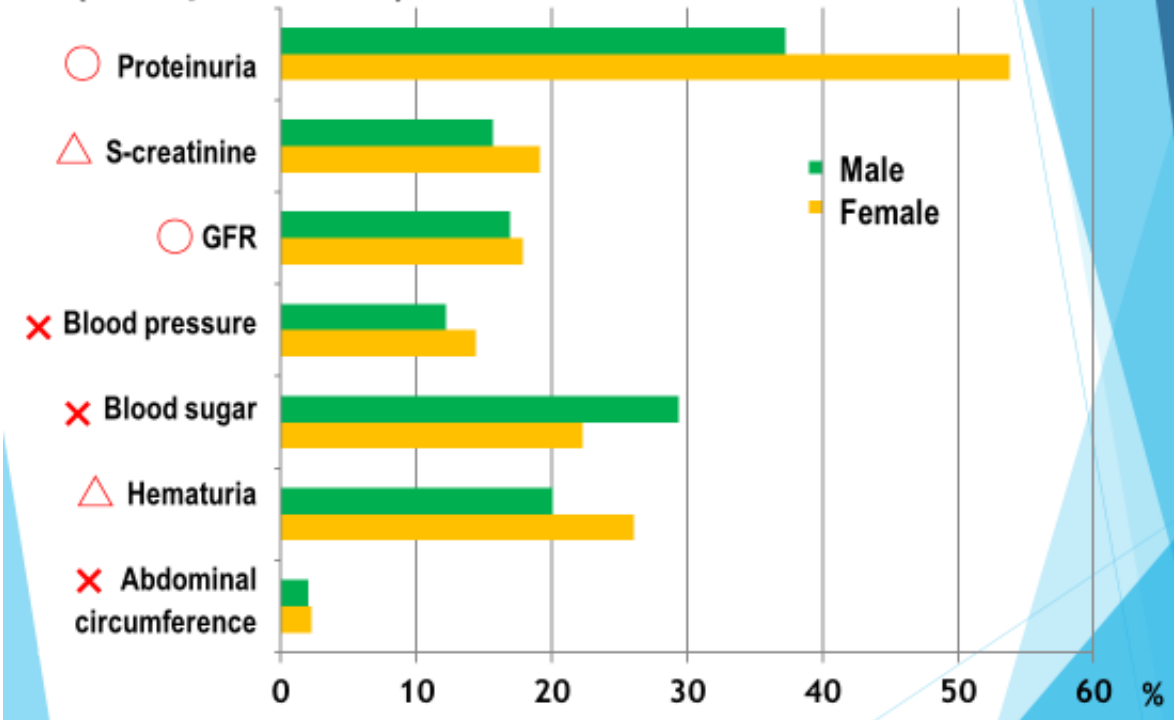
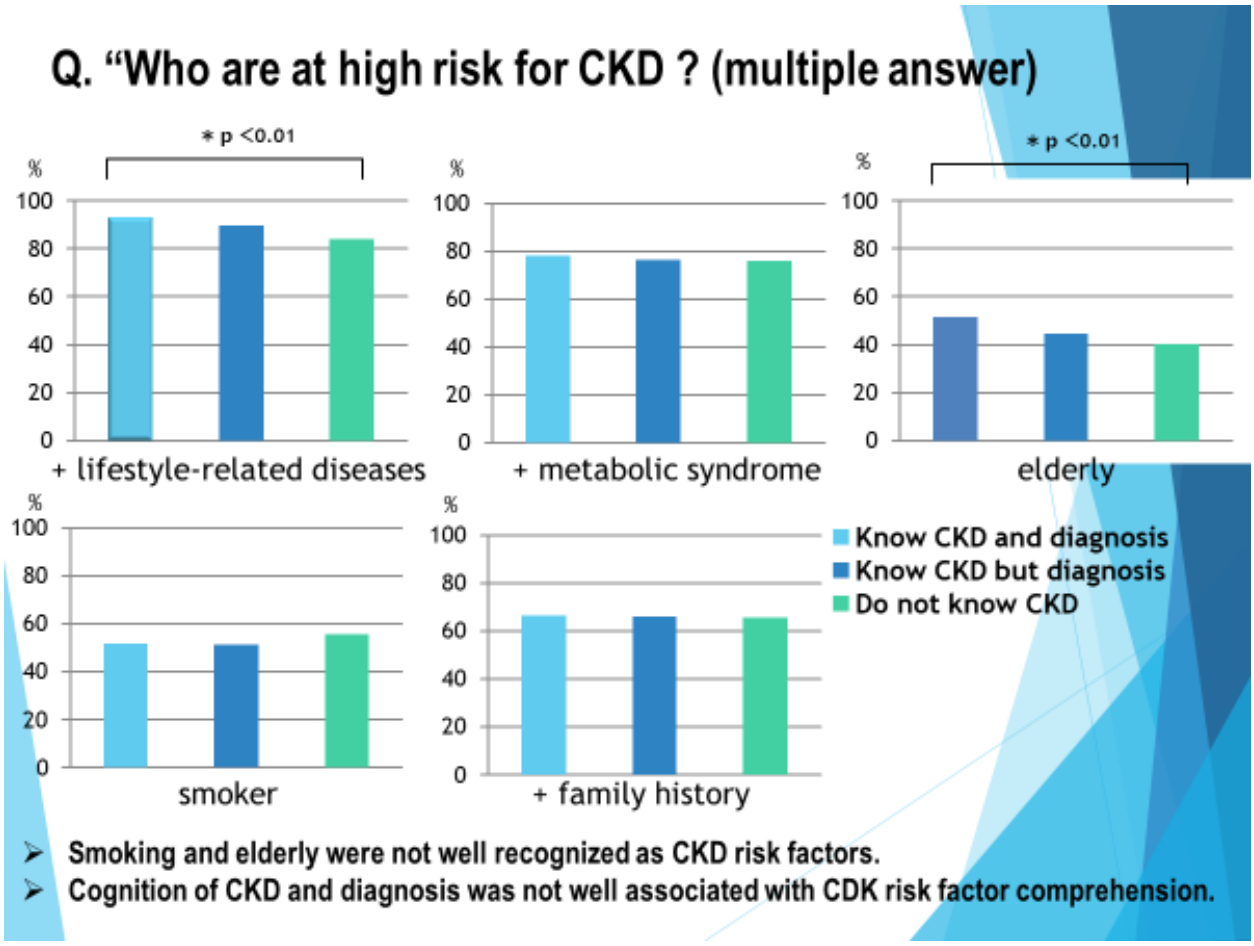
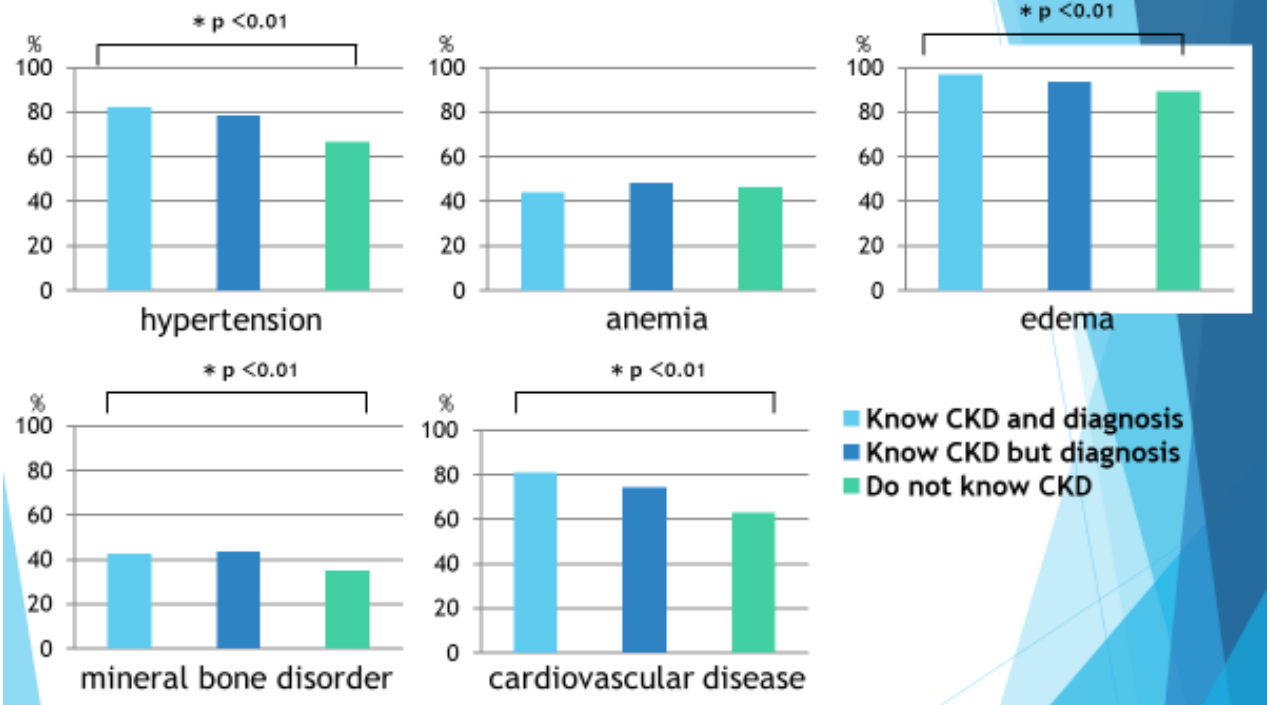
Q. "What are essential items for CKD diagnosis ? (multiple answer)



- Proteinuria was recognized at 58.9%, but GFR was poorly recognized at 31.5%.
- Proper understanding for CKD diagnosis was only at 4.6%.


Q. “Who are at high risk for CKD ? (multiple answer)
＊p <0.01
%
100
80
60
40
20
0
+ lifestyle-related diseases
+ metabolic syndrome
＊p <0.01
elderly
smoker
+ family history
Know CKD and diagnosis
Know CKD but diagnosis
Do not know CKD
Smoking and elderly were not well recognized as CKD risk factors.
Cognition of CKD and diagnosis was not well associated with CDK risk factor comprehension.

