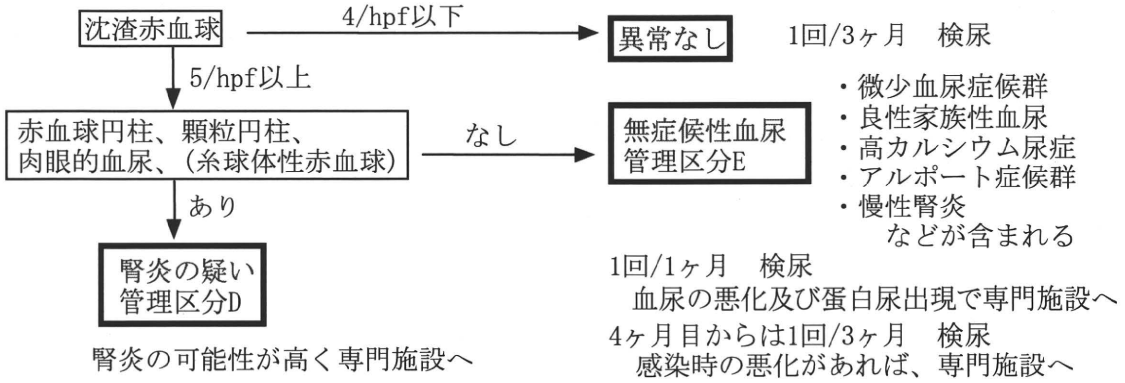
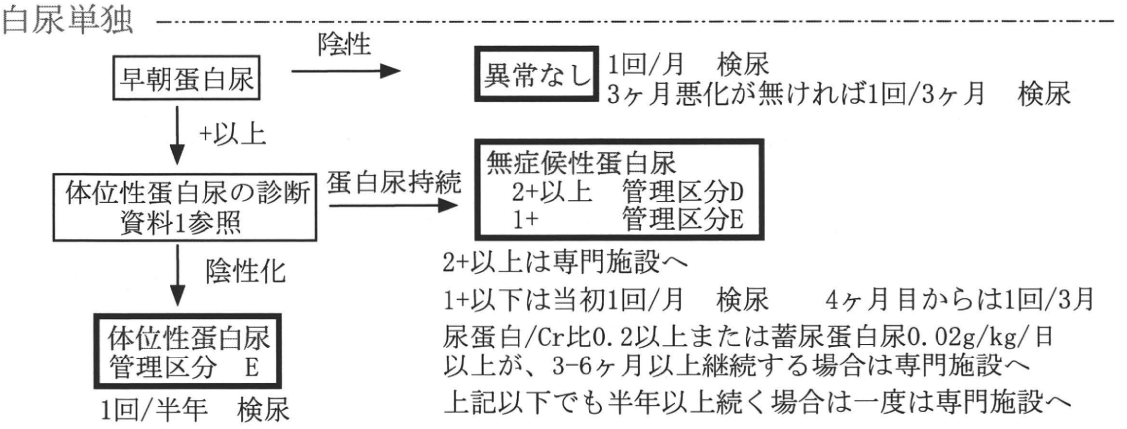
検尿異常早見表　-暫定診断と管理区分-

