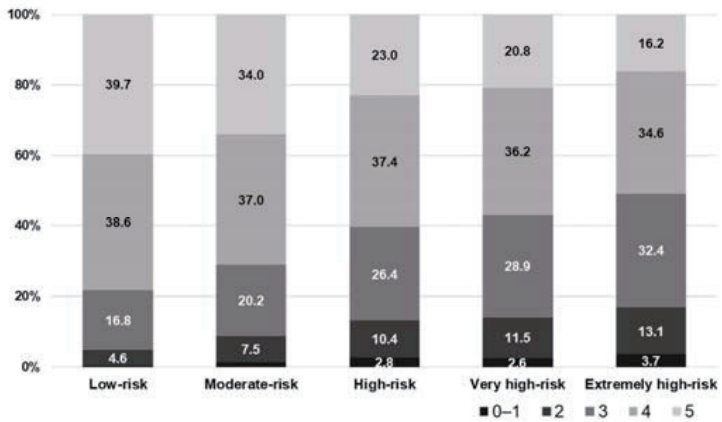

Fig. 2. Proportion of patients who achieved the treatment targets for cardiovascular risk factors by eGFR and ACR categories

Abbreviations: ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Table 4. Prevalence and treatment status of uncontrolled treatment targets for cardiovascular risk factors among patients with each risk factor

		Classification of CKD by eGFR and ACR categories				
	Total *n*=3407	Low-risk *n*=260	Moderate-risk *n*=533	High-risk *n*=647	Very high-risk *n*=1099	Extremely high-risk *n*=868
Hypertension						
Number of patients	2929	136	384	543	1023	843
Untreated but controlled, *n* (%)	53 (1.8)	1 (0.7)	11 (2.9)	10 (1.8)	21 (2.1)	10 (1.2)
Untreated and uncontrolled, *n* (%)	138 (4.7)	14 (10.3)	32 (8.3)	27 (5.0)	44 (4.3)	21 (2.5)
Treated and controlled, *n* (%)	1328 (45.3)	87 (64.0)	194 (50.5)	245 (45.1)	483 (47.2)	319 (37.8)
Treated but uncontrolled, *n* (%)	1410 (48.1)	34 (25.0)	147 (38.3)	261 (48.1)	475 (46.4)	493 (58.5)
Uncontrolled, *n* (%)	1548 (52.9)	48 (35.3)	179 (46.6)	288 (53.0)	519 (50.7)	514 (61.0)
Diabetes mellitus						
Number of patients	830	30	74	100	274	352
Untreated but controlled, *n* (%)	97 (11.7)	2 (6.7)	18 (24.3)	14 (14.0)	27 (9.9)	36 (10.2)
Untreated and uncontrolled, *n* (%)	24 (2.9)	0 (0.0)	3 (4.1)	6 (6.0)	10 (3.7)	5 (1.4)
Treated and controlled, *n* (%)	525 (63.3)	24 (80.0)	32 (43.2)	58 (58.0)	177 (64.6)	234 (66.5)
Treated but uncontrolled, *n* (%)	184 (22.2)	4 (13.3)	21 (28.4)	22 (22.0)	60 (21.9)	77 (21.9)
Uncontrolled, *n* (%)	208 (25.1)	4 (13.3)	24 (32.4)	28 (28.0)	70 (25.6)	82 (23.3)
Dyslipidemia						
Number of patients	2257	129	304	441	766	617
Untreated but controlled, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Untreated and uncontrolled, *n* (%)	681 (30.2)	45 (34.9)	105 (34.5)	124 (28.1)	233 (30.4)	174 (28.2)
Treated and controlled, *n* (%)	682 (30.2)	40 (31.0)	109 (35.9)	147 (33.3)	221 (28.9)	165 (26.7)
Treated but uncontrolled, *n* (%)	894 (39.6)	44 (34.1)	90 (29.6)	170 (38.5)	312 (40.7)	278 (45.1)
Uncontrolled, *n* (%)	1575 (69.8)	89 (69.0)	195 (64.1)	294 (66.7)	545 (71.2)	452 (73.3)
Overweight						
Number of patients	3407	260	533	647	1099	868
Uncontrolled, *n* (%)	1001 (29.4)	60 (22.9)	141 (26.4)	208 (32.2)	349 (31.8)	243 (28.0)
Smoking						
Number of patients	3407	260	533	647	1099	868
Uncontrolled, *n* (%)	381 (11.2)	35 (13.4)	47 (8.8)	76 (11.8)	111 (10.1)	112 (12.9)

Values are presented as number (percentage). Abbreviations: ACR, urinary albumin to creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

