Original Article

Chronic Kidney Disease Japan Cohort (CKD-JAC) Study: Design and Methods

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The prevalence and incidence of end-stage renal disease (ESRD) in Japan are the highest and the third highest, respectively, in the world, while the incidence of cardiac death in Japan is the lowest among developed countries. A recent study showed that the prevalence of chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m², is extremely high in Japan, about 20% of the adult population. However, the risk of ESRD and cardiovascular disease (CVD) in the CKD population has not been determined nationwide. For this observational study, we will establish a Chronic Kidney Disease Japan Cohort (CKD-JAC) by enrolling 3,000 patients with CKD in 17 clinical centers around Japan, which will be used to determine the incidence of ESRD and CVD in Japanese CKD patients. Risk factors associated with the development of CVD will also be examined. Comorbidity of diabetes in CKD patients will be analyzed to determine whether it is a risk for rapid progression of CKD and high incidence of CVD. In addition, we will study whether the burden of CKD decreases the QOL of patients, and increases hospitalization or health resource utilization. Insights from the CKD-JAC study will provide a basis for future interventional trials focused on reducing the burden of ESRD and CVD in patients with CKD in Japan. (*Hypertens Res* 2008; 31: 1101–1107)

Key Words: cardiovascular disease, stroke, heart failure, proteinuria, time to event analysis

Introduction

The number of Japanese patients with end-stage renal disease (ESRD) has increased over the last four decades; in 2006, the number of ESRD patients on chronic hemodialysis exceeded 260,000 (1). Patients with ESRD are at risk of developing various complications, such as cardiovascular disease (CVD), bone mineral disorders, eye diseases, infectious diseases and

malignancies. The comorbidity in addition to dialysis therapy *per se* decreases the quality of life (QOL) for ESRD patients (2). Furthermore, the life expectancy is significantly shorter in ESRD patients compared with healthy individuals (3, 4). Dialysis costs the Japanese medical system more than US \$10 billion/year, which significantly affects the policies of the Ministry of Health, Labour and Welfare. This cost explosion for ESRD is not only a regional, but also a global issue, requiring the implementation of local prevention programs

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for chronic kidney disease (CKD) in concert with physicians, health care workers, and governments (5).

Early detection and appropriate treatment for CKD is necessary to cut the number of ESRD patients and related costs. The Kidney Diseases Improving Global Outcome (KDIGO) program was established in 2003 by an international board of directors, with a stated mission of improving the care and outcomes of kidney disease patients (5). KDIGO developed core recommendations for the diagnosis, care, and treatment of CKD globally, defining CKD as a low glomerular filtration rate (GFR; less than 60 mL/min/1.73 m²) and/or kidney injury lasting more than 3 months (6). This definition simplifies diagnosis and helps to increase public awareness of kidney disease.

The prevalence of stage 3 to 5 CKD in Japan was predicted to be 19.1 million patients among the Japanese general adult population of 103.2 million (7), while stage 4 to 5 patients were predicted to number 200,000 (excluding patients on dialysis). Comorbidity with hypertension, diabetes, and proteinuria increased as the estimated GFR (eGFR) decreased (7). The QOL of patients with CKD is significantly higher than that of maintenance-hemodialysis patients, but significantly lower than in the normal population (2). The impact of an unexpectedly high number of CKD patients in the adult population prompted further study to clarify the outcomes for these patients.

The Chronic Renal Insufficiency Cohort (CRIC) study (8) was undertaken in the USA to examine the risk factors for progression of CKD, with respect to the development of CVD among CKD patients, and to develop models for the development of CVD that could identify high-risk subgroups. The study aimed to formulate future treatment trials and widen the application of preventative therapies. We saw the need to deal with the same issues in a Japanese cohort, and established the Chronic Kidney Disease Japan Cohort (CKD-JAC) study. Because the risk of coronary artery disease is much lower in Japan, 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 3,000 CKD patients, defined by a GFR of 10–59 mL/min/1.73 m². We will assess the frequency of hospitalization, QOL, and economic impact on the health budget in subcohort studies. Comparison of the CKD-JAC and CRIC studies is expected to form a basis for interesting future research.