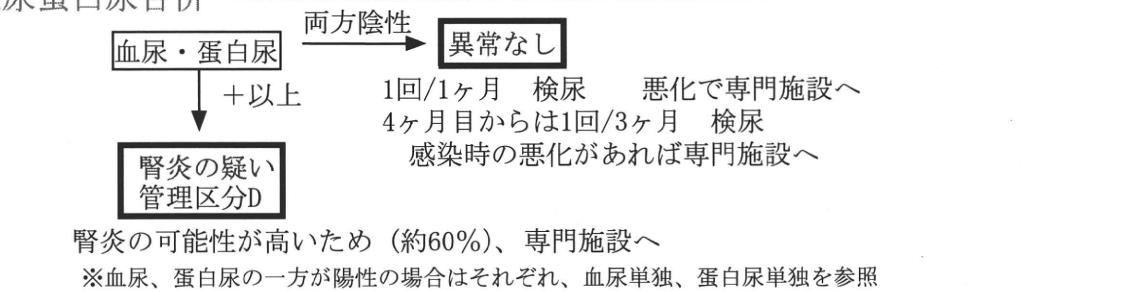
血尿単独



蛋白尿単独



血尿蛋白尿合併



※血尿、蛋白尿の一方が陽性の場合はそれぞれ、血尿単独、蛋白尿単独を参照

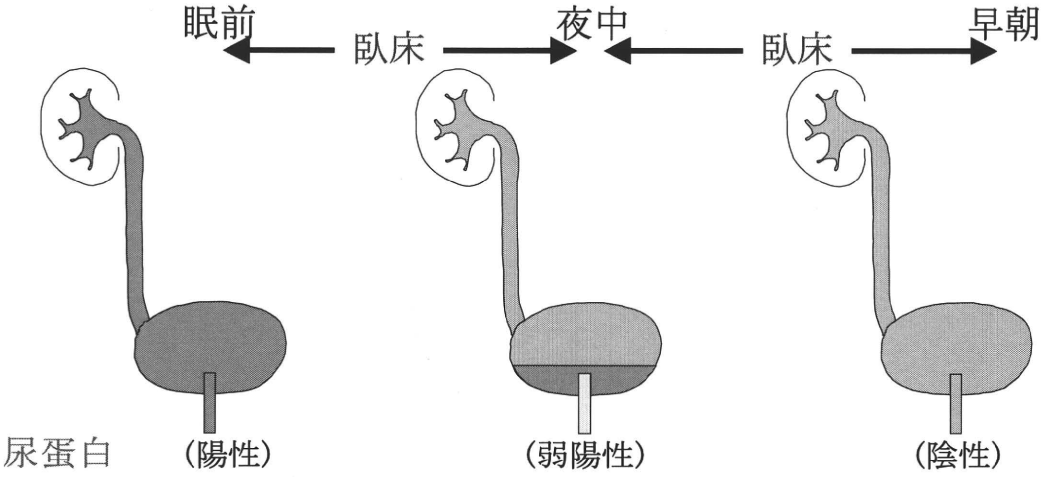
専門医紹介が必要な例

1、（２＋）以上の蛋白尿
2、スポット尿で蛋白/Crが0.2以上または蓄尿蛋白尿0.02g/kg/日が3-6ヶ月以上継続する場合
3、血尿/蛋白尿が合併している場合
4、肉眼的血尿
5、低蛋白血症
6、低補体血症
7、高血圧、浮腫、腎機能障害の存在
8、良性家族性血尿を除く、腎疾患の家族歴がある場合

なお、管理区分がE以外で、制限が必要と考えた場合は、その制限が妥当かどうかを判断するためにも一度専門施設に紹介する。

財団法人　愛知腎臓財団
（慢性腎臓病対策協議会　小児CKD対策専門部会）
専門部会長　あいち小児保健医療総合センター腎臓科　上村 治
（E-mail：osamu_uemura@mx.achmc.pref.aichi.jp）

体位性蛋白尿の診断方法の一つ（正確な安静時尿の採取法）



高血圧診断基準

年齢、体格別の血圧上限値（90パーセンタイル）

年齢	身長(cm) 男	身長(cm) 女	収縮期血圧(mmHg)	拡張期血圧(mmHg)
1-3 歳	95以下		105	60
4-6 歳	120以下		110	70
7-9 歳	135以下		115	75
10-12 歳	155以下		120	75
13-14 歳	165以下	160以下	125	78
15-16 歳	175以下	160以上	130	80
17歳以上	175以上		135	85

血清クレアチニン正常値　酵素法による基準値

年齢		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
男	上限	0.4		0.5						0.6				0.7		0.8		0.9
	平均	0.2		0.3				0.4				0.5			0.6		0.7	
女	上限	0.4		0.5		0.6						0.7				0.8		0.9
	平均	0.2			0.3				0.4						0.5		0.6	

血清クレアチニン正常値の簡易推算式（1ー12才）

血清クレアチニン（mg/dl）　＝　0.30×身長（m）

J-CKDI 日本慢性腎臓病対策協議会
Japan Association of Chronic Kidney Disease Initiative

Chronic Kidney Disease

慢性腎臓病（CKD）をご存知ですか？

私たちの健康を脅かす「新たな国民病」です。

CKD（慢性腎臓病）は重大な病気ですが、
進行に応じて適切な治療が可能です！

トピックス topics

東日本大震災により被災された皆様に心よりお見舞い申し上げます。
皆様の一日も早い安全、安心の確保、および皆様に繋がる方々のご無事をひより祈念しております。
この度の震災を受け、世界腎臓デーの一部イベントを中止・延期とさせていただきます。2011年世界腎臓デーのイベント情報はこちら

その他 2011年5月9日
ダウンロード資料集に新しい資料を追加いたしました。

世界腎臓デーへの取り組み

ダウンロード資料集
CKDに関する資料がダウンロードできます
ダウンロードはこちら New!