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Table 5. Odds ratios of uncontrolled treatment targets for cardiovascular risk factors in patients at risk for each risk factor

	Classification of CKD by eGFR and ACR categories					
	Low-risk	Moderate-risk	High-risk	Very high-risk	Extremely high-risk	*P* for trend
Hypertension						
Unadjusted OR	1.00 (reference)	1.60 (1.07–2.40)	2.07 (1.40–3.06)	1.89 (1.30–2.74)	2.86 (1.96–4.18)	<0.001
Age- and sex-adjusted OR	1.00 (reference)	1.68 (1.11–2.52)	2.34 (1.58–3.48)	2.29 (1.56–3.35)	3.62 (2.45–5.33)	<0.001
Multivariable-adjusted OR	1.00 (reference)	1.73 (1.15–2.61)	2.42 (1.62–3.60)	2.37 (1.61–3.49)	3.68 (2.47–5.49)	<0.001
Diabetes mellitus						
Unadjusted OR	1.00 (reference)	3.12 (0.98–9.95)	2.53 (0.81–7.90)	2.23 (0.75–6.61)	1.97 (0.67–5.82)	0.49
Age- and sex-adjusted OR	1.00 (reference)	3.23 (1.01–10.31)	2.76 (0.88–8.68)	2.44 (0.82–7.29)	2.14 (0.72–6.35)	0.62
Multivariable-adjusted OR	1.00 (reference)	2.72 (0.82–8.96)	2.10 (0.65–6.85)	1.86 (0.60–5.80)	1.46 (0.46–4.61)	0.18
Dyslipidemia						
Unadjusted OR	1.00 (reference)	0.80 (0.52–1.25)	0.90 (0.59–1.37)	1.11 (0.74–1.66)	1.23 (0.81–1.86)	0.005
Age- and sex-adjusted OR	1.00 (reference)	0.84 (0.53–1.31)	0.93 (0.60–1.43)	1.23 (0.81–1.87)	1.37 (0.89–2.10)	<0.001
Multivariable-adjusted OR	1.00 (reference)	0.87 (0.55–1.37)	0.99 (0.63–1.55)	1.31 (0.85–2.03)	1.39 (0.88–2.20)	0.002
Overweight						
Unadjusted OR	1.00 (reference)	1.20 (0.85–1.70)	1.58 (1.13–2.20)	1.55 (1.13–2.13)	1.30 (0.94–1.79)	0.13
Age- and sex-adjusted OR	1.00 (reference)	1.28 (0.90–1.81)	1.73 (1.24–2.43)	1.83 (1.32–2.54)	1.54 (1.10–2.16)	0.01
Multivariable-adjusted OR	1.00 (reference)	1.03 (0.72–1.48)	1.22 (0.85–1.74)	1.16 (0.82–1.64)	0.82 (0.59–1.23)	0.23
Smoking						
Unadjusted OR	1.00 (reference)	0.62 (0.39–0.99)	0.86 (0.56–1.31)	0.72 (0.48–1.08)	0.95 (0.63–1.43)	0.41
Age- and sex-adjusted OR	1.00 (reference)	0.70 (0.43–1.14)	1.03 (0.66–1.62)	1.03 (0.67–1.60)	1.39 (0.96–2.17)	0.006
Multivariable-adjusted OR	1.00 (reference)	0.67 (0.41–1.10)	0.95 (0.60–1.52)	0.94 (0.59–1.48)	1.23 (0.76–2.00)	0.04

Values are presented as ORs (95% CIs). Multivariable-adjusted models adjusted for age, sex, CVD history, cause of CKD (chronic glomerulonephritis [reference], diabetic nephropathy, hypertensive nephrosclerosis, other), presence of hypertension, diabetes mellitus, dyslipidemia, body mass index, and current smoking, except the variable relevant to the individual factor. Abbreviations: ACR, urinary albumin to creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; OR, odds ratio.

target in patient at risk. Compared with patients in the low risk group, those in the extremely high risk group had significantly higher ORs for uncontrolled hypertension treatment targets (adjusted ORs [95% CI]: 3.68 [2.47–5.49]). No significant differences were found in the treatment targets for diabetes mellitus, dyslipidemia, overweight, and current smoking among the different CKD severities according to the multivariable-adjusted risks (adjusted ORs [95% CI]: 1.46 [0.46–4.61], 1.39 [0.88–2.20], 0.82 [0.59–1.23], and 1.23 [0.76–2.00], respectively). In **Supplementary Table 2**, we conducted a multivariable-adjusted logistic regression in all patients as a sensitivity analysis. Compared with patients in the low risk group, those in the extremely high risk group had significantly higher ORs for uncontrolled hypertension and dyslipidemia treatment targets (adjusted ORs [95% CI]: 7.40 [5.14–10.66] and 1.94 [1.39–2.70], respectively). As a sensitivity analysis, we also confirmed the association between CKD severity and the treatment target for diabetes mellitus in patients excluding users of erythropoiesis-stimulating agents or iron supplementation **(Supplementary Table 3)**. The results were substantially unchanged with the whole population. Furthermore, when analyzed accounting for facility differences, the associations between CKD severity and treatment management status of each cardiovascular risk factor were not substantially different than in the main results **(Supplementary Table 4)**. **Table 6** shows the potential interaction between CKD severity and CVD history in terms of the risk of an uncontrolled treatment target for hypertension. No significant interaction between CKD severity and CVD history was shown.