Q. “What are clinical symptoms of CKD ? (multiple answer)



- Regarding clinical symptoms of CKD, edema and hypertension were recognized sufficiently followed by CVD, but renal anemia and mineral bone disorder were poorly recognized.
- Cognition of CKD and diagnosis was associated with CDK symptom comprehension.

Randomized Control Trial on CKD awareness

- Health-check subjects in Kasugai City Medical Care Center
- Questionnaire survey was conducted in 2013.
- Among Intervention group, a leaflet on CKD was handed.
- The same questionnaire survey is conducted in 2014 and CKD awareness and comprehension degree will be analyzed.

Do you think that a leaflet can change the world?

This study was supported by research grant from MHWL and was approved by the ethical committee of JSN.

Conclusion

- The mid-term result of our RCT revealed that CKD awareness and comprehension degree remained low in Japan even among health-check subjects.

- CKD enlightenment campaigns in collaboration with government, the mass media, health professionals and academic societies are essential to improve CKD awareness, and their effect should be adequately monitored at regular intervals.

主な研究成果物

Clin Exp Nephrol (2010) 14:558–570
DOI 10.1007/s10157-010-0328-6

ORIGINAL ARTICLE

Chronic Kidney Disease Japan Cohort study: baseline characteristics and factors associated with causative diseases and renal function

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Received: 23 April 2010 / Accepted: 6 July 2010 / Published online: 11 August 2010

Abstract
Background Prevalence of chronic kidney disease (CKD) is estimated to be 13.3 million in Japan, but patient characteristics during the predialysis period (CKD stages 3–5) are not well studied.
Methods We established the Chronic Kidney Disease Japan Cohort (CKD-JAC) to study the incidence of cardiovascular disease (CVD), end-stage renal disease (ESRD), and all-cause mortality in predialysis patients treated by nephrologists for 4 years. The inclusion criteria were (1) Japanese and Asian patients living in Japan, (2) age 20–75 years, and (3) estimated glomerular filtration rate (eGFR) 10–59 ml/min/1.73 m^2.
Results We analyzed 2977 participants for baseline characteristics. Mean eGFR was 28.6 ± 11.8 ml/min/1.73 m^2, and mean albuminuria was 976 ± 1340 mg/g Cr. In our study, 91.9% of participants had hypertension, but it was well controlled (131/76 mmHg). Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were used by most participants. Less than 15% of participants had history of ischemic heart disease, and 11.5% had history of stroke. Heart failure and arteriosclerosis obliterans were present in 3.9% and 3.6% of patients, respectively. Indicators of arteriosclerosis, higher pulse wave velocity (PWV), and high pulse pressure were associated with diabetes and particularly with diabetic nephropathy. Patients included due to glomerulonephritis seemed to be at low risk for atherosclerosis and also to show lower levels of hypertension.
Conclusions The difference between causative diseases is associated with different comorbidity and level of arteriosclerosis. Future analysis of the cohort will clarify whether incidence of ESRD and CVD differs among causative diseases.

Keywords CKD · Diabetes · Chronic glomerulonephritis · Hypertension · PWV · Pulse pressure

For The CKD-JAC Study Group.

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Introduction

The incidence of end-stage renal disease (ESRD) is on the increase worldwide [1], and Japan is one of the countries with the highest incidence of ESRD. More than 37,000

ESRD patients were introduced to renal replacement therapy in 2008 [2]. Diabetes, which has been a leading cause of ESRD during the last 10 years, accounted for 16126 new dialysis patients (43.2%). Glomerulonephritis and nephrosclerosis were responsible for 8602 (23.0%) and 3936 (10.5%) new dialysis patients, respectively [2]. Prevalence of chronic kidney disease (CKD) is estimated at 13.3 million (13% of adult population) in Japan, with CKD patients at stages 1 to 5 numbering 0.6 million, 1.7 million, 10.7 million, 200 thousand, and 40 thousand, respectively [3]. However, patient characteristics during the predialysis period (CKD stages 3–5) are not well studied because few cohort studies have been conducted.

Cardiovascular disease (CVD) is a major threat for patients with CKD [4]. In population-based studies, the risk of CVD increases in association with decreasing renal function in Western as well as in Asian countries [4, 5]. However, few prospective observational studies have been conducted to observe cardiovascular and renal outcomes in CKD population. A cohort of CKD patients treated with a high standard of care by nephrologists is necessary to analyze renal and cardiovascular events precisely.

A body of evidence has shown that arteriosclerosis contributes to high cardiovascular mortality. Increased arterial stiffness has been reported in CKD patients, and these findings have been associated with cardiovascular mortality. Aortic pulse wave velocity (PWV) and pulse pressure (PP) are strong independent predictors of cardiovascular mortality [6–9].

The Chronic Renal Insufficiency Cohort (CRIC) study [10] was undertaken in the USA to examine the risk factors for progression of CKD with respect to development of CVD among CKD patients, and to develop models for development of CVD that could identify high-risk subgroups. We saw the need to deal with the same issues in a Japanese cohort, and established the Chronic Kidney Disease Japan Cohort (CKD-JAC) [11]. While the risk of coronary artery disease is lower in the Japanese general population [12], the main aim of the prospective CKD-JAC study is to investigate the incidence of CVD, ESRD, and all-cause mortality for 4 years in 3000 CKD patients, defined by GFR 10–59 ml/min/1.73 m^2. Analysis by causative diseases and renal function will clearly shed light on the difference in cardiovascular and renal outcomes in CKD patients.

Methods

Inclusion and exclusion criteria

Methods have been described elsewhere [11].

The following inclusion criteria were used at screening: (1) Japanese and Asian patients living in Japan, (2) age 20–75 years, and (3) a broad spectrum of CKD with estimated GFR (eGFR) 10–59 ml/min/1.73 m^2. eGFR was calculated by a modified three-variable equation for estimating GFR in Japanese patients [13]:

$$\mathrm{eGFR} = 194 \times \mathrm{Age}^{-0.287} \times \mathrm{sCr}^{-1.094} \times (0.739 \text{ if female}).$$

The following patients were excluded from participation: (1) patients with polycystic kidney disease, human immunodeficiency virus (HIV) infection, liver cirrhosis, active cancer or cancer treatment within last 2 years; (2) transplant recipients and patients who have previously received long-term dialysis; and (3) individuals who refused to provide informed consent.

Screening and enrollment

Eligible patients were screened by eGFR as calculated by the Japanese equation for estimating GFR from serum creatinine, shown above. Eligible patients were evaluated at baseline, and sociodemographic information, individual and family history, medication records, anthropometric measurements, blood pressure, heart rate, and ankle-brachial index, were collected.

Blood pressure and PWV measurement

Blood pressure was measured at outpatient clinics by automated sphygmomanometer after 5 min of rest. Blood pressure was measured three times at intervals of 1 min on the right arm. A conventional sphygmomanometer was used when the participant showed frequent premature contraction, atrial fibrillation or atrial flutter. PP was calculated by subtracting diastolic blood pressure from systolic blood pressure. PWV was measured at each hospital. Pressure waveforms of the brachial and tibial arteries were recorded by oscillometry, using occlusion/sensing cuffs adapted to both arms and both ankles.

Definition of hypertension, diabetes, and glomerulonephritis

Definition of hypertension was 140 mmHg or higher in systolic blood pressure and/or 90 mmHg or higher in diastolic blood pressure, or taking antihypertensives. Diabetes was defined as A1C 6.5% or higher, or taking antidiabetics. Glomerulonephritis was defined by biopsy or clinical diagnosis by doctor in charge.

Collection of biological samples and measurements

Whole blood, serum, and urine samples were collected for measurement of serum creatinine and serum cystatin C,

HbA1c, intact parathyroid hormone (iPTH), urine albumin, and urine creatinine at a central laboratory. HbA1c measured by the Japanese Diabetes Society (JDS) method was corrected to the A1C value measured by the National Glycohemoglobin Standardization Program (NGSP) method by adding 0.4% as determined by JDS. Each clinical center measured serum creatinine at each visit. Twenty-four-hour urine samples were collected from each patient once every year to measure creatinine clearance.

General methods for statistical analysis

Standard descriptive statistics were used to describe baseline characteristics. Summary statistics such as means, medians, standard deviations, and ranges were calculated for measured variables. One-way analysis of variance was used to compare intergroup values as occasion demanded. Frequencies were tabulated for categorical and ordinal variables, and internal comparison was made using the chi-squared test.

The two-sided 95% confidence interval was calculated by estimation. The significance level was set at two-sided 5%.

Results

We enrolled outpatients as participants in the CKD-JAC study from April 2007 to December 2008. The number of registered cases was 3087. Sixteen patients were excluded because they met the exclusion criteria, and baseline data abstraction was not completed for an additional 25 patients. Sixty-nine patients dropped out after registration without completing baseline data abstraction: 59 of those patients withdrew their consent, and an additional 5 patients were excluded by doctors in charge. Four patients were lost to follow-up because they did not return to the hospital, and 1 patient died. After deleting these patients from the registry, a total of 2977 cases were analyzed for baseline characteristics.

Baseline demographics and clinical characteristics of participants (Table 1)

The final enrolled cohort consisted of 1848 Japanese males (62.1%) and 1129 Japanese females (37.9%). Age [mean ± standard deviation (SD)] was 60.8 ± 11.6 years. Of these participants, 1120 (37.6%) had diabetes, and 613 (20.6%) of that group were diagnosed with diabetic nephropathy, among whom 57 cases (9.3%) were biopsy-proven diabetic nephropathy. Of 691 diabetic patients who did not have diabetic nephropathy, 190 cases (27.5%) were diagnosed as having primary glomerulonephritis by biopsy. Diagnosis of primary glomerulonephritis without diabetes was reached for 948 patients (31.9%), of whom 601 (63.4%) had biopsy-proven glomerulonephritis. Of patients diagnosed as nondiabetes and nonprimary glomerulonephritis, 177 cases (19.7%) were diagnosed by renal biopsy.

