# Cardiovascular events and death in Japanese patients with chronic kidney disease



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**The incidence of cardiovascular disease (CVD) is higher in patients with chronic kidney disease (CKD) than in the general population, and the risk of CVD increases with reductions in renal function. However, the incidence of CVD in Japanese patients with CKD has not been sufficiently investigated. To measure this we conducted the Chronic Kidney Disease Japan Cohort (CKD-JAC) Study over four years in 2,966 Japanese patients with CKD to examine the incidence of CVD and all-cause death. These patients had an estimated glomerular filtration rate (eGFR) of 10–59 ml/min/1.73 m$^2$, were under nephrologist care, and pooled from 17 medical institutions in Japan. At the median follow-up of 3.9 years, 69 patients had died, 217 had cardiovascular events, and 514 started maintenance dialysis therapy. The incidences of cardiovascular events were 11.9, 19.1, 25.0, and 39.4 per 1,000 person-years at eGFRs of 45–59, 30–44, 15–29, and under 15 ml/min/1.73 m$^2$, respectively. The adjusted Cox proportional hazards models showed that the risk of cardiovascular events increased as the eGFR decreased, with a significant difference only between CKD stage G5 (eGFR: under 15 ml/min/1.73 m$^2$) and CKD stage G3a (eGFR: 45–59 ml/min/1.73 m$^2$) (hazard ratio 3.16, 95% confidence interval 1.28 to 7.76). Thus, the risk of CVD and all-cause death was related to the decrease in eGFR, but not necessarily elevated in proportion to progression of the CKD stage in Japanese patients with predialysis CKD under a nephrologist's care.**

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Chronic kidney disease (CKD), an independent risk factor for end-stage renal disease (ESRD), cardiovascular disease (CVD), and all-cause mortality in the general population in Western countries[1–4] has become a worldwide public health problem.

Japan is one of the countries with the highest incidence of ESRD, and the number of Japanese patients with ESRD has increased over the past 4 decades. In 2013, the number of ESRD patients on chronic dialysis exceeded 310,000.[5] The number of CKD patients is estimated to be 13.3 million (corresponding to 13% of the adult population) in Japan.[6] However, patients with predialysis CKD have not been examined sufficiently because few cohort studies have been conducted. Recent population-based studies in Japan also have confirmed CKD as a significant risk for CVD and all-cause mortality, suggesting that CKD represents a major public health problem that is independent of ethnicity.[7–9] Nevertheless, few prospective observational studies have been conducted to investigate cardiovascular events in the CKD patient population. The Chronic Renal Insufficiency Cohort (CRIC) Study[10] was conducted in the United States to examine risk factors for the progression of CKD with respect to the development of CVD in CKD patients, as well as to develop models for CVD development that could identify the high-risk subgroups. Hence, we intended to address the same challenges in a 4-year, multicenter, prospective cohort study, the Chronic Kidney Disease-Japan Cohort (CKD-JAC) Study. The design and methods of the CKD-JAC Study have been published previously.[11] The incidences of coronary artery disease and stroke events among cardiovascular events differ between Western and Asian populations, and the risk of coronary artery disease is much lower in the Japanese general population.[12] The aim of the present study was to investigate the incidence of the primary end points, cardiovascular events, and all-cause death in Japanese patients with predialysis CKD defined as an estimated glomerular filtration rate (eGFR) of 10 to 59 ml/min/1.73 m$^2$.

## RESULTS

Patient disposition is shown in Figure 1. A total of 421 patients were lost to follow-up evaluation because they