Study Hypothesis

The study hypothesis encompasses the following four core issues:

1) Common risk factors are associated with both progression of CKD and development of ESRD in Japanese CKD patients with GFR less than 60 mL/min/1.73 m².

2) Japanese patients with CKD and a GFR less than 60 mL/min/1.73 m² are susceptible to CVD. Risk factors are associated with development of CVD in CKD patients.

3) Comorbidity of diabetes in CKD patients is a risk for rapid progression of CKD and high incidence of CVD.

4) The burden of CKD decreases the QOL of patients, and increases both hospitalization and health resource utilization.

Methods

Population Sample

We started the enrollment in September 2007. Each clinical center will enroll approximately 200 patients over 12 months to establish a total cohort of 3,000 participants. Participants will be followed until death or dropout from the study. The following inclusion criteria will be used: 1) Japanese and Asian patients living in Japan; 2) age 20–75 years; and 3) a broad spectrum of CKD with an eGFR of 10–59 mL/min/1.73 m². The eGFR will be calculated by a modified three variable equation for estimating GFR for Japanese (9) as follows (sCr, serum creatinine):

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

The following exclusion criteria will be used: 1) patients with polycystic kidney disease, HIV infection, liver cirrhosis, or cancer; 2) transplant recipients and patients who have previously received chronic dialysis; 3) pregnant women; and 4) individuals who refuse to provide informed consent.

Screening and Enrollment

Eligible patients will be screened by eGFR calculated by the Japanese Equation for estimating GFR from serum creatinine. Eligible patients will be evaluated at baseline, and socio-demographic information, past and family history, medication records, anthropometric measurements, blood pressure, heart rate, and ankle-brachial index, will be collected. Patients will complete a questionnaire designed to assess QOL, dietary assessment, physical activity, symptoms of depression, and cognitive function.

Follow-Up Studies

Participants will visit the clinic every 6 months for in-person follow-up visits. Allowance of early and delayed visits will be 3 months and 1 month from the appointment, respectively. Participants who change their residence will be followed up by telephone call or by mail.

Blood Pressure Measurement

Blood pressure will be measured at outpatient clinics by an automated sphygmomanometer after a 5 min rest. Blood pressure will be measured three times at intervals of 1 min on the right arm. A conventional sphygmomanometer will be used when the participant shows frequent premature contraction, atrial fibrillation, or atrial flutter.

Collection of Biological Samples and Measurements

Plasma and urine samples will be collected annually and stored for the measurement of serum creatinine and serum cystatin C, HbA1c, intact parathyroid hormone (iPTH), urine albumin, and urine creatinine at a central laboratory. Each clinical center will measure serum creatinine at each visit. Twenty-four-hour urine samples will be collected from each patient once every year to measure creatinine clearance (Ccr).

Patient Questionnaires

A QOL assessment will be performed using KD-QOL which includes SF-36 every 2 years. The questionnaire will cover dietary history, physical activity, depressive symptoms, and socio-economic status, including working status, marital status, annual income, transportation costs, and loss of income due to CKD disease.

Study Outcomes

The primary outcomes are progression of CKD defined by reduction in eGFR, CVD events, and all-cause mortality. The eGFR will be evaluated annually using the modified MDRD equation. Cystatin C will be measured annually. Subclinical CVD events will be evaluated annually by electrocardiography and echocardiography.

Identification and Classification of Clinical Cardiovascular Outcomes

Clinical centers will question participants every 6 months about CVD-related hospitalizations and interventions. Deaths will be classified as cardiac, non-cardiac, or unknown.

CVD events including fatal and non-fatal myocardial infarction, angina pectoris, stroke, arrhythmia, congestive heart failure, aorta dissection, cerebrovascular disorder, and peripheral artery diseases including arteriosclerosis obliterans will be identified.

Substudy: Twenty-Four Hour Ambulatory Blood Pressure Monitoring

Circadian fluctuations in blood pressure will be monitored over a period of 24 h. Dipper and non-dipper patterns of blood pressure will be evaluated together with progression of CKD, CVD events, and all-cause mortality.