4. Factors Associated with Uncontrolled Treatment Targets for Cardiovascular Risk Factors

Finally, we used the multivariable analysis to identify factors independently associated with uncontrolled treatment targets for hypertension **(Table 7)**. Logistic regression using the stepwise backward method revealed that, for example, a higher BMI, the absence of a history of CVD, the presence of diabetes mellitus, and a higher ACR were independently associated with hypertension treatment targets.

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Table 6. Multivariable-adjusted odds ratios for uncontrolled treatment targets for hypertension according to the presence of CVD history

			Patients, *n*	Uncontrolled, *n* (%)	Multivariable-adjusted OR	*P* for interaction[§]
Hypertension						
Classification of CKD by eGFR and ACR categories	Low-risk	CVD (–)	122	42 (34.4)	1.00 (reference)	0.88
		CVD (+)	14	6 (42.9)	1.00 (reference)	
	Moderate-risk	CVD (–)	331	157 (47.4)	1.77 (1.14–2.75)	
		CVD (+)	53	22 (41.5)	1.07 (0.31–3.72)	
	High-risk	CVD (–)	433	242 (55.9)	2.57 (1.67–3.93)	
		CVD (+)	110	46 (41.8)	1.28 (0.39–4.17)	
	Very high-risk	CVD (–)	711	401 (56.4)	2.61 (1.73–3.95)	
		CVD (+)	312	118 (37.8)	1.17 (0.38–3.67)	
	Extremely high-risk	CVD (–)	497	315 (63.4)	3.40 (2.20–5.26)	
		CVD (+)	346	199 (57.5)	2.47 (0.79–7.76)	

Values are presented as ORs (95% CIs). Multivariable-adjusted models adjusted for age, sex, CVD history, cause of CKD (chronic glomerulonephritis [reference], diabetic nephropathy, hypertensive nephrosclerosis, other), presence of diabetes mellitus, dyslipidemia, body mass index, and current smoking. [§]: "*P* for interaction" tested the interaction of the association of CKD severity with uncontrolled treatment targets for hypertension between the presence and the absence of a history of CVD. Abbreviations: ACR, urinary albumin to creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; OR, odds ratio.

Table 7. Multivariable analysis of factors independently associated with uncontrolled treatment targets for hypertension

Variable	Adjusted OR (95% CI)	*P*-value
Age (per 10-year increment)	0.94 (0.88–1.03)	0.06
Men (vs. women)	0.93 (0.79–1.09)	0.36
Body mass index (per 5-kg/m^2 increment)	1.24 (1.12–1.37)	<0.001
History of CVD (vs. without)	0.66 (0.55–0.79)	<0.001
Diabetes mellitus (vs. without)	1.36 (1.13–1.64)	0.001
ACR (per 1-log mg/gCr increment)	1.39 (1.33–1.46)	<0.001
Serum albumin (per 1-g/dL increment)	1.81 (1.44–2.27)	<0.001
Serum calcium (per 1-mg/dL increment)	0.75 (0.63–0.90)	0.002
Use of antihypertensive agents (vs. without)	0.25 (0.18–0.36)	<0.001
Use of sodium bicarbonate (vs. without)	0.55 (0.38–0.79)	0.001

Values were selected by a logistic regression model and stepwise backward selection with a *P*-value of <0.01 for the remaining variables (age and sex were included as initial candidate variables) and presented as ORs (95% CIs). Conversion factors for units: albumin in g/dL to g/L, ×10; calcium in mg/dL to mmol/L, ×0.2495. Abbreviations: ACR, urinary albumin to creatinine ratio; CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio.