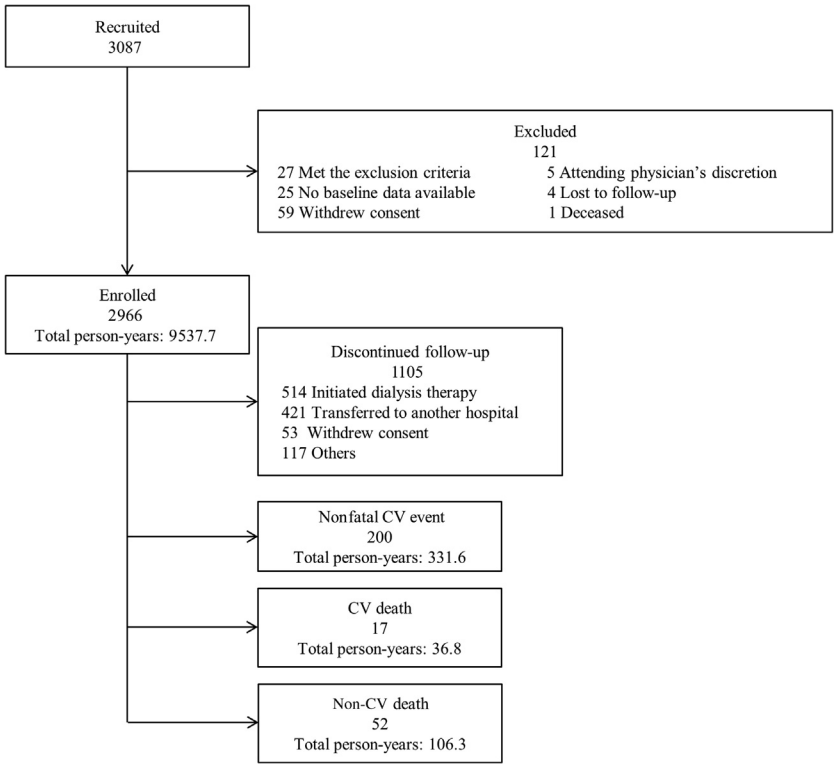


**Figure 1 | Patient disposition.** CV, cardiovascular.

transferred to other medical institutions or stopped visiting the hospital as a result of socioeconomic reasons, and the follow-up evaluation of 514 patients was terminated because maintenance dialysis therapy was initiated. Baseline clinical and laboratory characteristics of Japanese patients with predialysis CKD by CKD stage have been published previously.[13] Overall, 217 cardiovascular events and 69 all-cause deaths occurred, with only 17 cardiovascular deaths. The differences in the incidences of cardiovascular events among the 17 centers in the cohort are shown in Supplementary Table S1. The incidences of cardiovascular events and all-cause death were 22.8 and 7.2 per 1000 person-years, respectively, and they showed increases with decreases in eGFR (Figure 2). The incidences of cardiovascular events were increased significantly in patients with diabetes mellitus (DM) compared with patients without it (Table 1); however, the incidences of myocardial infarctions and cardiovascular death were markedly low both in patients with DM and in those without (Table 2). Significant differences ($P < 0.001$) were found in the incidence of cardiovascular events and primary end points (cardiovascular events plus all-cause death) with CKD stages at baseline in Japanese patients with predialysis CKD (Figure 3 and Supplementary Figure S1). The Cox proportional hazards models unadjusted for confounding factors showed significant associations between CKD stage at baseline and the primary end points (Table 2); however, these significant associations were weakened after multivariate adjustments for confounding factors (model 1, adjustment for age and sex; model 2, adjustment for covariates in model 1 plus classic cardiovascular risk factors such as body mass index, DM, current smoking, systolic blood pressure, and history of cardiovascular disease; model 3, adjustment for covariates in model 2 plus CKD-related cardiovascular risk factors such as hemoglobin, serum albumin, urine albumin, and high-sensitivity C-related protein). The risk of the primary end points was significantly different only between CKD stage G5 (eGFR, <15 ml/min/1.73 $m^2$) and CKD stage G3a (eGFR, 45–59 ml/min/1.73 $m^2$) (hazard ratio, 3.155; 95% confidence interval, 1.284–7.756; $P = 0.012$) (Table 2, model 3).

Associations between CKD stage at baseline, cardiovascular events, and the primary end points in patients with or without DM also were investigated. The incidence of both cardiovascular events and the primary end points increased significantly ($P = 0.002$) with progression of CKD stage at baseline in DM (Figure 4a and Supplementary Figure S2). Significant differences ($P = 0.038$) were found in the incidences of the primary end point along with CKD stage at baseline in patients without DM (Supplementary Figure S3), but not in the incidences of cardiovascular events (Figure 4b). The Cox proportional hazards models adjusted for confounding factors showed significant associations between CKD stage at baseline and the primary end points only in patients with DM (Table 3). Table 4 shows the comparison of the incidences of cardiovascular disease and death among the present study, CKD cohorts of the United States, and epidemiologic cohorts of Japan and the United States. The incidences of both cardiovascular disease and all-cause death