Mean BMI was 23.5 ± 3.8 kg/m^2. Mean serum creatinine was 2.15 ± 1.06 mg/dl, and mean eGFR was 28.7 ± 12.2 ml/min/1.73 m^2. Mean cystatin C was 1.88 ± 0.71 mg/l. Mean albuminuria was 976 ± 1340 mg/g Cr.

Most participants had hypertension (91.9%) and were under treatment with antihypertensives. Mean blood pressure in participants was 131.7 (18.6) ± 76.3 (11.8) mmHg. ACEIs/ARBs were used by most participants. However, ARBs were used more frequently (73.4%) than ACEIs (27.5%). β-Blockers and diuretics were used by 27.1% and 29.7% of participants, respectively. Ca channel blockers were used by 55.4% of patients. Of patients, 1384 were being treated for dyslipidemia with lipid-lowering agents.

Less than 15% of participants had history of ischemic heart disease, and 11.5% had history of stroke. Heart failure and arteriosclerosis obliterans were present in 3.9% and 3.6% of patients, respectively. Current smokers accounted for 16.4% of all participants. Presence of diabetic nephropathy significantly changed patient characteristics. Patients with nephropathy had lower eGFR and more advanced anemia than those without nephropathy.

Patients with CKD due to glomerulonephritis were younger and less likely to have hypertension or cardiovascular comorbidity.

PWV and PP values were lowest in patients with CKD caused by glomerulonephritis (Tables 2, 3). Association with higher PWV and large PP was greatest in patients with diabetic nephropathy, followed by diabetes mellitus (DM) without nephropathy, and the lowest level of association was seen in non-DM patients.

Baseline characteristics by eGFR level (Table 4)

The numbers of participants with eGFR $\geq$ 45, 45 > eGFR $\geq$ 30, 30 > eGFR $\geq$ 15, and <15 ml/min/1.73 m^2 were 304, 1037, 1160, and 476, respectively. Systolic and mean blood pressures increased in association with decreasing eGFR, but diastolic blood pressure was not significantly different. Proteinuria increased in proportion to declining eGFR. Both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol decreased with declining eGFR. There was also a decrease in triglycerides, but it was not statistically significant. Serum calcium decreased and serum phosphate increased in proportion to decreased eGFR, which was associated with increased parathyroid hormone.

Comorbidity of cardiovascular diseases was more prevalent in proportion to declining eGFR.

Table 1 Patient characteristics classified by causative disease

Variable	Cohort, $N = 2977$	No diabetes		Diabetes		P value
		No CGN, $N = 909$	CGN, $N = 948$	No nephropathy, $N = 507$	Nephropathy, $N = 613$	
Sex						
Female	1129 (37.9)	333 (36.6)	440 (46.4)	168 (33.1)	188 (30.7)	<0.0001
Male	1848 (62.1)	576 (63.4)	508 (53.6)	339 (66.9)	425 (69.3)	
Age (years)						
Mean (SD)	60.8 (11.6)	60.6 (12.5)	57.6 (12.5)	64.4 (8.9)	63.0 (9.3)	<0.0001
Median (min, max)	63.0 (22–77)	64.0 (22–77)	60.0 (22–77)	66.0 (25–77)	64.0 (30–77)	
1Q–3Q	55.0–70.0	53.0–71.0	49.0–67.5	59.0–71.0	58.0–71.0	
Smoking [*n* (%)]	405 (13.6)	135 (14.9)	103 (10.9)	66 (13.0)	101 (16.5)	0.0004
Medical history [*n* (%)]						
Hypertension	2427 (81.5)	713 (78.4)	735 (77.5)	448 (88.4)	531 (86.6)	<0.0001
Cardiovascular disease	761 (25.6)	224 (24.6)	118 (12.4)	168 (33.1)	251 (40.9)	<0.0001
MI	146 (4.9)	31 (3.4)	17 (1.8)	45 (8.9)	53 (8.6)	<0.0001
Angina	254 (8.5)	71 (7.8)	49 (5.2)	64 (12.6)	70 (11.4)	<0.0001
Congestive heart failure	115 (3.9)	32 (3.5)	11 (1.2)	24 (4.7)	48 (7.8)	<0.0001
ASO	108 (3.6)	19 (2.1)	16 (1.7)	27 (5.3)	46 (7.5)	<0.0001
Stroke	342 (11.5)	112 (12.3)	52 (5.5)	68 (13.4)	110 (17.9)	<0.0001
Diabetic retinopathy	423 (14.2)	0 (0.0)	0 (0.0)	61 (12.0)	362 (59.1)	<0.0001
Cancer	214 (7.2)	71 (7.8)	53 (5.6)	51 (10.1)	39 (6.4)	0.0115
Diastolic blood pressure (mmHg)						
Mean (SD)	76.3 (11.8)	77.8 (11.8)	77.3 (11.2)	75.5 (12.4)	73.1 (11.7)	<0.0001
Median (min–max)	76.0 (33–128)	78.0 (38–128)	77.0 (42–124)	75.0 (35–127)	72.7 (33–116)	
1Q–3Q	68.7–84.0	70.0–85.3	70.0–84.0	67.0–83.0	65.8–80.7	
Systolic blood pressure (mmHg)						
Mean (SD)	131.7 (18.6)	130.2 (18.3)	129.1 (17.4)	132.3 (18.4)	137.2 (19.8)	<0.0001
Median (min–max)	130.6 (68–235)	130.0 (68–235)	127.3 (80–218)	132.0 (86–202)	136.5 (72–208)	
1Q–3Q	119.7–142.5	118.7–140.3	117.7–139.0	119.7–143.7	124.3–148.3	
Mean blood pressure (mmHg)						
Mean (SD)	95.1 (13.5)	95.4 (13.6)	95.2 (13.0)	94.7 (13.8)	94.7 (13.8)	0.7166
Median (min–max)	94.7 (35–163)	95.3 (35–162)	94.7 (59–155)	93.9 (54–163)	93.9 (52–144)	
1Q–3Q	86.3–103.2	87.0–103.3	86.7–103.3	85.7–103.3	86.0–102.3	
Pulse pressure (mmHg)						
Mean (SD)	55.4 (14.3)	52.5 (12.9)	51.9 (12.4)	56.9 (13.8)	64.2 (15.3)	<0.0001
Median (min–max)	53.7 (9–121)	51.5 (22–107)	50.3 (16–110)	55.7 (9–107)	63.7 (14–121)	
1Q–3Q	45.7–63.7	43.7–59.7	44.0–58.3	47.3–66.0	53.3–74.7	
PWV (pulse wave velocity) (cm/s)						
Mean (SD)	1670.0 (473.8)	1689.6 (601.3)	1456.3 (282.1)	1703.2 (403.3)	1861.9 (365.4)	<0.0001
Median (min–max)	1611.0 (788–7105)	1599.0 (788–7105)	1432.5 (1012–2322)	1620.0 (1094–3079)	1818.0 (1161–3022)	
1Q–3Q	1373.0–1885.0	1366.0–1924.0	1233.0–1626.5	1408.5–1920.0	1633.0–2048.0	
Height (cm)						
Mean (SD)	161.51 (8.78)	161.10 (8.83)	161.52 (8.82)	161.57 (8.81)	162.02 (8.59)	0.2939
Median (min–max)	162.00 (134.0–189.6)	161.60 (134.0–189.6)	161.85 (136.0–186.0)	163.00 (135.8–185.0)	162.50 (138.1–184.4)	
1Q–3Q	155.00–168.00	154.00–168.00	155.00–168.00	155.00–168.00	155.90–168.40	
Body weight (kg)						
Mean (SD)	61.58 (12.50)	60.07 (13.20)	59.70 (11.27)	63.48 (12.74)	65.04 (12.17)	<0.0001
Median (min–max)	61.00 (23.5–120.0)	59.60 (23.5–111.0)	59.00 (31.2–111.0)	63.00 (32.5–110.0)	64.20 (32.0–120.0)	
1Q–3Q	52.80–69.00	51.00–68.00	52.00–66.80	55.00–70.00	57.00–72.48	
BMI (kg/m^2)						
Mean (SD)	23.51 (3.81)	22.97 (3.84)	22.80 (3.43)	24.26 (3.89)	24.75 (3.85)	<0.0001
Median (min–max)	23.16 (10.3–39.8)	22.68 (10.3–36.2)	22.48 (12.7–36.7)	23.88 (13.7–39.8)	24.45 (12.8–38.7)	
1Q–3Q	20.96–25.73	20.42–25.39	20.42–24.76	21.94–26.31	22.10–27.29	

