

News Release

Title

Excess risk of cardiovascular events in patients in the United States vs. Japan with chronic kidney disease is mediated mainly by left ventricular structure and function

Key Points

- Cardiovascular disease (CVD) is very common in patients with chronic kidney disease (CKD). There was no direct comparison in the incidence of CVD between Japan and the United States.
- We found that US patients with CKD had higher rates of heart failure and heart attack than Japanese patients, which was mainly due to enlargement of heart and weak contractility, using patient data from both countries.
- Obesity and inflammation, which were related to each other, were associated with the enlargement of the heart. Countermeasures against obesity can protect patients with CKD from heart disease.

Summary

Dr. Takahiro Imaizumi, Specially Appointed Assistant Professor at Nagoya University, Professor Shoichi Maruyama of the same University, Professor Takayuki Hamano at Nagoya City University, Dr. Naohiko Fujii at Nishinomiya Hospital, Professor Masafumi Fukagawa at Tokai University, Professor Harold I. Feldman at University of Pennsylvania, and other researchers conducted an international collaborative study comparing chronic kidney disease in Japan and the United States. The study found that US patients have enlarged hearts and weaker contractility, which play important roles in the cardiovascular morbidity and mortality. These features explain most of the differences in cardiovascular outcomes between the United States and Japan. Checking the heart with echocardiography may help identify high-risk patients. In addition, obesity and inflammation, which were related to each other, were associated with enlarged heart. Therefore, countermeasures against obesity can protect patients with chronic kidney disease from heart disease. The study results were published in *Kidney International*.

Research Background

Cardiovascular disease (CVD) is a serious complication in patients with chronic kidney disease (CKD). Clinical studies have been conducted in different

countries around the world in patients with CKD and suggested that patients in East Asian countries are less susceptible to CVD than those in the United States and European countries. However, because the studies were conducted independently in each country or region, background factors, such as kidney function, urinary protein, and history of CVD and diabetic mellitus, varied from study to study. While a previous study discussed comparisons between Japan and the United States (Tanaka et al. *Kidney international* 2017), this study did not use individual patient data, and it remained unclear to what extent these background differences would affect the results. In this study, we attempted to answer this unanswered question by analyzing individual patient-level data.

In recent years, more patients are developing CVD, particularly congestive heart failure, as kidney function declines. Previous studies have shown that cardiac structure and function are important predictors of future CVD outcomes. We focused on left ventricular contractility and myocardial hypertrophy to investigate the extent to which these indices explain the differences in CVD morbidity and mortality between Japan and the United States. This study would provide important insight into the clinically relevant question of what nephrologists can do in this era of the "heart failure pandemic^s".

Research Results

A total of 4222 participants were included in the analysis: 1097 of 2966 in the CKD-JAC and 3125 of 3939 in the CRIC study underwent echocardiography. Mean estimated glomerular filtration rate was 28.7 (standard deviation [SD], 12.6) mL/min/1.73 m² and 42.9 (SD, 16.9) mL/min/1.73 m², respectively, and urinary albumin-creatinine ratio was 520 [interquartile range [IQR], 135–1338] mg/gCr and 46 [IQR, 8–424] mg/gCr, respectively. The analysis focused on CVD, death, and kidney failure with a maximum follow-up period of 5 years.

Figure 1 compares echocardiographic findings between Japan and the United States, showing that CRIC participants had larger left atrial diameter and left ventricular mass index and lower left ventricular ejection fraction. This suggests that blood is congested in the left atrium before entering the left ventricle, reflecting the thicker wall of the heart and its inability to expand. In addition, the decreased contractility indicates that the pump function is also impaired. Another characteristic morphological change in CRIC participants is a disproportionate thickening of the septal wall. This is a common finding in patients with hypertrophic cardiomyopathy.

Myocardial hypertrophy correlates with body mass index (BMI), indicating that as body weight increases, the myocardium becomes larger



(Figure 2). C-reactive protein, an indicator of inflammation, also increases with increasing BMI, suggesting that controlling obesity may prevent left ventricular hypertrophy.

Figure 3 shows that there is a large difference in CVD morbidity and mortality between Japan and the United States. The individual patient-level data allowed us to examine the differences in CVD morbidity and mortality after adjusting for background factors. Mediation analysis quantified the extent to which the differences could be explained by (1) myocardial hypertrophy, (2) decreased contractility, or (3) both (Fig. 4). The importance of echocardiographic findings was highlighted, particularly in congestive heart failure, where the combination of reduced contractility and myocardial hypertrophy explained as much as 70% of the difference between Japan and the United States.

Research Summary and Future Perspective

This study has the impact of pushing nephrologists to rethink patient care by emphasizing the importance of controlling obesity and detecting risk signals at an early stage through regular echocardiography in patients with CKD. For Japan, which is on the verge of "heart failure pandemic," this study demonstrates the importance of early assessment of CVD risk. For the United States, where a high percentage of obesity in patients with CKD, taking measures against obesity may reduce heart failure and other CVD. Thus, we believe that this study has made a tremendous contribution to healthcare in both Japan and the United States. In recent years, new treatments for heart failure have emerged one after another and treatment strategies have shifted, and it is important to continue international comparative studies.