Discussion

This cross-sectional study analyzed the relationship between CKD severity when classified into eGFR and ACR categories and the cardiovascular risk factor burden or success of therapeutic management in patients with non-dialysis-dependent CKD. Advanced CKD was positively associated with a high burden of cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidemia, as well as nontraditional risk factors. Furthermore, patients with advanced eGFR and ACR categories had greater difficulty in achieving hypertension treatment targets. Compared with patients in the low risk group, those in the extremely high risk group had significantly higher (3.7-fold) ORs for uncontrolled hypertension treatment targets. In contrast, there were no significant differences among eGFR and ACR categories in terms of the treatment targets for diabetes mellitus, dyslipidemia, overweight, and current smoking. The findings of this study suggest that patients with advanced CKD have a high burden of cardiovascular risk factors, and that in this population, it is difficult to manage these cardiovascular risk factors in clinical practice.

Previous reports have shown that CKD progression is associated with more frequent cardiovascular risk factors[38, 39]. The National Health and Nutrition Examination Survey conducted among a large civilian noninstitutionalized population in the

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United States reported a 1.2- to 1.6-fold increase in the prevalence of hypertension, diabetes mellitus, and dyslipidemia in patients with a reduced eGFR[38]. In addition, the Chronic Renal Insufficiency Cohort (CRIC) Study revealed that the prevalence of hypertension, diabetes mellitus, and dyslipidemia increased as eGFR decreased in a population with CKD[39]. The present study showed similar results in a Japanese population with CKD. Together, these findings highlight that patients with CKD present multiple cardiovascular risk factors in clinical practice.

Moreover, this study examined the therapeutic management status of cardiovascular risk factors. Our findings showed that it was more difficult to treat hypertension with greater severity of CKD whereas the management status of diabetes mellitus, dyslipidemia, overweight, and smoking were not associated with CKD severity. In the CRIC Study, the proportion of patients with blood pressure $<130/80$ mmHg decreased as the eGFR category progressed with only approximately 50% of patients with eGFR <30 mL/min/1.73 m^2 being appropriately treated[24]. There are several explanations that have been postulated to explain the association between CKD severity and uncontrolled hypertension. The effect of uremia-related factors (e.g., uremic toxins, intravascular volume overload, renal anemia, microinflammation, and activation of the sympathetic nervous system) becomes more apparent as CKD advances, resulting in uncontrolled hypertension[40]. Clinical inertia should also be mentioned[41], which often occurs in patients with CKD, partially because of multimorbidity[27, 42]. Furthermore, we previously reported that the number of medications increased linearly with the progression of the CKD stage[27]. Polypharmacy may be one reason why it is difficult to manage hypertension. These increase the difficulty in treating patients with CKD.

We did not find a significant association between CKD severity and therapeutic management status of dyslipidemia among patients with dyslipidemia. In our previous study, we reported hypertriglyceridemia and hypo-HDL-cholesterolemia as clinical characteristics of dyslipidemia in patients with CKD[43]. The use of fibrates should be avoided in patients with CKD owing to concerns about rhabdomyolysis[44], which may lead to hypertriglyceridemia. Furthermore, no effective treatment strategy to increase serum HDL-cholesterol concentrations has been established[45]. On the other hand, statin therapy effectively reduces the serum LDL-cholesterol concentration in patients with CKD[46-48]. Namely, the progression of CKD severity itself may not be associated with difficulty in overall managing dyslipidemia.

Interestingly, the association between the therapeutic management status of hypertension and CKD severity was not significantly different among patients with or without a history of CVD in the present study. This finding may explain why even patients with a history of CVD are not always adequately treated for hypertension in clinical practice. Furthermore, we found no significant association between CKD severity and therapeutic management status of diabetes mellitus or overweight. However, in the logistic regression model with stepwise backward selection, the presence of diabetes mellitus and a higher BMI remained risk factors for uncontrolled hypertension, suggesting that management of patients classified as diabetes mellitus or overweight may be important for treating hypertension. Because this was a cross-sectional study, we cannot determine whether intervention for overweight in the early stage of CKD may improve hypertension. Further studies are needed to elucidate whether controlling overweight can improve hypertension in patients with CKD.

The present study has several important strengths. The FKR Study enrolled patients with non-dialysis-dependent CKD of all stages, ages, and causes, who were managed by nephrologists. The results of this study apply to Japanese patients with CKD who were treated by nephrologists in clinical practice. In addition, demographic data, blood and urine tests, use of medications, and CVD history were investigated in detail, allowing for a more precise examination of treatment management status. Furthermore, we assessed CKD severity using eGFR and ACR categories based on KDIGO guidelines. To the best of our knowledge, this was the first study to examine the burden of cardiovascular risk factors and overall treatment control in patients with non-dialysis-dependent CKD according to eGFR and ACR categories.