Table 1 continued

Variable	Cohort, $N = 2977$	No diabetes		Diabetes		P value
		No CGN, $N = 909$	CGN, $N = 948$	No nephropathy, $N = 507$	Nephropathy, $N = 613$	
<25	1845 (62.0)	578 (63.6)	669 (70.6)	289 (57.0)	309 (50.4)	<0.0001
25≤, <30	692 (23.2)	180 (19.8)	169 (17.8)	137 (27.0)	206 (33.6)	
30≤	149 (5.0)	40 (4.4)	29 (3.1)	35 (6.9)	45 (7.3)	
Cr (mg/dl)						
Mean (SD)	2.15 (1.06)	2.15 (1.04)	2.06 (1.05)	2.05 (0.97)	2.38 (1.14)	<0.0001
Median (min–max)	1.82 (0.7–8.4)	1.83 (0.8–8.4)	1.74 (0.7–6.7)	1.76 (0.8–6.1)	2.07 (0.8–6.6)	
1Q–3Q	1.38–2.63	1.41–2.61	1.32–2.49	1.36–2.43	1.50–3.09	
Cystatin C (mg/l)						
Mean (SD)	1.883 (0.707)	1.888 (0.706)	1.790 (0.683)	1.841 (0.660)	2.060 (0.754)	<0.0001
Median (min–max)	1.720 (0.62–5.71)	1.720 (0.72–4.45)	1.640 (0.62–5.07)	1.680 (0.81–5.71)	1.920 (0.78–4.49)	
1Q–3Q	1.320–2.320	1.335–2.305	1.250–2.200	1.335–2.295	1.440–2.570	
eGFR (ml/min/1.73 m^2)						
Mean (SD)	28.73 (12.24)	28.78 (12.15)	29.86 (12.50)	29.38 (11.63)	26.38 (12.15)	<0.0001
Median (min–max)	28.05 (5.4–73.6)	27.90 (6.4–73.6)	29.37 (6.0–65.6)	28.67 (8.2–64.9)	25.04 (5.4–62.4)	
1Q–3Q	18.66–37.74	18.91–37.49	19.96–40.13	20.16–38.29	15.67–34.93	
Ccr (ml/min)						
Mean (SD)	41.51 (22.56)	40.38 (21.63)	43.54 (24.13)	41.14 (21.60)	39.69 (21.62)	0.2568
Median (min–max)	38.70 (4.8–240.0)	38.70 (7.0–139.5)	40.45 (4.8–240.0)	36.30 (10.7–158.0)	35.30 (9.8–135.3)	
1Q–3Q	24.80–54.60	23.90–52.70	26.20–56.90	26.70–53.50	23.00–51.40	
Uric acid (mg/dl)						
Mean (SD)	7.18 (1.56)	7.06 (1.55)	7.12 (1.47)	7.15 (1.54)	7.48 (1.70)	<0.0001
Median (min–max)	7.10 (1.2–14.2)	7.00 (2.2–13.4)	7.00 (1.2–14.2)	7.00 (2.3–13.8)	7.30 (3.7–14.2)	
1Q–3Q	6.20–8.10	6.10–8.00	6.20–8.00	6.20–8.00	6.30–8.50	
U-protein (g/day)						
Mean (SD)	1.339 (1.998)	0.967 (1.418)	1.087 (1.896)	1.229 (1.367)	2.570 (2.875)	<0.0001
Median (min–max)	0.682 (0.00–28.08)	0.448 (0.00–13.70)	0.584 (0.00–28.08)	0.695 (0.00–6.68)	1.460 (0.00–14.36)	
1Q–3Q	0.210–1.677	0.140–1.240	0.210–1.300	0.180–1.964	0.587–3.680	
u-Albumin (mg/g Cr)						
Mean (SD)	976.14 (1339.90)	635.19 (1001.06)	817.44 (982.01)	950.68 (1403.43)	1740.23 (1823.09)	<0.0001
Median (min–max)	481.30 (2.5–14168.2)	295.55 (3.1–13275.6)	477.55 (2.5–8630.2)	419.80 (2.5–14168.2)	1128.70 (3.0–9445.2)	
1Q–3Q	120.20–1298.20	54.80–837.00	168.95–1132.85	74.20–1327.10	310.90–2702.80	
A1C (%)						
Mean (SD)	5.92 (0.91)	5.49 (0.37)	5.45 (0.35)	6.36 (0.85)	6.92 (1.12)	<0.0001
Median (min–max)	5.70 (4.1–11.7)	5.50 (4.1–6.4)	5.40 (4.3–6.4)	6.30 (4.2–10.3)	6.70 (4.5–11.7)	
1Q–3Q	5.30–6.20	5.30–5.70	5.20–5.70	5.80–6.70	6.10–7.60	
Glucose (mg/dl)						
Mean (SD)	119.8 (44.5)	106.7 (24.1)	102.5 (20.3)	131.2 (48.4)	149.9 (62.5)	<0.0001
Median (min–max)	106.0 (35–456)	101.0 (54–232)	98.0 (64–228)	117.0 (37–343)	136.0 (35–456)	
1Q–3Q	93.0–131.0	92.0–114.0	91.0–108.0	102.0–146.0	105.0–184.0	
HDL-chol (mg/dl)						
Mean (SD)	54.4 (18.4)	55.0 (18.5)	59.6 (19.2)	52.7 (18.3)	48.4 (15.0)	<0.0001
Median (min–max)	50.0 (15–161)	51.0 (15–129)	56.0 (23–161)	48.5 (25–129)	45.0 (17–115)	
1Q–3Q	42.0–64.0	42.0–65.0	46.0–70.0	40.0–61.0	38.0–56.0	
LDL-chol (mg/dl)						
Mean (SD)	108.2 (32.9)	107.5 (33.2)	111.0 (33.7)	106.0 (31.9)	106.8 (32.4)	0.0403
Median (min–max)	106.0 (17–361)	105.0 (27–361)	109.0 (17–261)	102.0 (17–236)	103.5 (31–249)	
1Q–3Q	86.0–127.0	85.0–126.0	89.0–129.3	85.0–124.0	85.0–128.0	

Table 1 continued

Variable	Cohort, $N = 2977$	No diabetes		Diabetes		P value
		No CGN, $N = 909$	CGN, $N = 948$	No nephropathy, $N = 507$	Nephropathy, $N = 613$	
TG (mg/dl)						
Mean (SD)	166.7 (109.0)	160.1 (98.6)	158.1 (101.6)	181.9 (109.7)	175.6 (128.2)	0.0002
Median (min–max)	139.0 (22–1191)	133.0 (30–860)	134.0 (27–1191)	155.0 (22–716)	140.0 (34–1043)	
1Q–3Q	98.0–203.0	95.0–197.0	96.0–194.0	105.0–229.0	100.0–204.5	
Ca (mEq/l)						
Mean (SD)	9.00 (0.53)	9.06 (0.51)	9.07 (0.48)	9.03 (0.51)	8.80 (0.59)	<0.0001
Median (min–max)	9.00 (5.4–11.6)	9.10 (7.0–11.3)	9.10 (5.4–11.6)	9.10 (6.4–10.7)	8.80 (5.9–10.6)	
1Q–3Q	8.70–9.30	8.80–9.40	8.80–9.40	8.70–9.40	8.50–9.20	
P (mg/dl)						
Mean (SD)	3.53 (0.69)	3.46 (0.68)	3.47 (0.67)	3.46 (0.65)	3.79 (0.74)	<0.0001
Median (min–max)	3.50 (1.6–8.6)	3.40 (1.8–7.8)	3.40 (1.7–7.3)	3.40 (1.6–6.7)	3.70 (1.7–8.6)	
1Q–3Q	3.10–3.90	3.00–3.80	3.00–3.90	3.00–3.90	3.30–4.10	
Ferritin (ng/dl)						
Mean (SD)	137.52 (137.22)	139.06 (142.45)	124.46 (123.33)	148.56 (156.18)	144.74 (132.43)	0.0641
Median (min–max)	100.50 (2.6–1520.0)	99.50 (2.6–1520.0)	91.30 (3.2–1043.0)	109.80 (7.8–1150.0)	108.00 (3.4–1119.0)	
1Q–3Q	51.00–183.00	47.26–187.50	43.20–168.00	58.00–191.80	57.00–192.00	
CRP (mg/dl)						
Mean (SD)	0.263 (0.832)	0.256 (0.521)	0.196 (0.575)	0.429 (1.508)	0.238 (0.734)	0.0001
Median (min–max)	0.100 (0.00–23.08)	0.100 (0.00–5.47)	0.060 (0.00–8.79)	0.100 (0.00–23.08)	0.100 (0.00–10.21)	
1Q–3Q	0.040–0.200	0.040–0.210	0.030–0.140	0.040–0.270	0.040–0.200	
WBC (/μl)						
Mean (SD)	6535.1 (2025.3)	6375.4 (1961.3)	6399.6 (2020.9)	6925.3 (2213.0)	6654.5 (1913.3)	<0.0001
Median (min–max)	6240.0 (2090–22300)	6100.0 (2100–16600)	6100.0 (2200–16920)	6600.0 (2410–16800)	6490.0 (2090–22300)	
1Q–3Q	5175.0–7500.0	5060.0–7350.0	5005.0–7400.0	5400.0–7880.0	5400.0–7600.0	
RBC ($\times 10^4$/μl)						
Mean (SD)	389.2 (62.0)	395.4 (64.6)	391.1 (56.4)	394.3 (63.8)	372.8 (61.8)	<0.0001
Median (min–max)	386.0 (107–940)	393.0 (173–890)	386.0 (220–564)	391.0 (243–586)	369.0 (107–940)	
1Q–3Q	347.0–428.0	352.0–435.0	352.5–427.0	349.0–435.0	332.0–409.0	
Ht (%)						
Mean (SD)	36.15 (5.24)	36.74 (5.42)	36.61 (4.86)	36.65 (5.48)	34.20 (4.86)	<0.0001
Median (min–max)	35.85 (17.4–55.2)	36.50 (17.4–53.2)	36.30 (21.9–54.7)	36.30 (22.5–55.2)	33.90 (20.0–52.6)	
1Q–3Q	32.60–39.55	33.10–40.40	33.20–39.70	32.80–40.20	30.80–37.15	
Hb (g/dl)						
Mean (SD)	12.06 (1.84)	12.25 (1.90)	12.20 (1.74)	12.24 (1.92)	11.45 (1.71)	<0.0001
Median (min–max)	11.90 (5.2–19.7)	12.10 (6.0–18.5)	12.10 (6.7–19.7)	12.10 (7.3–18.5)	11.30 (5.2–17.7)	
1Q–3Q	10.80–13.20	11.00–13.50	11.00–13.30	10.90–13.40	10.30–12.50	
iPTH (pg/ml)						
Mean (SD)	105.8 (91.8)	110.8 (110.6)	98.0 (78.8)	98.0 (75.8)	117.3 (91.5)	<0.0001
Median (min–max)	78.0 (5–1540)	82.0 (5–1540)	75.0 (6–789)	75.0 (5–618)	90.0 (6–639)	
1Q–3Q	54.0–125.0	54.5–127.5	53.0–115.0	53.0–118.0	59.0–145.0	
Classification of medication						
Antihypertensives [*n* (%)]	2735 (91.9)	784 (86.2)	889 (93.8)	479 (94.5)	583 (95.1)	<0.0001
ARB [*n* (%)]	2186 (73.4)	579 (63.7)	734 (77.4)	382 (75.3)	491 (80.1)	<0.0001
ACEI [*n* (%)]	818 (27.5)	200 (22.0)	281 (29.6)	141 (27.8)	196 (32.0)	<0.0001
Diuretics [*n* (%)]	885 (29.7)	193 (21.2)	167 (17.6)	169 (33.3)	356 (58.1)	<0.0001
Ca blockade [*n* (%)]	1649 (55.4)	497 (54.7)	430 (45.4)	297 (58.6)	425 (69.3)	<0.0001
β-Blocker [*n* (%)]	806 (27.1)	250 (27.5)	169 (17.8)	169 (33.3)	218 (35.6)	<0.0001
Antiplatelet/anticoagulant [*n* (%)]	1059 (35.6)	240 (26.4)	346 (36.5)	212 (41.8)	261 (42.6)	<0.0001
Antiplatelet [*n* (%)]	983 (33.0)	217 (23.9)	323 (34.1)	192 (37.9)	251 (40.9)	<0.0001
Warfarin [*n* (%)]	154 (5.2)	38 (4.2)	47 (5.0)	35 (6.9)	34 (5.5)	0.1588