Figure 1. Echocardiographic findings

CKD-JAC		TTE findings	CRIC	
	37 (7)	LAD (mm)	39 (6)	
	65.4 (9.4)	EF (%)	54.2 (8.6)	
	46.6 (14.9)	LVMI (g/m ^{2.7})	55.7 (19.3)	
	36%	LVH	59%	
	5%	ASH	30%	

LAD: left atrial dimension
 EF: ejection fraction
 LVMI: left ventricular mass index
 LVH: left ventricular hypertrophy
 ASH: asymmetric septal hypertrophy
 (Data are expressed as mean (standard deviation) for continuous variables and percentage for categorical variables.)

Figure 2. Association between BMI and LVMI

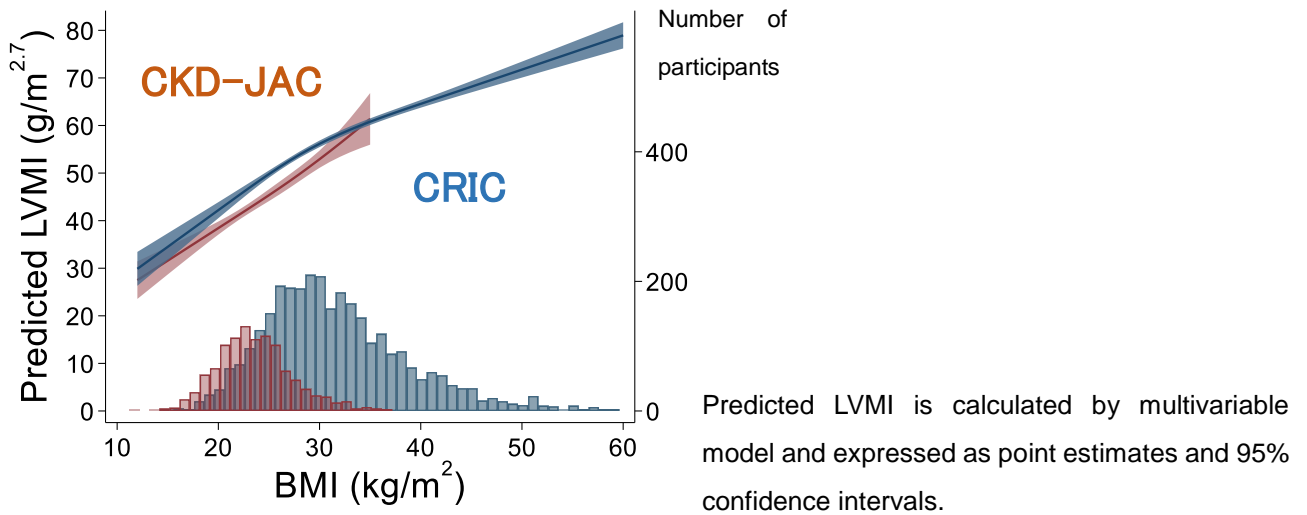


Figure 3. CVD morbidity and mortality between CKD-JAC and CRIC

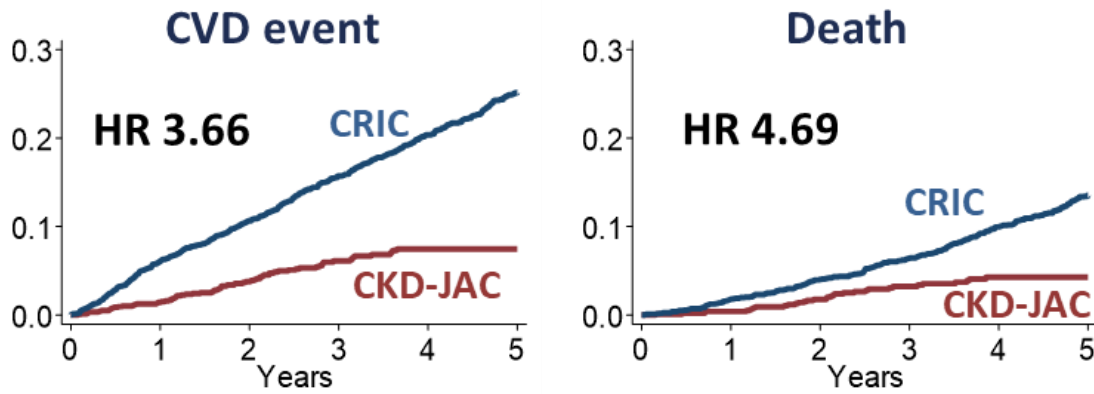
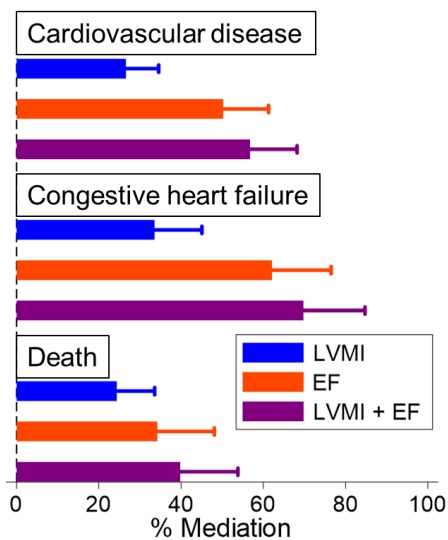


Figure 4. Contribution of cardiac indices to outcome events (Mediation analysis)



Acknowledgments

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Publication

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