This study also has some limitations. First, the laboratory tests were single measurements, which may have led to misclassification. Second, we did not measure glycated albumin, which is unaffected by anemia. The treatment status of diabetes mellitus might be underestimated in patients with anemia although we confirmed a sensitivity analysis excluding users of erythropoiesis-stimulating agents and/or iron supplementation. Third, causal relationships between CKD severity and treatment status for cardiovascular risk factors could not be determined because this was a cross-sectional study. In patients who do not achieve target levels, kidney diseases may be more likely to progress. This may result in advanced CKD, which is positively associated with a high burden of cardiovascular risk factors. The reason there were no

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significant differences among eGFR and ACR categories in terms of the treatment targets for diabetes mellitus, dyslipidemia, overweight, and current smoking may be owing to the difficulty in their achievement rather than different impacts on the progression of CKD. Moreover, it was impossible to examine whether achieving the treatment management targets established in this study reduced the incidence of CVD. Lowering blood pressure is not always good for frail patients, according to the previous studies[49]. In addition, glycemic targets in elderly patients with diabetes mellitus are determined by taking into account each patient's age, duration of diabetes mellitus, risk for hypoglycemia, as well as any available patient support, cognitive function, basic/instrumental activities of daily living, comorbidities, and functional impairments[50]. The presence of frailty or dementia may confound our results. In the future, we wish to examine the association between treatment status and CVD incidence using the data from our prospective ongoing study. Despite these limitations, we believe that this detailed examination of the prevalence of cardiovascular risk factors and their therapeutic management in patients with CKD will lead to appropriate therapeutic strategies, helping to improve patients' life quality and renal outcomes and preventing the development of CVD.

Conclusion

This study showed that the cardiovascular risk factor burden increased as CKD severity, including eGFR and ACR categories, progressed in patients with non-dialysis-dependent CKD, and that advanced CKD was associated with difficulty in managing hypertension. The FKR Study will now be longitudinally analyzed to determine the association between the cardiovascular risk factor burden and treatment management status and CVD development.

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Conflict of Interest:

The authors declare that they have no relevant financial interests.

Authors' Contributions

Hiromasa Kitamura contributed to the study design, statistical analysis, data interpretation, and drafting the manuscript. Shigeru Tanaka contributed to the study design, data acquisition, statistical analysis, data interpretation, and drafting the manuscript. Hiroto Hiyamuta contributed to data interpretation and drafting the manuscript. Sho Shimamoto contributed to data interpretation and drafting the manuscript. Kazuhiko Tsuruya contributed to critical revision of the manuscript and supervised the study. Toshiaki Nakano contributed to the study design, data acquisition, and drafting the manuscript. Takanari Kitazono contributed to critical revision of the manuscript and supervised the study. All authors provided critical review of the draft and approved the final version for submission.

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Supplementary Table 1. Prevalence of traditional and non-traditional cardiovascular risk factors according to the classification of CKD by eGFR and ACR categories

		Classification of CKD by eGFR and ACR categories					
	Total (n=3407)	Low-risk n=260	Moderate-risk n=533	High-risk n=647	Very high-risk n=1099	Extremely high-risk n=868	P for trend
Traditional risk factors							
Hypertension	2929 (86.0)	136 (52.3)	384 (72.1)	543 (83.9)	1023 (93.1)	843 (97.1)	<0.001
Diabetes mellitus	830 (24.4)	30 (11.5)	74 (13.9)	100 (15.5)	274 (24.9)	352 (40.6)	<0.001
Dyslipidemia	2257 (66.3)	129 (49.6)	304 (57.0)	441 (68.2)	766 (69.7)	617 (71.1)	<0.001
Overweight	1001 (29.4)	60 (23.1)	141 (26.5)	208 (32.2)	349 (31.8)	243 (28.0)	0.13
Current smoking	381 (11.2)	35 (13.5)	47 (8.8)	76 (11.8)	111 (10.1)	112 (12.9)	0.41
Non-traditional risk factors							
Anemia	880 (25.8)	19 (7.3)	34 (6.4)	50 (7.7)	268 (24.4)	509 (58.6)	<0.001
High serum hs-CRP	1076 (31.6)	53 (20.4)	127 (23.8)	179 (27.7)	391 (35.6)	326 (37.6)	<0.001
Hyperuricemia	1955 (57.4)	32 (12.3)	152 (28.5)	275 (42.5)	767 (69.8)	729 (84.0)	<0.001
Hypokalemia/hyperkalemia	962 (28.2)	78 (30.0)	127 (23.8)	143 (22.1)	242 (22.0)	372 (42.9)	<0.001
Frequency (no. of conditions)							
0–1	304 (8.9)	88 (33.9)	123 (23.1)	79 (12.2)	56 (5.1)	8 (0.9)	<0.001[§]
2	555 (16.3)	74 (28.5)	152 (28.5)	143 (22.1)	152 (13.8)	34 (3.9)	
3	743 (21.8)	48 (18.5)	128 (24.0)	178 (27.5)	262 (23.8)	127 (14.6)	
4	728 (21.4)	33 (12.7)	65 (12.2)	138 (21.3)	279 (25.4)	213 (24.5)	
5	586 (17.2)	12 (4.6)	46 (8.6)	81 (12.5)	210 (19.1)	237 (27.3)	
6	299 (8.8)	5 (1.9)	17 (3.2)	21 (3.3)	104 (9.5)	152 (17.5)	
7–9	142 (4.2)	0 (0.0)	2 (0.38)	7 (1.1)	36 (3.3)	97 (11.2)	