Substudy: Medical Expenses for Patients with CKD

Direct and indirect medical care costs will be evaluated from medical billings issued by the hospital, including medical and

technical service payments. Pharmacological costs will be calculated by obtaining a copy of all prescriptions.

General Methods for Statistical Analysis

The details of statistical analysis will be included in the Statistical Analysis Plan to be submitted before interim analysis. In addition, the two-sided 95% confidence interval will be calculated with estimation. The significance level will be set at two-sided 5%.

Descriptive Epidemiology of Baseline Data and Longitudinal Data

Standard descriptive statistics will be used to describe baseline characteristics and follow-up measures, both overall and within comparison subgroups. Summary statistics such as means, medians, standard deviations, and ranges will be produced for measured variables. One-way analysis of variance will compare inter-group values as occasion demands. Graphical methods such as box plots or scatter plots will be used to review data characteristics containing normality and symmetry properties. Frequencies will be tabulated for categorical and ordinal variables, and internal comparison will be made using χ^2 test.

Analysis of Primary Endpoints

Predictors of Decreasing Rate of Renal Function

Using time to event analysis, we will examine the associations of various baseline predictors and declining rate of renal function as calculated from decreasing GFR. We will also analyze the associations of various baseline predictors and doubling of serum creatinine, initiation of ESRD therapy such as renal transplantation or dialysis treatment and 50% reduction of GFR from the baseline GFR by time to event analysis.

Predictors of Cardiovascular and Cerebrovascular Events

Using time to event analysis, we will examine the association of various baseline predictors and cardiovascular/cerebrovascular events, such as myocardial infarction, angina pectoris, congestive heart failure, arrhythmia, brain infarction, cerebral hemorrhage, aortic dissection, peripheral artery disease, and sudden death.

Death from All Causes

We will examine the association of various baseline predictors and all-cause death with time to event analysis.

Analysis of Secondary Endpoints

We will also consider secondary endpoints, such as hospital admission for various reasons, QOL, and medical economics. The details are set out in the Statistical Analysis Plan.

Complement for Statistical Methods

Time to Event Analysis

We will examine the various baseline predictors and main endpoints as above using standard methods: Kaplan-Meier curves, log-rank tests, and the Cox proportional hazards model. For estimating the effects of single factors, we will use the proportional hazards model to adjust for possible confounding variables.

Repeated Measures Analysis

Several study outcomes will be repeated as measures of continuous or categorical variables. For these analyses, we will use the generalized estimation equation or mixed effect model. Regression diagnosis will be used to assess the adequacy of all models and to examine potential outlying or influential datapoints.

Midterm Report

An interim analysis will be presented to the participating facilities.

Sample Size

The necessary sample size will depend on the endpoint being evaluated, although there are numerous endpoints in this study with various magnitudes of incidence rates. In addition, this study will function in part as an explanatory research. We have therefore selected myocardial infarction, one of the important endpoints of CKD-JAC study, as an endpoint for calculating the sample size. If patients are evenly categorized into 4 groups, Q1 to Q4, according to their eGFR values, where Q1 is the top quartile of the eGFR and Q4 the bottom quartile, we can calculate a sample size sufficient to detect statistically significant risk ratios of Q4 to Q1 when the true risk ratio is 1.5 to 2.

In the MEGA study (10), the incidence rate of myocardial infarction was reported to be 5.0 per 1,000 person-years in mild hypercholesterolemic male patients with no history of vascular events. If we assume that the incidence is double in CKD patients, the necessary sample size is derived as 741×4 using the following formula with an α error of 0.05, a power of 90% and 4 years follow-up:

$$n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2}{\Delta p^2} \bar{p}(1 - \bar{p})$$

p , incidence rate; $\Delta p = p_{Q4} - p_{Q1}$; $\bar{p}$ = average of p_{Q4} and p_{Q1} ; risk ratio = 2; $\alpha = 0.05$ (two-sided), $\beta = 0.10$.

The sample size was therefore set to 3,000 subjects. In selecting this value, we considered the sample size of the CRIC study.

Study Organization

There are several stakeholders in the CKD-JAC study: a scientific steering committee, 17 clinical centers, a data management center, and an independent committee to evaluate cardiac function and CVD events. This study is sponsored by an unrestricted grant from Kirin Pharma Co., Ltd.