CKDについて
about Chronic Kidney Disease

リーフレット

毎年3月第二木曜日は「世界腎臓デー」
“あなたの腎臓は大丈夫？”必ず健康診断をうけましょう

■作成者
厚生労働省科学研究「慢性腎臓病(CKD)に関する普及啓発のあり方に関する研究」
（主任研究者 昭和大学腎臓内科 秋澤忠男）

PDF600KB

プレビューを見る

アンケートに回答してダウンロード

ポスター

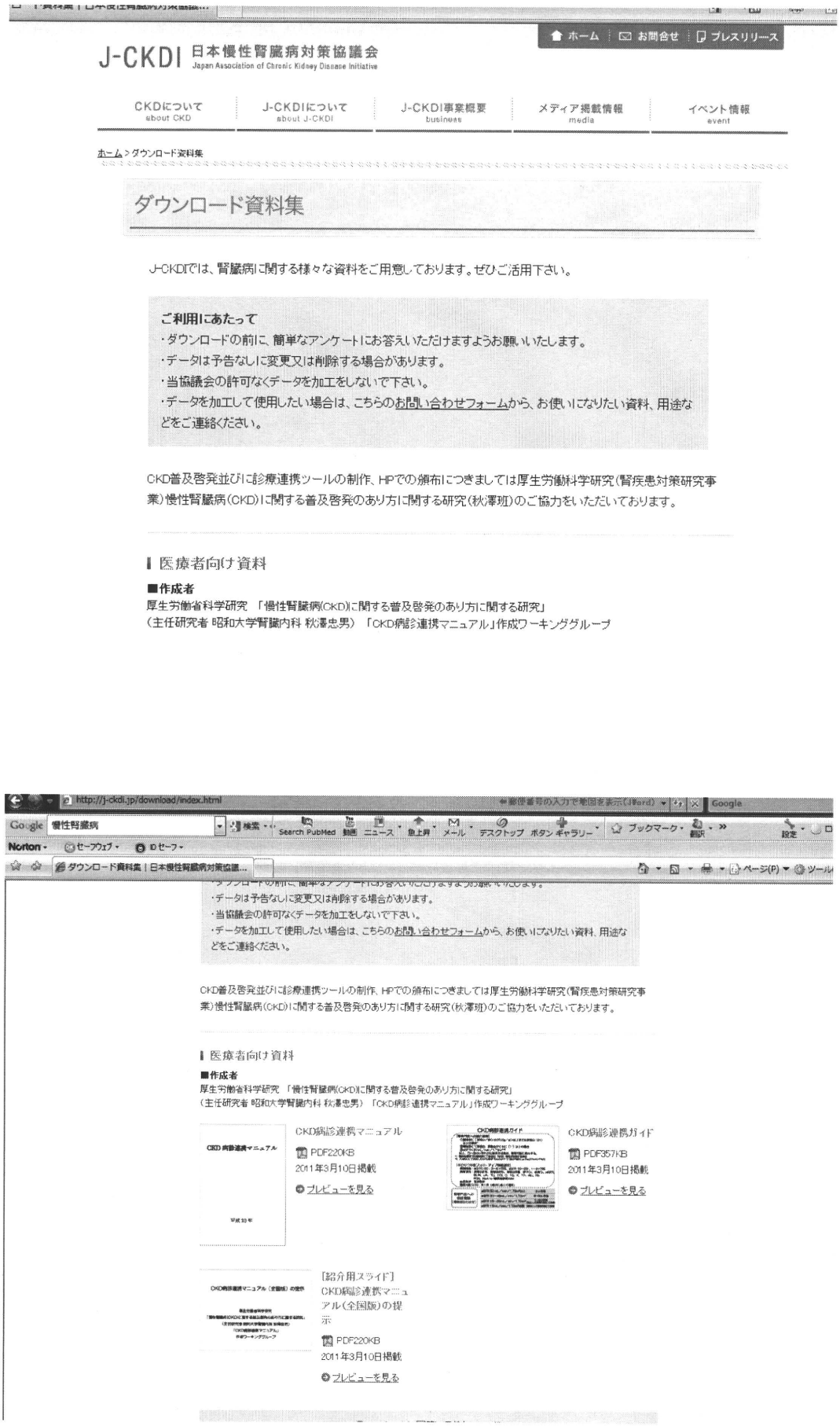
慢性腎臓病は私達の生活をおびやかす新たな「国民病」です！

■作成者
厚生労働省科学研究「慢性腎臓病(CKD)に関する普及啓発のあり方に関する研究」
（主任研究者 昭和大学腎臓内科 秋澤忠男）

PDF297KB

プレビューを見る

アンケートに回答してダウンロード



J-CKDI 日本慢性腎臓病対策協議会
Japan Association of Chronic Kidney Disease Initiative

ホーム | お問合せ | プレスリリース

CKDについて about CKD | J-CKDIについて about J-CKDI | J-CKDI事業概要 business | メディア掲載情報 media | イベント情報 event

ホーム > ダウンロード資料集

ダウンロード資料集

J-CKDIでは、腎臓病に関する様々な資料をご用意しております。ぜひご活用下さい。

ご利用にあたって
・ダウンロードの前に、簡単なアンケートにお答えいただけますようお願いいたします。
・データは予告なしに変更又は削除する場合があります。
・当協議会の許可なくデータを加工をしないで下さい。
・データを加工して使用したい場合は、こちらのお問い合わせフォームから、お使いになりたい資料、用途などをご連絡ください。

CKD普及啓発並びに診療連携ツールの制作、HPでの頒布につきましては厚生労働科学研究(腎疾患対策研究事業)慢性腎臓病(CKD)に関する普及啓発のあり方に関する研究(秋澤班)のご協力をいただいております。

医療者向け資料

■作成者
厚生労働省科学研究 「慢性腎臓病(CKD)に関する普及啓発のあり方に関する研究」
(主任研究者 昭和大学腎臓内科 秋澤忠男) 「CKD病診連携マニュアル」作成ワーキンググループ

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PDF220KB
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Clin Exp Nephrol (2010) 14:558–570
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ORIGINAL ARTICLE

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

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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 ≥ 45, 45 > eGFR ≥ 30, 30 > eGFR ≥ 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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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.

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ORIGINAL ARTICLE

Maintaining high hemoglobin levels improved the left ventricular mass index and quality of life scores in pre-dialysis Japanese chronic kidney disease patients