Baseline data are expressed as number (percentage). Frequency is the sum of the number of hypertension, diabetes mellitus, dyslipidemia, overweight, current smoking, anemia, high serum hs-CRP, hyperuricemia, and hypo/hyperkalemia. Abbreviations: ACR, urinary albumin to creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein. [§]: Trend test for patients with 5 or more conditions.

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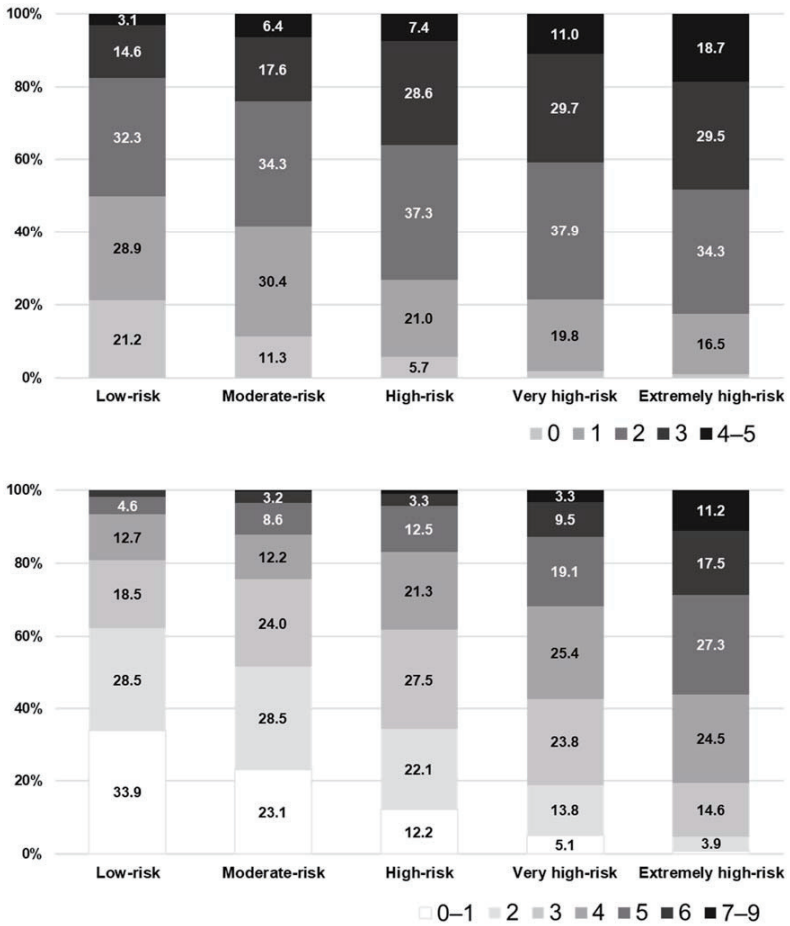

Supplementary Fig. 1. Proportion of the prevalence of traditional (top) and both traditional and non-traditional (bottom) cardiovascular risk factors by eGFR and ACR categories

Traditional cardiovascular risk factors include hypertension, diabetes mellitus, dyslipidemia, obesity, and current smoking. Non-traditional cardiovascular risk factors include anemia, a high concentration of high-sensitivity C-reactive protein, hyperuricemia, and hypokalemia/hyperkalemia. Abbreviations: ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