Table 1 continued

Variable	Cohort, $N = 2977$	No diabetes		Diabetes		P value
		No CGN, $N = 909$	CGN, $N = 948$	No nephropathy, $N = 507$	Nephropathy, $N = 613$	
Glucose-lowering agents [*n* (%)]	831 (27.9)	0 (0.0)	0 (0.0)	309 (60.9)	522 (85.2)	<0.0001
Insulin [*n* (%)]	366 (12.3)	0 (0.0)	0 (0.0)	74 (14.6)	292 (47.6)	<0.0001
Sulfonil urea [*n* (%)]	247 (8.3)	0 (0.0)	0 (0.0)	88 (17.4)	159 (25.9)	<0.0001
αGI [*n* (%)]	268 (9.0)	0 (0.0)	0 (0.0)	107 (21.1)	161 (26.3)	<0.0001
Biguanide [*n* (%)]	42 (1.4)	0 (0.0)	0 (0.0)	12 (2.4)	30 (4.9)	<0.0001
Lipid-lowering agents [*n* (%)]	1384 (46.5)	353 (38.8)	404 (42.6)	286 (56.4)	341 (55.6)	<0.0001
Statin [*n* (%)]	1198 (40.2)	294 (32.3)	354 (37.3)	247 (48.7)	303 (49.4)	<0.0001
Renal function improving [*n* (%)]	605 (20.3)	194 (21.3)	202 (21.3)	124 (24.5)	85 (13.9)	<0.0001
Carbonic adsorbent [*n* (%)]	315 (10.6)	104 (11.4)	91 (9.6)	44 (8.7)	76 (12.4)	0.1241
Anemia treatment [*n* (%)]	536 (18.0)	135 (14.9)	139 (14.7)	94 (18.5)	168 (27.4)	<0.0001
ESA [*n* (%)]	387 (13.0)	104 (11.4)	91 (9.6)	61 (12.0)	131 (21.4)	<0.0001
Iron [*n* (%)]	243 (8.2)	63 (6.9)	74 (7.8)	43 (8.5)	63 (10.3)	0.1257
Mineral bone disease treatment [*n* (%)]	467 (15.7)	144 (15.8)	154 (16.2)	108 (21.3)	61 (10.0)	<0.0001
Phosphate binder [*n* (%)]	96 (3.2)	32 (3.5)	25 (2.6)	18 (3.6)	21 (3.4)	0.6696
Vitamin D3 [*n* (%)]	260 (8.7)	91 (10.0)	76 (8.0)	55 (10.8)	38 (6.2)	0.0165
Antiuric acids [*n* (%)]	1495 (50.2)	513 (56.4)	498 (52.5)	253 (49.9)	231 (37.7)	<0.0001
Ion exchange resin [*n* (%)]	301 (10.1)	81 (8.9)	86 (9.1)	47 (9.3)	87 (14.2)	0.0026

Cardiovascular diseases means participant had medical history of myocardial infarction, angina, congestive heart failure, arteriosclerosis obliterans or stroke

MI myocardial infarction, *ASO* arteriosclerosis obliterans, *BMI* body mass index, *ARB* angiotensin receptor blocker, *ACEI* angiotensin converting enzyme inhibitor, *αGI* α-glucosidase inhibitor, *CGN* chronic glomerulonephritis, *CRP* C-reactive protein, *ESA* erythrocyte stimulating agents, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *RBC* red blood cells, *TG* triglyceride, *WBC* white blood cells

Table 2 Distribution of PWV in the cohort

PWV (cm/s)	Sex	Age (years)	*n*	Mean	SD
Cohort	Female	<65	82	1449.2	277.0
		≥65	55	1801.5	380.8
	Male	<65	139	1518.7	296.6
		≥65	120	1935.8	620.8
No DM					
No CGN	Female	<65	30	1449.9	295.8
		≥65	15	1852.0	413.6
	Male	<65	43	1530.6	357.1
		≥65	53	1908.4	815.5
CGN	Female	<65	32	1372.0	246.3
		≥65	16	1692.3	310.1
	Male	<65	46	1372.3	198.1
		≥65	10	1734.2	315.2
DM					
No nephropathy	Female	<65	7	1512.0	204.9
		≥65	12	1754.9	374.9
	Male	<65	21	1537.6	271.1
		≥65	20	1913.1	491.2
Nephropathy	Female	<65	13	1603.6	291.1
		≥65	12	1930.4	425.5
	Male	<65	29	1719.8	221.4
		≥65	37	2041.8	370.1

Table 3 Distribution of pulse pressure in the cohort

Pulse pressure (mmHg)	Sex	Age (years)	*n*	Mean	SD
Cohort	Female	<65	655	51.1	13.2
		≥65	455	60.3	14.6
	Male	<65	944	52.8	13.0
		≥65	877	59.0	14.5
No DM					
No CGN	Female	<65	183	48.3	11.9
		≥65	141	58.7	14.0
	Male	<65	273	49.1	11.9
		≥65	288	55.3	12.1
CGN	Female	<65	300	49.2	11.5
		≥65	137	56.5	12.8
	Male	<65	313	49.9	10.3
		≥65	191	56.1	14.5
DM					
No nephropathy	Female	<65	79	53.5	13.4
		≥65	87	60.4	13.9
	Male	<65	138	53.4	11.8
		≥65	197	59.1	14.4
Nephropathy	Female	<65	93	60.8	15.6
		≥65	90	68.6	15.8
	Male	<65	220	61.1	14.7
		≥65	201	67.0	14.7

Table 4 Baseline characterization

Variable	Stage 3A GFR ≥ 45, $N = 304$	Stage 3B 45 > GFR ≥ 30, $N = 1037$	Stage 4 30 > GFR ≥ 15, $N = 1160$	Stage 5 GFR < 15, $N = 476$	*P* value
Sex					
Female	113 (37.2)	367 (35.4)	445 (38.4)	204 (42.9)	0.0478
Male	191 (62.8)	670 (64.6)	715 (61.6)	272 (57.1)	
Age (years)					
Mean (SD)	55.0 (13.3)	60.4 (12.0)	61.9 (10.6)	62.5 (10.7)	<0.0001
Median (min–max)	58.0 (22–76)	63.0 (22–77)	64.0 (24–77)	65.0 (25–77)	
1Q–3Q	45.0–66.0	54.0–70.0	56.0–70.0	57.0–71.0	
Smoking [*n* (%)]	44 (14.5)	150 (14.5)	144 (12.4)	67 (14.1)	0.4646
Medical history [*n* (%)]					
Hypertension	225 (74.0)	816 (78.7)	966 (83.3)	420 (88.2)	<0.0001
Cardiovascular disease	55 (18.1)	248 (23.9)	307 (26.5)	151 (31.7)	0.0001
MI	9 (3.0)	47 (4.5)	62 (5.3)	28 (5.9)	0.2377
Angina	20 (6.6)	85 (8.2)	100 (8.6)	49 (10.3)	0.3155
Congestive heart failure	4 (1.3)	35 (3.4)	46 (4.0)	30 (6.3)	0.0034
ASO	11 (3.6)	32 (3.1)	48 (4.1)	17 (3.6)	0.6284
Stroke	31 (10.2)	114 (11.0)	132 (11.4)	65 (13.7)	0.3978
Diabetic retinopathy	29 (9.5)	128 (12.3)	171 (14.7)	95 (20.0)	<0.0001
Cancer	21 (6.9)	75 (7.2)	88 (7.6)	30 (6.3)	0.8317
Diastolic blood pressure (mmHg)					
Mean (SD)	76.2 (11.3)	76.5 (11.4)	76.0 (12.2)	76.3 (12.3)	0.6793
Median (min–max)	76.2 (47–107)	76.3 (38–118)	76.0 (33–128)	76.8 (34–127)	
1Q–3Q	69.7–82.3	69.0–84.0	68.0–84.0	70.0–84.0	
Systolic blood pressure (mmHg)					
Mean (SD)	128.9 (17.3)	130.0 (17.8)	132.2 (19.1)	135.8 (19.1)	<0.0001
Median (min–max)	128.0 (80–185)	129.3 (72–202)	132.0 (68–235)	133.0 (90–202)	
1Q–3Q	117.0–140.0	118.7–140.0	120.0–143.7	123.0–148.7	
Mean blood pressure (mmHg)					
Mean (SD)	94.1 (12.6)	94.6 (12.9)	95.3 (13.9)	96.5 (14.1)	0.0448
Median (min–max)	93.4 (60–128)	94.0 (53–147)	94.7 (35–162)	95.6 (54–163)	
1Q–3Q	85.5–102.7	86.2–102.1	86.3–103.3	87.6–104.7	
Pulse pressure (mmHg)					
Mean (SD)	52.7 (13.1)	53.6 (13.8)	56.1 (14.5)	59.4 (14.2)	<0.0001
Median (min–max)	51.0 (23–107)	51.7 (9–112)	54.3 (24–121)	58.0 (23–107)	
1Q–3Q	43.7–60.0	44.0–61.0	46.0–64.3	50.0–68.0	
PWV (pulse wave velocity) (cm/s)					
Mean (SD)	1463.2 (383.5)	1647.6 (389.3)	1728.5 (577.9)	1767.8 (332.7)	0.2021
Median (min–max)	1367.5 (1025–2316)	1545.0 (925–3079)	1697.0 (788–7105)	1740.0 (1088–2738)	
1Q–3Q	1163.0–1554.0	1370.0–1875.0	1398.0–1917.0	1551.0–1945.0	
Height (cm)					
Mean (SD)	163.24 (8.85)	162.33 (8.66)	160.80 (8.70)	160.36 (8.85)	<0.0001
Median (min–max)	163.00 (135.8–189.6)	163.00 (134.0–188.0)	161.00 (138.0–185.0)	161.00 (137.5–184.4)	
1Q–3Q	157.00–170.00	156.00–169.00	154.30–167.30	153.00–167.20	
Body weight (kg)					
Mean (SD)	65.04 (12.19)	62.46 (12.65)	60.54 (12.38)	60.03 (12.14)	0.0002
Median (min–max)	64.50 (36.0–110.9)	61.60 (28.6–120.0)	60.00 (23.5–107.0)	60.00 (31.2–99.8)	
1Q–3Q	56.00–72.00	53.00–70.00	51.95–68.00	51.30–68.00	
BMI (kg/m^2)					
Mean (SD)	24.30 (3.56)	23.68 (3.88)	23.28 (3.80)	23.19 (3.76)	0.0294
Median (min–max)	24.15 (13.7–39.8)	23.18 (12.1–38.7)	23.01 (10.3–36.3)	22.88 (12.7–36.3)	
1Q–3Q	22.04–26.44	20.98–25.78	20.83–25.49	20.67–25.66	