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Abstract
Background Anemia is common among patients with chronic kidney disease (CKD). The introduction of erythropoietin treatment has changed anemia management, but the therapeutic hemoglobin (Hb) target is still under debate, and clinical evidence for its effect on cardiac functions and QOL is sparse.
Methods A 16-week dose–response study and a 32-week follow-Up study were combined. After correcting anemia of less than 10 g/dl in pre-dialysis Japanese CKD patients, a higher Hb target (12–13 g/dl) by darbepoetin alfa (DPO) was compared with the conventional Hb target by epoetin alfa (EPO). Outcomes were anemia correction, management of the left ventricular mass index (LVMI) and QOL scores.
Results No significant difference was seen in Hb at baseline and week 16, but a significant difference was recorded at week 34 (12.34 ± 0.93 g/dl for DPO and 10.43 ± 0.90 g/dl for EPO). In both groups, LVMI decreased similarly until week 16, but the decrease of EPO was retarded, and a significant difference between LVMI was seen only in DPO at week 34 (100.7 ± 16.6 g/m^2 for

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DPO and 110.9 ± 25.2 g/m^2 for EPO). Relationships between Hb and LVMI change at week 34 were examined by stratifying Hb into four groups (Hb <10 g/dl, 10 g/dl ≤ Hb <11 g/dl, 11 g/dl ≤ Hb <12 g/dl and 12 g/dl ≤ Hb), and a decrease of LVMI was prominent in the 12 g/dl ≤ Hb group. Correction of anemia to 11 g/dl or more led to improved QOL scores. No safety difference was observed among the treatments.

Conclusions Targeting a higher Hb around 12 g/dl was more beneficial than targeting conventional Hb in terms of reduction of LVMI and QOL. Further studies to determine the appropriate Hb target are necessary.