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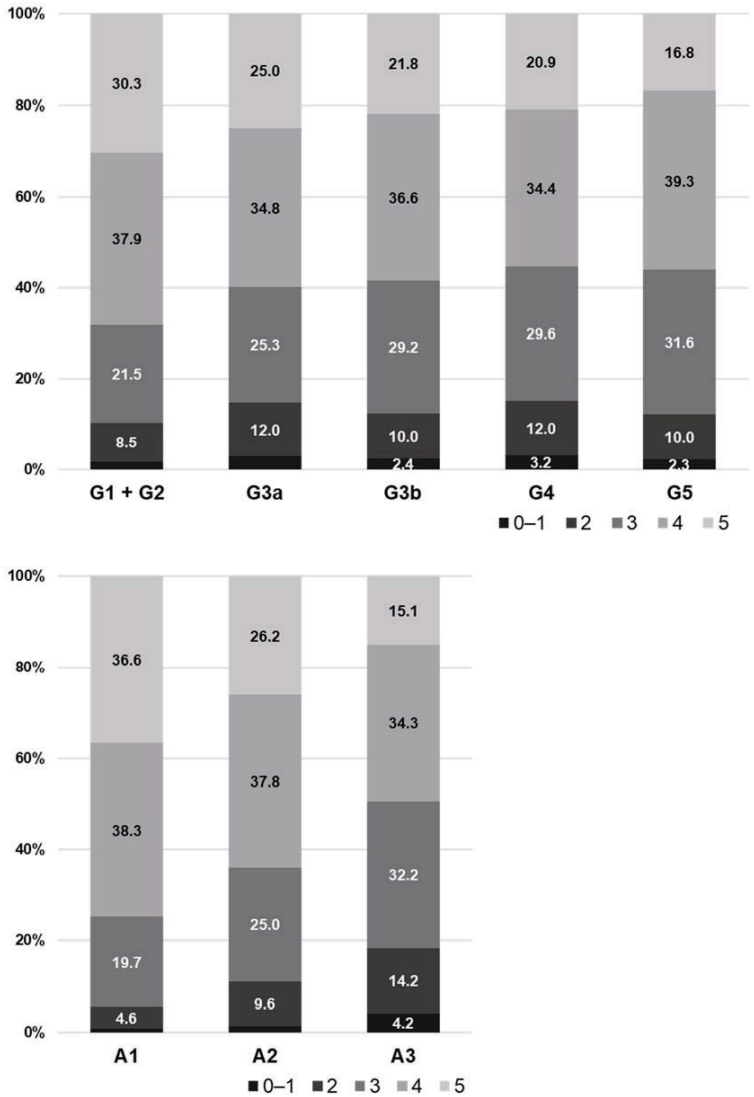

Supplementary Fig. 2. Proportion of patients who achieved the treatment targets for cardiovascular risk factors by eGFR stage (top) and ACR stage (bottom)

Abbreviations: ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

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Supplementary Table 2. Odds ratios of uncontrolled treatment targets for hypertension, diabetes mellitus, and dyslipidemia using all patients as the denominator

		Classification of CKD by eGFR and ACR categories					
	Total *n*=3407	Low-risk *n*=260	Moderate-risk *n*=533	High-risk *n*=647	Very high-risk *n*=1099	Extremely high-risk *n*=868	*P* for trend
Hypertension							
Uncontrolled, *n* (%)[§]	1630 (47.8)	49 (18.9)	201 (37.7)	314 (48.5)	545 (49.6)	521 (60.0)	
Unadjusted OR		1.00 (reference)	2.61 (1.83–3.72)	4.06 (2.87–5.74)	4.24 (3.04–5.91)	6.47 (4.61–9.08)	<0.001
Age- and sex-adjusted OR		1.00 (reference)	2.79 (1.95–4.00)	4.56 (3.20–6.49)	5.04 (3.58–7.12)	7.87 (5.53–11.22)	<0.001
Multivariable-adjusted OR		1.00 (reference)	2.72 (1.89–3.90)	4.32 (3.03–6.17)	4.81 (3.40–6.82)	7.40 (5.14–10.66)	<0.001
Diabetes mellitus							
Uncontrolled, *n* (%)	208 (6.1)	4 (1.5)	24 (4.5)	28 (4.3)	70 (6.4)	82 (9.5)	
Unadjusted OR		1.00 (reference)	3.02 (1.04–8.79)	2.90 (1.01–8.34)	4.35 (1.58–12.04)	6.78 (2.42–18.39)	<0.001
Age- and sex-adjusted OR		1.00 (reference)	2.82 (0.97–8.24)	2.55 (0.88–7.38)	3.67 (1.31–10.27)	5.46 (1.95–15.30)	<0.001
Multivariable-adjusted OR		1.00 (reference)	2.00 (0.67–5.97)	1.45 (0.49–4.30)	1.50 (0.52–4.32)	1.24 (0.42–3.62)	0.30
Dyslipidemia							
Uncontrolled, *n* (%)	1575 (46.2)	89 (34.2)	195 (36.6)	294 (45.4)	545 (49.6)	452 (52.1)	
Unadjusted OR		1.00 (reference)	1.11 (0.81–1.51)	1.60 (1.19–2.16)	1.89 (1.43–2.51)	2.09 (1.56–2.79)	<0.001
Age- and sex-adjusted OR		1.00 (reference)	1.12 (0.82–1.53)	1.61 (1.19–2.19)	1.94 (1.45–2.60)	2.14 (1.58–2.89)	<0.001
Multivariable-adjusted OR		1.00 (reference)	1.11 (0.81–1.54)	1.53 (1.11–2.10)	1.83 (1.34–2.50)	1.94 (1.39–2.70)	<0.001