Table 4 continued

Variable	Stage 3A GFR ≥ 45, $N = 304$	Stage 3B 45 > GFR ≥ 30, $N = 1037$	Stage 4 30 > GFR ≥ 15, $N = 1160$	Stage 5 GFR < 15, $N = 476$	*P* value
<25	170 (55.9)	618 (59.6)	752 (64.8)	305 (64.1)	0.0175
25≤, <30	93 (30.6)	240 (23.1)	248 (21.4)	111 (23.3)	
30<	17 (5.6)	59 (5.7)	55 (4.7)	18 (3.8)	
Cr (mg/dl)					
Mean (SD)	1.11 (0.17)	1.44 (0.25)	2.29 (0.52)	4.04 (0.90)	<0.0001
Median (min–max)	1.13 (0.7–1.6)	1.42 (0.9–2.4)	2.20 (1.4–4.1)	3.90 (2.6–8.4)	
1Q–3Q	0.96–1.24	1.27–1.63	1.91–2.60	3.44–4.53	
Cystatin C (mg/l)					
Mean (SD)	1.102 (0.195)	1.388 (0.271)	2.061 (0.434)	3.000 (0.473)	<0.0001
Median (min–max)	1.080 (0.62–1.82)	1.350 (0.72–3.32)	2.010 (1.07–4.49)	2.950 (1.93–5.71)	
1Q–3Q	0.970–1.200	1.200–1.540	1.750–2.310	2.680–3.270	
eGFR (ml/min/1.73 m^2)					
Mean (SD)	50.48 (4.81)	37.08 (4.24)	22.51 (4.27)	11.82 (2.00)	<0.0001
Median (min–max)	49.12 (45.1–73.6)	36.66 (30.0–45.0)	22.43 (15.0–30.0)	11.96 (5.4–15.0)	
1Q–3Q	46.89–52.84	33.56–40.62	18.92–26.13	10.38–13.44	
Ccr (ml/min)					
Mean (SD)	76.75 (20.68)	54.34 (18.61)	33.22 (10.52)	17.68 (6.15)	<0.0001
Median (min–max)	74.90 (30.9–158.0)	52.25 (8.8–240.0)	31.90 (7.2–86.2)	17.00 (4.8–50.0)	
1Q–3Q	63.50–87.35	44.10–61.20	26.05–39.70	13.90–21.00	
Uric acid (mg/dl)					
Mean (SD)	6.59 (1.48)	7.02 (1.39)	7.35 (1.60)	7.48 (1.72)	<0.0001
Median (min–max)	6.55 (1.2–12.2)	7.00 (1.9–14.2)	7.20 (2.3–14.2)	7.30 (3.3–13.9)	
1Q–3Q	5.60–7.35	6.10–7.90	6.30–8.20	6.30–8.60	
U-protein (g/day)					
Mean (SD)	0.759 (1.528)	1.016 (1.681)	1.452 (1.883)	1.978 (2.671)	<0.0001
Median (min–max)	0.198 (0.00–12.31)	0.410 (0.00–14.36)	0.800 (0.00–13.70)	1.250 (0.00–28.08)	
1Q–3Q	0.075–0.735	0.140–1.080	0.280–1.875	0.580–2.640	
u-Albumin (mg/g Cr)					
Mean (SD)	551.01 (981.88)	766.84 (1295.45)	1058.94 (1302.10)	1484.11 (1528.16)	<0.0001
Median (min–max)	148.55 (2.5–6072.6)	297.90 (2.5–14168.2)	630.70 (2.7–9605.1)	1027.10 (14.4–9445.2)	
1Q–3Q	28.40–585.20	60.90–849.00	195.80–1408.25	412.20–1972.80	
A1C (%)					
Mean (SD)	5.95 (1.01)	5.97 (0.95)	5.90 (0.84)	5.86 (0.92)	0.0551
Median (min–max)	5.70 (4.5–11.7)	5.70 (4.1–11.4)	5.60 (4.2–10.4)	5.60 (4.2–10.1)	
1Q–3Q	5.30–6.20	5.40–6.20	5.40–6.20	5.30–6.20	
Glucose (mg/dl)					
Mean (SD)	121.3 (52.3)	119.7 (44.8)	118.3 (41.8)	122.9 (45.2)	0.1987
Median (min–max)	102.0 (47–390)	105.0 (35–456)	106.0 (50–385)	108.0 (42–339)	
1Q–3Q	92.0–126.0	93.0–131.0	94.0–128.0	93.0–139.0	
HDL-chol (mg/dl)					
Mean (SD)	57.0 (18.4)	56.2 (18.7)	53.4 (18.3)	51.5 (17.4)	0.0001
Median (min–max)	53.0 (30–134)	52.0 (15–161)	49.0 (17–149)	48.0 (20–124)	
1Q–3Q	44.0–66.0	43.0–66.0	40.0–62.0	38.0–60.0	
LDL-chol (mg/dl)					
Mean (SD)	114.0 (28.6)	110.2 (34.5)	106.6 (31.0)	103.8 (35.9)	0.0065
Median (min–max)	114.0 (40–222)	106.8 (28–361)	105.0 (17–252)	100.0 (17–258)	
1Q–3Q	95.0–130.0	88.0–129.0	85.0–125.0	80.0–122.0	
TG (mg/dl)					
Mean (SD)	175.9 (133.2)	165.4 (108.1)	168.5 (110.2)	158.8 (87.1)	0.3154
Median (min–max)	142.0 (47–1043)	138.0 (22–868)	139.0 (27–1191)	136.5 (30–602)	
1Q–3Q	96.0–213.0	97.0–199.0	98.0–206.0	98.0–201.5	