Keywords Anemia · Cardiac functions · Chronic kidney disease · Erythropoietin · Quality of life

Introduction

Anemia is a common problem among patients with advanced chronic kidney disease (CKD). Prior to the availability of erythropoietic stimulating agents (ESAs), chronic blood transfusions represented the standard of care for treating anemia. Chronic treatment with transfusions carried inherent risks associated with infection, such as viral hepatitis, iron overload and the risk of alloimmunization [1]. With the approval of recombinant erythropoietin (EPO), the care of patients with CKD and anemia dramatically changed, and the necessity of transfusion to treat anemia in this group was greatly diminished. Currently, the objective of anemia treatment with EPO is not just to avoid transfusion, but also to improve the symptoms of anemia, such as shortness of breath and fatigue. However, the optimal hemoglobin (Hb) target applied in EPO therapy is still under debate and is being examined closely by the medical community.

The KDOQI guideline for anemia treatment was updated in 2006 to raise the upper limit of the Hb target, which previously had been set at 12 g/dl [2]. Afterward, negative patient outcomes of the CHOIR study in which a higher Hb target (13.5 g/dl) was compared to conventional treatment (11.3 g/d) were reported [3], and the therapeutic Hb target for patients with CKD became a topic of heated discussion once again [4, 5]. While several observational studies suggested that higher Hb indicated better patient outcomes or good patient health status [6–9], prospective studies such as CHOIR and CREATE [10], to correct anemia higher than the recommended Hb, failed to demonstrate a benefit. The difference might derive from the situations of daily clinical practice and clinical study settings that require strict protocol compliance with closer attention to the specific therapeutic effect of the treatment [4]. In Japan, the therapeutic Hb target for EPO treatment in regular clinical practice for patients with CKD, regardless of renal replacement therapy, is set at around 10 g/dl by the government. There are few reports in which a high Hb target has been applied and its effects examined in a large Asian population, including the Japanese. Additionally, Fukuhara et al. [11] reported that a decline in quality of life (QOL) was associated with an increase in serum creatinine and a decline in hematocrit in CKD patients. Although KDOQI and other guidelines, including European ones [12], recommend that the Hb target level should be 11.0 g/dl or greater in terms of QOL, it has not been well validated in Asian populations. On the other hand, it was reported that normalization of the hematocrit level in Japanese CKD patients led to favorable cardiovascular changes in a small prospective study [13]. Therefore, we report the results of a clinical trial in pre-dialysis CKD patients that compared the therapeutic Hb target of 12–13 g/dl to that of 10–12 g/dl, and investigated its impact on left ventricular mass index (LVMI) reduction and QOL. This is a combined analysis of two consecutive comparative randomized clinical studies comprised of the dose–response and follow-up studies of darbepoetin alfa (DPO) and EPO. Originally, the dose–response study was conducted to examine the dose–response relationship of DPO with Hb in anemia correction. The follow-up study was to evaluate the safety and efficacy of DPO at a higher therapeutic Hb target compared with EPO at the conventional Hb target.

Materials and methods

Study population

The dose–response and follow-up studies were multicenter, randomized, open-label, parallel-group studies conducted from July 2004 through December 2005. Fifty-two medical centers and hospitals in Japan participated in the studies. The studies were conducted in accordance with the Declaration of Helsinki and international guidelines for good clinical practice. The protocols were approved by each local institutional review board prior to implementation.

The dose–response study enrolled adults with anemia (Hb <10 g/dl without administration of EPO in the last 4 weeks) and CKD [creatinine ≥2 mg/dl (177 μmol/l)] who were aged 20–80 years and weighed 40–80 kg, and who were not expected to initiate regular renal replacement therapy within 16 weeks. However, those with uncontrolled hypertension, congestive heart failure [New York Heart Association (NYHA) class III–IV] and known history of symptomatic myocardial, pulmonary and cerebral infarction, unstable angina and obstructive arteriosclerosis (Fontaine's class II–IV) were excluded together with those

with malignancy, major bleeding, recent surgery, transfusion or investigational products within 16 weeks. All patients gave written informed consent prior to study enrollment. Those who completed the dose–response study and were not expected to initiate regular renal replacement therapy within another 32 weeks were asked to enroll in the follow-up study. Those subjects who agreed to participate in the follow-up study were asked to provide additional written informed consent.