1) Steering Committee: Akira Hishida, M.D. (Hamamatsu University), Seiichi Matsuo, M.D. (Nagoya University), Tsuyoshi Watanabe, M.D. (Fukushima Medical University), Yasuo Ohashi, Ph.D. (The University of Tokyo), Hirofumi Makino, M.D. (Okayama University), Tadao Akizawa, M.D. (Showa University), Kosaku Nitta, M.D. (Tokyo Women's Medical University), Enyu Imai, M.D. (Osaka University).

2) Clinical Centers (located prefecture): Sendai Social Insurance Hospital (Miyagi), Jichi Medical University (Tochigi), Toride Kyodo Hospital (Ibaraki), St. Luke's International Hospital (Tokyo), Tokyo Women's Medical University Hospital (Tokyo), Showa University Hospital (Tokyo), Showa University Yokohama Northern Hospital (Kanagawa), Showa University Fujigaoka Hospital (Kanagawa), Tosei General Hospital (Aichi), Kasugai Municipal Hospital (Aichi), Gifu Prefectural General Medical Center (Gifu), Osaka University Hospital (Osaka), Osaka City General Hospital (Osaka), Osaka General Medical Center (Osaka), Kurashiki Central Hospital (Okayama), Iizuka Hospital (Fukuoka), Fukuoka Red Cross Hospital (Fukuoka).

3) Data Center: Public Health Research Foundation (Tokyo).

4) Independent Cardiac Function Evaluation Committee: Kyoichi Mizuno, M.D. (Nippon Medical School Hospital), Hiroshi Nishimura, M.D. (The University of Tokyo), Satoshi Iimuro, M.D. (The University of Tokyo).

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6) Medical Economics Adviser: Takashi Fukuda, Ph.D. (The University of Tokyo).

7) International Adviser: Harold I. Feldman, M.D. (University of Pennsylvania).

8) General Adviser: Kiyoshi Kurokawa, M.D. (National Graduate Institute for Policy Study).

Discussion

CVD in Patients with CKD

Patients with CKD are at higher risk of CVD than the general population (11–13). The hazard ratio (HR) for cardiovascular events increases inversely with eGFR. Based on the integrated system of health care delivery in the USA, an eGFR of 45 to 59 mL/min/1.73 m² is associated with an HR of 1.4, an eGFR of 30 to 44 mL/min/1.73 m² with an HR of 2.0, an eGFR of 15–29 mL/min/1.73 m² with an HR of 2.8, and an eGFR of less than 15 mL/min/1.73 m² with an HR of 3.4 (11). The Framingham Study Group reported CVD and all-cause

mortality rates in individuals with mild renal insufficiency (Ccr 60 ± 18 mL/min for men, 37 ± 11 mL/min for women) (14). The rate of CVD events was 21.3 per 1,000 person-years in men and 25.6 per 1,000 person-years in women, which was not significantly different from the values in men and women with normal Ccr. For all-cause mortality, the rate was 33.3 per 1,000 person-years for men and 39.5 per 1,000 person-years for women. The event rate of all-cause mortality (HR 1.31 [1.02–1.67]) was significantly higher in men with mild renal insufficiency than in those with normal Ccr, although this was not the case for women (HR 1.08 [0.87–1.34]).