Table 4 continued

Variable	Stage 3A GFR ≥ 45, $N = 304$	Stage 3B 45 > GFR ≥ 30, $N = 1037$	Stage 4 30 > GFR ≥ 15, $N = 1160$	Stage 5 GFR < 15, $N = 476$	*P* value
Ca (mEq/l)					
Mean (SD)	9.20 (0.43)	9.11 (0.45)	8.98 (0.49)	8.70 (0.66)	<0.0001
Median (min–max)	9.20 (7.6–10.7)	9.10 (6.4–10.6)	9.00 (6.8–11.6)	8.70 (5.4–10.6)	
1Q–3Q	8.90–9.50	8.80–9.40	8.70–9.30	8.30–9.10	
P (mg/dl)					
Mean (SD)	3.28 (0.57)	3.31 (0.60)	3.55 (0.62)	4.09 (0.77)	<0.0001
Median (min–max)	3.30 (1.7–5.0)	3.30 (1.6–8.6)	3.50 (1.7–7.8)	4.00 (2.1–7.3)	
1Q–3Q	2.90–3.70	2.90–3.70	3.10–3.90	3.60–4.50	
Ferritin (ng/dl)					
Mean (SD)	129.06 (124.77)	126.01 (120.63)	141.72 (152.82)	155.03 (134.91)	0.0159
Median (min–max)	97.10 (3.4–1088.9)	95.00 (4.0–1043.0)	100.00 (3.2–1520.0)	118.00 (2.6–749.0)	
1Q–3Q	43.90–174.70	44.90–173.00	51.10–177.25	62.00–203.00	
CRP (mg/dl)					
Mean (SD)	0.195 (0.456)	0.241 (0.605)	0.280 (0.792)	0.307 (1.340)	0.4328
Median (min–max)	0.080 (0.00–4.92)	0.100 (0.00–10.21)	0.100 (0.00–11.99)	0.080 (0.00–23.08)	
1Q–3Q	0.040–0.150	0.040–0.200	0.040–0.200	0.030–0.200	
WBC (/μl)					
Mean (SD)	6733.7 (2005.6)	6623.5 (1980.1)	6528.7 (2064.6)	6235.1 (2011.1)	0.0025
Median (min–max)	6400.0 (2100–16600)	6300.0 (2090–16920)	6280.0 (2230–22300)	6000.0 (2300–16360)	
1Q–3Q	5300.0–7990.0	5200.0–7600.0	5200.0–7500.0	4800.0–7200.0	
RBC ($\times 10^4$/μl)					
Mean (SD)	430.1 (56.6)	412.9 (59.1)	375.4 (55.7)	345.7 (46.6)	<0.0001
Median (min–max)	431.0 (233–588)	410.0 (216–940)	374.0 (107–890)	345.0 (173–531)	
1Q–3Q	396.0–464.0	374.0–449.0	340.0–408.0	317.0–372.0	
Ht (%)					
Mean (SD)	39.59 (4.99)	38.20 (4.98)	34.99 (4.57)	32.41 (4.13)	<0.0001
Median (min–max)	39.80 (20.0–53.2)	38.10 (19.9–55.2)	34.80 (18.4–50.5)	32.60 (17.4–49.8)	
1Q–3Q	36.30–42.90	34.80–41.30	32.00–37.70	29.70–35.10	
Hb (g/dl)					
Mean (SD)	13.35 (1.84)	12.79 (1.74)	11.65 (1.59)	10.69 (1.37)	<0.0001
Median (min–max)	13.40 (6.7–19.7)	12.70 (5.2–18.5)	11.50 (6.2–17.4)	10.70 (6.0–16.8)	
1Q–3Q	12.20–14.60	11.60–13.90	10.60–12.60	9.80–11.50	
iPTH (pg/ml)					
Mean (SD)	56.1 (26.5)	67.9 (34.8)	107.7 (69.1)	213.2 (146.2)	<0.0001
Median (min–max)	51.0 (11–195)	61.0 (5–376)	93.0 (5–1020)	179.0 (18–1540)	
1Q–3Q	36.0–70.0	46.0–82.0	66.0–132.0	120.0–274.0	
Classification of medication					
Antihypertensives [*n* (%)]	259 (85.2)	933 (90.0)	1089 (93.9)	454 (95.4)	<0.0001
ARB [*n* (%)]	216 (71.1)	735 (70.9)	871 (75.1)	364 (76.5)	0.0415
ACEI [*n* (%)]	68 (22.4)	305 (29.4)	336 (29.0)	109 (22.9)	0.0067
Diuretics [*n* (%)]	58 (19.1)	266 (25.7)	368 (31.7)	193 (40.5)	<0.0001
Ca blockade [*n* (%)]	115 (37.8)	485 (46.8)	705 (60.8)	344 (72.3)	<0.0001
β-Blocker [*n* (%)]	53 (17.4)	228 (22.0)	340 (29.3)	185 (38.9)	<0.0001
Antiplatelet/anticoagulant [*n* (%)]	90 (29.6)	375 (36.2)	419 (36.1)	175 (36.8)	0.1493
Antiplatelet [*n* (%)]	81 (26.6)	338 (32.6)	396 (34.1)	168 (35.3)	0.0591
Warfarin [*n* (%)]	14 (4.6)	67 (6.5)	54 (4.7)	19 (4.0)	0.1274
Glucose-lowering agents [*n* (%)]	68 (22.4)	284 (27.4)	331 (28.5)	148 (31.1)	0.0602
Insulin [*n* (%)]	26 (8.6)	110 (10.6)	152 (13.1)	78 (16.4)	0.002
Sulfonil urea [*n* (%)]	25 (8.2)	101 (9.7)	83 (7.2)	38 (8.0)	0.1802
αGI [*n* (%)]	25 (8.2)	105 (10.1)	101 (8.7)	37 (7.8)	0.4197
Biguanide [*n* (%)]	7 (2.3)	20 (1.9)	13 (1.1)	2 (0.4)	0.0504

Table 4 continued

Variable	Stage 3A GFR ≥ 45, $N = 304$	Stage 3B 45 > GFR ≥ 30, $N = 1037$	Stage 4 30 > GFR ≥ 15, $N = 1160$	Stage 5 GFR < 15, $N = 476$	*P* value
Lipid-lowering agents [*n* (%)]	153 (50.3)	480 (46.3)	558 (48.1)	193 (40.5)	0.0204
Statin [*n* (%)]	133 (43.8)	416 (40.1)	484 (41.7)	165 (34.7)	0.0323
Renal function improving [*n* (%)]	48 (15.8)	146 (14.1)	259 (22.3)	152 (31.9)	<0.0001
Carbonic adsorbent [*n* (%)]	2 (0.7)	34 (3.3)	146 (12.6)	133 (27.9)	<0.0001
Anemia treatment [*n* (%)]	9 (3.0)	72 (6.9)	241 (20.8)	214 (45.0)	<0.0001
Erythropoiesis stimulating agent [*n* (%)]	3 (1.0)	26 (2.5)	178 (15.3)	180 (37.8)	<0.0001
Iron [*n* (%)]	6 (2.0)	53 (5.1)	103 (8.9)	81 (17.0)	<0.0001
Mineral bone disease treatment [*n* (%)]	48 (15.8)	136 (13.1)	163 (14.1)	120 (25.2)	<0.0001
Phosphate binder [*n* (%)]	1 (0.3)	12 (1.2)	29 (2.5)	54 (11.3)	<0.0001
Vitamin D3 [*n* (%)]	27 (8.9)	74 (7.1)	93 (8.0)	66 (13.9)	0.0002
Antiuric acids [*n* (%)]	115 (37.8)	465 (44.8)	637 (54.9)	278 (58.4)	<0.0001
Ion exchange resin [*n* (%)]	6 (2.0)	22 (2.1)	139 (12.0)	134 (28.2)	<0.0001

Cardiovascular diseases means participant had medical history of myocardial infarction, angina, congestive heart failure, arteriosclerosis obliterans or stroke

MI myocardial infarction, *ASO* arteriosclerosis obliterans, *BMI* body mass index, *ARB* angiotensin receptor blocker, *ACEI* angiotensin converting enzyme inhibitor, *αGI* α-glucosidase inhibitor, *ESA* erythrocyte stimulating agents

Declining renal function was associated with progressive anemia and elevated serum ferritin.

PWV and PP increases were associated with decreasing renal function.

Discussion

The CKD-JAC study has enrolled a representative Japanese cohort of individuals with CKD, composed of about 3000 outpatients mostly with CKD stage 3–5. In some patients, renal function improved beyond 60 ml/min/1.73 m^2 after enrollment. Participants are under treatment by nephrologists and are receiving a high standard of care. The majority of participants had hypertension and proteinuria on enrollment, but mean blood pressure was normal (132/76 mmHg). More than 90% of participants were under treatment with ACEI/ARB. Prevalence of pre-existing cardiovascular diseases, such as heart failure (3.9%), myocardial infarction (4.9%), and stroke (11.5%), was higher than in the general Japanese population [12]. Diabetes was present in 36.7% of participants, but blood glucose was well controlled. Mean A1C for diabetes with and without nephropathy was 6.92% and 6.36%, respectively. More than one-third of enrolled participants had CKD due to glomerulonephritis, and this subgroup showed lower comorbidity and better physical condition at baseline. Long-term follow-up of the participants will provide clinical insights into the epidemiology of CKD and complications of cardiovascular diseases.

Medication for CKD patients was characterized by frequent use of ARB rather than ACEI. One of the reasons for this is the high prevalence of cough experienced by users of ACEI in Asian populations [14].

The CKD-JAC study was planned to establish a counterpart cohort for the Chronic Renal Insufficiency Cohort (CRIC) study [10], which examined risk factors for progression of CKD and for development of cardiovascular diseases in CKD patients with GFR 15–60 ml/min/1.73 m^2. The major differences in baseline data between CKD-JAC and CRIC were ethnicity, cause of CKD, age, population of diabetes, BMI, medical history of CVD, and eGFR. CKD-JAC is a cohort of Japanese and Asian participants living in Japan, while CRIC is a mix of 45% White, 46% Black, and 5% Hispanic. The percentage of diabetes within the CKD-JAC and CRIC populations was 37.6% and 46.6%, respectively. Blood glucose control in diabetic participants was better in the CKD-JAC study (mean A1C 6.8%) than in CRIC (mean A1C 7.7%). In the CRIC, the mean BMI of participants was 32.1 kg/m^2 and 55% of participants had BMI >30 kg/m^2, reflecting the high level of obesity in the population. In contrast, the mean BMI in the CKD-JAC study was 23.5 kg/m^2 and only 5% of participants had BMI >30 kg/m^2.

High cardiovascular mortality and comorbidity are common among CKD patients [3]. CKD-JAC patients had a history of pre-existing MI and stroke in 4.9% and 11.5% of cases, respectively. In Kidney Early Evaluation Program (KEEP), a history of pre-existing MI and stroke in a CKD population defined by eGFR <60 ml/min/1.73 m^2 was present in 4.5% and 3.8% of participants, respectively [15]. However, the incidence of CVD and organs susceptible to CVD differ by ethnicity. In White patients, coronary heart disease, such as myocardial infarction and unstable angina,

are the leading causes of death in the general population. Within the National Health and Nutrition Examination Survey (NHANES) III population, pre-existing MI and stroke were present in 2.5% and 1.5%, respectively [15]. The incidence of stroke in Japanese participants is twice that seen in Whites and Blacks. Japan Arteriosclerosis Longitudinal Study (JALS), a meta-analysis of 16 Japanese cohort studies of the general population, showed the incidence of stroke and MI in men to be 43.8 and 12.3 per 10000 person-years, respectively, while in women those figures were 29.2 and 4.6 per 10000 person-years, respectively [12]. Mortality and incidence of CVD are, however, little studied in a prospective manner regarding Japanese CKD patients treated by the nephrologists [16]. It is hoped that CKD-JAC will answer a number of these questions, but the medical history of CVD needs to be adjusted.