Study design

The design of the dose–response and follow-up studies is shown in Fig. 1; the first 16 weeks were allocated to the dose–response study and the latter 32 weeks to the follow-up study. Eligible patients were randomly assigned to receive 30, 60 or 90 μg of DPO subcutaneously every other week or 6,000 IU of EPO subcutaneously once a week in the dose–response study. The dosage of the drug was not changed until Hb reached above 12 g/dl. Administration was suspended if severe adverse events occurred or the rate of Hb rise was over 3 g/dl in 4 weeks as set in the previous similar study [14]. After achieving the lower bound of the therapeutic target, the dosage was adjusted to maintain the target range at a physician's discretion. Randomization of patients was performed centrally into four treatment groups with dynamic allocation, stratified by Hb, serum creatinine and institution. In this analysis, all groups in the study were integrated to investigate the relationship between QOL and Hb or Hb rise.

In the follow-up study, allocation of DPO and EPO for each patient was not changed from the dose–response study. Therefore, the ratio of patients with DPO to EPO was expected to be about 3:1. Patients treated with DPO were assigned to maintain a target of 12–13 g/dl, whereas those treated with EPO were to maintain a target of 10–12 g/dl. DPO was administered every 2 or 4 weeks subcutaneously, and the maximum dose was limited to 180 μg. The dose of DPO was adjusted to maintain the target range at the discretion of each investigator and selected from the following: 15, 30, 60, 90, 120 and 180 μg. Dose increase per time was limited to the next higher dose. Dosage of EPO was subcutaneous 6,000 IU weekly or 6,000–12,000 IU every 2 weeks, which was the approved dosage on the product label in Japan.

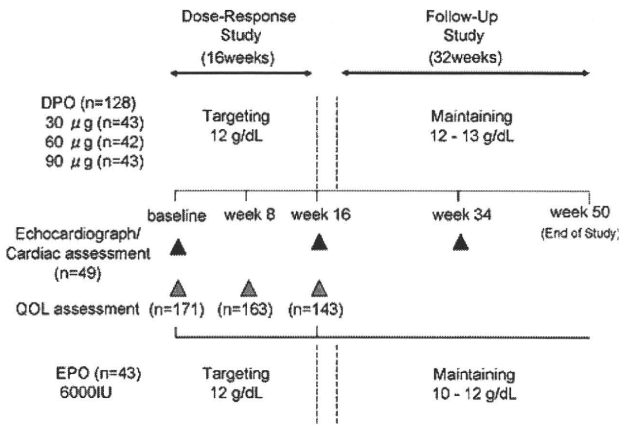

Fig. 1 Study design of the dose–response and follow-up studies. The first 16 weeks were allocated to the dose–response study and the latter 32 weeks to the follow-up study

An iron supplement was prescribed as appropriate to keep transferrin saturation above 20% or ferritin above 100 ng/ml.

All patients had a clinical assessment at least every 2 weeks throughout the two trials. Echocardiographic images were obtained at baseline, week 16 and 34 after the initiation of the dose–response study for the assessment of cardiac functions together with electrocardiograms and chest X-rays. With patient information blinded, independent cardiologists excluded those that were incomparable for drawing a comparison for each of the three points. LVMI was measured with two-dimensional echo-guided M-mode echocardiograms, and the calculation used for the body surface correction was the Devereux formula: $0.8 \times \{1.04 \times [(\mathrm{LVDd} + \mathrm{IVST} + \mathrm{PWT})^3 - \mathrm{LVDd}^3]\} + 0.6$ (LVDd: left ventricular end-diastolic diameter, IVST: interventricular septal thickness, PWT: left ventricular posterior wall thickness).

For QOL assessments, a self-administered medical outcomes study, the 36-item short-form health survey (SF-36), and a functional assessment of chronic illness therapy (FACIT) fatigue scale, instruments widely employed [3, 10, 11, 15, 16] to measure perceived health status and daily functioning, were conducted at baseline, week 8 and 16 after the initiation of the dose–response study.

Study objectives

The objective of this exploratory combined analysis was to investigate whether the differences of anemia correction and management had an effect on LVMI reduction and QOL in Japan.

Statistical analysis

The chi-square test was applied to compare categorical data, and the Student's t test was applied to compare means, while analysis of variance was applied to compare serial changes among the groups over time. Analysis of covariance was used to calculate the effects of Hb on the values that demonstrate cardiac functions like LVMI and QOL scores. $P < 0.05$ was considered significant.