Values are presented as ORs (95% CIs). Multivariable-adjusted models adjusted for age, sex, CVD history, cause of CKD (chronic glomerulonephritis [reference], diabetic nephropathy, hypertensive nephrosclerosis, other), presence of hypertension, diabetes mellitus, dyslipidemia, body mass index, and current smoking, except the variable relevant to the individual factor. Abbreviations: ACR, urinary albumin to creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; OR, odds ratio. [§]: Including patients who did not diagnose with hypertension but did not achieve the treatment target in this study.

Supplementary Table 3. Odds ratios of uncontrolled treatment targets for diabetes mellitus after excluding individuals with use of ESAs and/or iron supplementation

		Classification of CKD by eGFR and ACR categories					
	Total *n*=619	Low-risk *n*=30	Moderate-risk *n*=71	High-risk *n*=92	Very high-risk *n*=219	Extremely high-risk *n*=207	*P* for trend
Diabetes mellitus							
Uncontrolled, *n* (%)	166 (26.8)	4 (13.3)	24 (33.8)	25 (27.2)	60 (27.4)	53 (25.6)	
Unadjusted OR		1.00 (reference)	3.32 (1.04–10.61)	2.43 (0.77–7.65)	2.45 (0.82–7.32)	2.24 (0.75–6.71)	0.96
Age- and sex-adjusted OR		1.00 (reference)	3.38 (1.06–10.82)	2.56 (0.81–8.13)	2.59 (0.86–7.79)	2.35 (0.78–7.07)	0.95
Multivariable-adjusted OR		1.00 (reference)	2.75 (0.83–9.08)	1.85 (0.56–6.06)	1.84 (0.59–5.77)	1.53 (0.48–4.94)	0.41

Values are presented as ORs (95% CIs). Multivariable-adjusted models adjusted for age, sex, CVD history, cause of CKD (chronic glomerulonephritis [reference], diabetic nephropathy, hypertensive nephrosclerosis, other), presence of hypertension, dyslipidemia, body mass index, and current smoking. Abbreviations: ACR, urinary albumin to creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; OR, odds ratio.

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Supplementary Table 4. Odds ratios of uncontrolled treatment targets for cardiovascular risk factors, adjusting for facility-level clustering effects

	Classification of CKD by eGFR and ACR categories					*P* for trend
	Low-risk	Moderate-risk	High-risk	Very high-risk	Extremely high-risk	
Hypertension (*n*=2929)						
Multivariable-adjusted OR	1.00 (reference)	1.76 (1.42–2.17)	2.45 (1.95–3.08)	2.38 (1.89–2.99)	3.83 (2.98–4.91)	<0.001
Diabetes mellitus (*n*=830)						
Multivariable-adjusted OR	1.00 (reference)	2.79 (0.73–10.59)	2.02 (0.47–8.56)	1.85 (0.48–7.19)	1.43 (0.39–5.25)	0.02
Dyslipidemia (*n*=2257)						
Multivariable-adjusted OR	1.00 (reference)	0.88 (0.62–1.26)	0.98 (0.70–1.36)	1.31 (1.06–1.62)	1.43 (1.13–1.81)	<0.001
Overweight (*n*=3407)						
Multivariable-adjusted OR	1.00 (reference)	1.02 (0.67–1.54)	1.18 (0.79–1.76)	1.12 (0.79–1.59)	0.86 (0.57–1.28)	0.16
Smoking (*n*=3407)						
Multivariable-adjusted OR	1.00 (reference)	0.68 (0.38–1.21)	0.95 (0.54–1.67)	0.94 (0.63–1.41)	1.22 (0.67–2.22)	0.02

Values are presented as ORs (95% CIs). The risk estimates were calculated using the logistic regression model with generalized estimating equation methods, adjusting for facility-level clustering effects. Multivariable-adjusted models adjusted for age, sex, CVD history, cause of CKD (chronic glomerulonephritis [reference], diabetic nephropathy, hypertensive nephrosclerosis, other), presence of hypertension, diabetes mellitus, dyslipidemia, body mass index, and current smoking, except the variable relevant to the individual factor. Abbreviations: ACR, urinary albumin to creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; OR, odds ratio.

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