Arteriosclerosis is a central cause of CVD in CKD patients as well as in the general population. PWV and PP are good indicators of aortic stiffness. Although the number of PWV measurement was small (369 cases, 13.3%), PWV was increased in association with declining eGFR. High PWV and large PP in the CKD population suggest presence of aortic stiffness [17–19]. Both central aortic PP and brachial PP have been closely associated with increasing carotid intima media thickness (IMT) and plaque formation in the CRIC study [20].

The cross-sectional baseline data from the CKD-JAC shed light on the association between advanced arteriosclerosis in patients with decreasing renal function and with advanced diabetes. Differences in causative disease may lead to different outcomes for CVD in a longitudinal study. Future analysis of the cohort will clarify whether incidence of CVD differs by causative disease.

Appendix

This study was conducted by principal investigators at the following medical centers:

Yoshio Taguma, Sendai Social Insurance Hospital (Miyagi); Yoshitaka Maeda, Toride Kyodo Hospital (Ibaragi); Eiji Kusano, Jichi Medical University (Tochigi); Kosaku Nitta, Tokyo Women's Medical University Hospital (Tokyo); Yasuhiro Komatsu, St. Luke's International Hospital (Tokyo); Tadao Akizawa, Showa University Hospital (Tokyo); Eriko Kinugasa, Showa University Yokohama Northern Hospital (Kanagawa); Ashio Yoshimura, Showa University Fujigaoka Hospital (Kanagawa); Hiroshige Ohashi, Gifu Prefectural General Medical Center (Gifu); Yuzo Watanabe, Kasugai Municipal Hospital (Aichi); Daijyo Inaguma, Kei Kurata, Tosei General Hospital (Aichi); Enyu Imai, Yoshitaka Isaka, Osaka University Hospital (Osaka); Yoshiharu Tsubakihara, Osaka General Medical Center (Osaka); Masahito Imanishi, Osaka City General Hospital (Osaka); Masaki Fukushima, Kurashiki Central Hospital (Okayama); Hideki Hirakata, Fukuoka Red Cross Hospital (Fukuoka); Kazuhito Takeda, Iizuka Hospital (Fukuoka).

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2. Data Center: Public Health Research Foundation (Tokyo).
3. Independent Cardiac Function Evaluation Committee: Kyoichi Mizuno (Nippon Medical School Hospital), Hiroshi Nishimura (the University of Tokyo), Satoshi Iimuro (the University of Tokyo).
4. Biostatistics Adviser: Yasuo Ohashi (the University of Tokyo).
5. Medical Economics Adviser: Takashi Fukuda (the University of Tokyo).
6. Nutrition Evaluation Adviser: Satoshi Sasaki (the University of Tokyo).
7. International Adviser: Harold I. Feldman (University of Pennsylvania).
8. General Adviser: Kiyoshi Kurokawa (National Graduate Institute for Policy Study).
9. Sponsor: Kyowa-Hakko-Kirin Co. Ltd.

References

1. USRDS. International comparison. Am J Kidney Dis. 2010;55(Suppl 1):S343–54.
2. Japanese Society of Dialysis Therapy. An overview of regular dialysis treatment in Japan as of Dec 31, 2008. 2009. http://docs.jsdt.or.jp/overview/. Accessed 1 March 2010.
3. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol. 2009;13:621–30.
4. Sarnak M, Levey A, Schoolwerth A, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, and epidemiology and prevention. Circulation. 2003;108:2154–69.
5. 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. 2004;351:1296–305.
6. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension. 1999;33:1111–7.

7. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001;37:1236–41.
8. Shoji T, Emoto M, Shinohara K, Kakiya R, Tsujimoto Y, Kishimoto H, et al. Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. J Am Soc Nephrol. 2001;12:2117–24.
9. Nakayama M, Metoki H, Terawaki H, Ohkubo T, Kikuya M, Sato T, et al. Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population—the Ohasama study. Nephrol Dial Transplant. 2007;22:1910–5.
10. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rahman M, et al. Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. Clin J Am Soc Nephrol. 2009;4:1302–11.
11. Imai E, Matsuo S, Makino H, Watanabe T, Akizawa T, Nitta K, et al. Chronic Kidney Disease Japan Cohort (CKD-JAC) study: design and methods. Hypertens Res. 2008;3:1101–7.
12. Miura K, Nakagawa H, Ohashi Y, Harada A, Taguri M, Kushiro T, et al. Four blood pressure indexes and the risk of stroke and myocardial infarction in Japanese men and women: a meta-analysis of 16 cohort studies. Circulation. 2009;119:1892–8.
13. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
14. McDowell SE, Coleman JJ, Ferner RE. Systemic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. BMJ. 2006;332:1177–81.
15. McCullough PA, Li S, Jurkovitz CT, Stevens LA, Wang C, Collins AJ, et al. CKD and cardiovascular disease in screened high-risk volunteer and general populations: the Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999–2004. Am J Kidney Dis. 2008;51(4 Suppl 2):S38–45.
16. Nakayama M, Sato T, Sato H, Yamaguchi Y, Takeuchi K, Obara K, Kurihara I, Sato K, Hotta O, Seino J, Miyata M, Takeuchi K, Otaka T, Nakayama K, Matsushima M, Otaka T, Kinoshita Y, Taguma Y, Ito S. Different clinical outcomes for cardiovascular events and mortality in chronic kidney disease according to underlying renal disease, Clin Exp Nephrol. 2010. doi: 10.1007/s10157-010-0295-y.
17. Kimoto E, Shoji T, Shinohara K, Hatsuda S, Mori K, Fukumoto S, et al. Regional arterial stiffness in patients with type 2 diabetes and chronic kidney disease. J Am Soc Nephrol. 2006;17:2245–52.
18. Wang MC, Tsai WC, Chen JY, Huang JJ. Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. Am J Kidney Dis. 2005;45:494–501.
19. Townsend RR, Wimmer NJ, Chirinos JA, Parsa A, Weir M, Perumal K, et al. Aortic PWV in chronic kidney disease: a CRIC ancillary study. Am J Hypertens. 2010;23:282–9.
20. DeLoach SS, Appel LJ, Chen J, Joffe MM, Gadegbeku CA, Mohler ER 3rd, et al. Aortic pulse pressure is associated with carotid IMT in chronic kidney disease: report from Chronic Renal Insufficiency Cohort. Am J Hypertens. 2009;22:1235–41.

Clinical Correlates of Ambulatory BP Monitoring among Patients with CKD

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Summary

Background and objectives Ambulatory BP monitoring (ABPM) allows a better risk stratification than office BP in hypertensive patients. However, the clinical relevance of ABPM has not been extensively investigated in the CKD population.

Design, setting, participants, & measurements Within the Chronic Kidney Disease Japan Cohort study, 2977 patients enrolled (62% men, aged 60.8±11.6 years) and ABPM was conducted in a subgroup of patients from September 2007 to April 2010. Data from 1075 patients (682 men) were analyzed to determine BP control and factors associated with the ABPM parameters.

Results The prevalence of masked hypertension was 30.9%, whereas that of white-coat hypertension was 5.6%. With advancing CKD stage, the percentage of persistent hypertension increased from 21.7% to 36.1%. Diabetes, antihypertensive medicine use, and low estimated GFR (eGFR) were significantly associated with the difference between office BP and ambulatory BP (1.7 mmHg, 2.6 mmHg, and 0.6 mmHg per 10 ml/min per 1.73 m^2, respectively). There tended to be fewer nondippers and risers in stage 3 than in stages 4 and 5. In the nocturia-negative group, low eGFR, diabetes, and summer season were identified as factors associated with lower nocturnal BP change (−0.5 mmHg, −2.0 mmHg, and −2.8 mmHg, respectively). Morning BP change was greater with older age (0.2 mmHg per 10 years) and higher body mass index (0.6 mmHg per 1 kg/m^2), and in winter (4.5 mmHg) versus summer.

Conclusions Various factors including eGFR, diabetes, antihypertensive medication use, and season are associated with higher BP and abnormal BP patterns in CKD patients.

Clin J Am Soc Nephrol 8: 721–730, 2013. doi: 10.2215/CJN.06470612

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Introduction

BP fluctuates diurnally and seasonally. In epidemiologic studies, office BP has been used as representative BP. Despite its fluctuating nature, the office BP was identified as the most important risk factor for cardiovascular diseases. It dates back to the Framingham Heart Study (1–3) for the BP to be named as the risk factor, and as the study continues to the third generations of the participants, BP was controlled at ever lower levels (4). In the past decade, BP has frequently been discussed in association with CKD (5–7).

Because the concepts of masked hypertension (MHT) and white-coat hypertension (WCHT) are well recognized (8–10), studies measured only by the office BP are thought to be insufficient. At the same time, parameters derived from ambulatory BP monitoring (ABPM) have been reported to serve as predicting factors for various organ failures (11–15). In particular, the association between circadian variations in BP and cardiovascular events has been studied from various approaches (12,16–20).

The Chronic Kidney Disease Japan Cohort (CKD-JAC) observational study was started in 2007 to investigate CKD among Japanese adults and 2977 participants were enrolled (21,22). For each patient, ABPM was performed once at the start of the study. The purpose of this study is to describe the characteristics of BP in CKD patients using registration data and to evaluate the background factors that influence ABPM data.

Materials and Methods

CKD-JAC

A detailed description of this study was previously published (22). In brief, CKD-JAC participants were Japanese or Asian living in Japan, aged 20–75 years, and had stage 3–5 CKD. The major exclusion criteria were patients with polycystic kidney disease, HIV infection, liver cirrhosis, or cancer, and transplant recipients and patients who previously received dialysis.

ABPM and Patient Questionnaire

ABPM was conducted within a half year after the patient's investigation start. BP was measured every