In Japan, low GFR is considered a CVD risk in the general population. However, the HR for CKD in the population has not been determined, and CKD is a known and striking risk for developing CVD, even though the incidence of CVD in Japan is much less than in Western countries. Few reports are available in regard to the incidence of CVD in the general population. In the Hisayama cohort study, which included 2,637 residents aged 40 and over from 1988, the incidences of coronary heart disease in men and women were 348 and 181 per 100,000 person-years, respectively (15), and the incidence of stroke was 529 and 388 per 100,000 person-years in men and women, respectively. In the Morbidity of Myocardial Infarction Multicenter study (3M study) (16), the incidence and case fatality rates of acute myocardial infarction were 40.2 per 100,000 person-year and 22.2%, respectively. Even in patients with hypercholesterolemia in the J-LIT study (17), the incidence of cardiovascular events was 3.50 and 7.39 per 1,000 patients over 6 years in non-diabetic and diabetic subjects, respectively. In the MEGA study, the incidence of myocardial infarction was 5.0 and 3.3 per 1,000 person-years in hypercholesterolemic patients treated with diet and diet plus pravastatin, respectively. In contrast, the annual event rates for myocardial infarction and coronary death are much higher in Western countries; the MONICA study found an incidence rate of myocardial infarction and coronary death in men of 500–800 per 100,000 (18). In addition, hypercholesterolemic patients treated without and with pravastatin had an incidence of coronary events of 93 and 68 per 1,000 person-years, respectively, over 5 years (19). These results imply that the general Japanese population, including hypercholesterolemic individuals, has a lower risk of CVD than comparable Western populations. The CKD-JAC study will clarify the relevant risk factors for CVD in a Japanese CKD population for the first time.

Effects of Proteinuria on Patients with CKD

Proteinuria is a hallmark of progressive CKD and predicts ESRD (20), and remission or regression of CKD can be achieved with treatment to reduce proteinuria. The RENAAL (21) and IDNT (22) studies reported that a 30% and 50% reduction in proteinuria, respectively, following treatment with angiotensin II type 1 receptor blockers predicted significantly better outcomes for patients with diabetic nephropathy.

Proteinuria is a risk factor for CVD and mortality in patients with CKD (23), moreover, microalbuminuria or even normal-range albuminuria constitutes a risk for CVD (24, 25). Microalbuminuria is associated with carotid atherosclerosis (26). The level of proteinuria during treatment is a powerful predictor for subsequent risk of CVD (27). For this reason, our study will measure urinary albumin and creatinine at the central laboratory, as described in the Methods section.

Effects of Hypertension on CKD Patients

Numerous studies have defined hypertension as an important risk factor for CVD and all-cause mortality. Ambulatory blood pressure (ABP) was recently demonstrated to be more important than office blood pressure for predicting CVD and mortality (28, 29). Kario *et al.* (30) also showed the relevance of morning surge in blood pressure as a predictor of stroke in the general population. In a CKD-JAC substudy, we will measure ABP at different times to distinguish between the impact of high night blood pressure and morning surge for predicting CVD.

Diabetes and CKD

Diabetes is the leading cause of ESRD in Japan as well as in Western countries. Diabetes increases the risk of CVD, including ischemic heart disease, stroke, and peripheral vascular disease. Asians with hypertensive type 2 diabetes are also at high risk of developing nephropathy (31, 32). The number of diabetic patients defined by an HbA1c of 6.1% is increasing in Japan, with an estimated number of more than 6 million in 2002 (report from the Ministry of Health, Labour and Welfare). CKD-JAC study will measure the risk of comorbidity of diabetes in the CKD population.

Progression of CKD in Patients with Low GFR

GFR decreases with aging (33, 34–36). However, one-third of normal individuals showed no change in Ccr in a 20-year longitudinal study (37).

Low GFR was a risk factor for progression in CKD patients with GFRs of 25–55 mL/min/1.73 m² in the MDRD study. However, it is not well established that a GFR less than 60 mL/min/1.73 m² predicts progression to ESRD in Japanese, and few longitudinal studies exist to clarify these figures. Many traditional and non-traditional risk factors, including hypertension, proteinuria, diabetes, dyslipidemia, anemia, male sex, and lifestyle, are reported to affect the incidence of ESRD, and several interventions can modify the rate of CKD progression.

Conclusion

Japan is a remarkably aging society, in which more than 20% of the population is older than 65 years and half are older than

75 years. This is at least partly because Japan is one of the world's leading countries in terms of longevity. One of the reasons for this longevity is that Japan has a lower CVD-related death rate than any Western country. Aging is a well-established risk factor for CKD and ESRD; however, it remains unclear whether CKD is a risk for CVD in Japan. We will attempt to determine the cut-off value of eGFR in terms of the risk of CVD and ESRD. The CKD-JAC study will help to clarify the dimensions of risk for ESRD and CVD among individuals with CKD stages 3 or 4, which together account for about 20% of the adult population in Japan.

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