Evolution of Echocardiographic Measures of Cardiac Disease From CKD to ESRD and Risk of All-Cause Mortality: Findings From the CRIC Study

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Rationale & Objective: Abnormal cardiac structure and function are common in chronic kidney disease (CKD) and end-stage renal disease (ESRD) and linked with mortality and heart failure. We examined changes in echocardiographic measures during the transition from CKD to ESRD and their associations with post-ESRD mortality.

Study Design: Prospective study.

Setting & Participants: We studied 417 participants with CKD in the Chronic Renal Insufficiency Cohort (CRIC) who had research echocardiograms during CKD and ESRD.

Predictor: We measured change in left ventricular mass index, left ventricular ejection fraction (LVEF), diastolic relaxation (normal, mildly abnormal, and moderately/severely abnormal), left ventricular end-systolic (LVESV), end-diastolic (LVEDV) volume, and left atrial volume from CKD to ESRD.

Outcomes: All-cause mortality after dialysis therapy initiation.

Analytical Approach: Cox proportional hazard models were used to test the association of change in each echocardiographic measure with postdialysis mortality.

Results: Over a mean of 2.9 years between pre- and postdialysis echocardiograms, there was worsening of mean LVEF (52.5% to 48.6%; $P < 0.001$) and LVESV (18.6 to 20.2 mL/m$^{2.7}$; $P < 0.001$). During this time, there was improvement in left ventricular mass index (60.4 to 58.4 g/m$^{2.7}$; $P = 0.005$) and diastolic relaxation (11.11% to 4.94% with moderately/severely abnormal; $P = 0.02$). Changes in left atrial volume (4.09 to 4.15 mL/m^2; $P = 0.08$) or LVEDV (38.6 to 38.4 mL/m$^{2.7}$; $P = 0.8$) were not significant. Worsening from CKD to ESRD of LVEF (adjusted HR for every 1% decline in LVEF, 1.03; 95% CI, 1.00-1.06) and LVESV (adjusted HR for every 1 mL/m$^{2.7}$ increase, 1.04; 95% CI, 1.02-1.07) were independently associated with greater risk for postdialysis mortality.

Limitations: Some missing or technically inadequate echocardiograms.

Conclusions: In a longitudinal study of patients with CKD who subsequently initiated dialysis therapy, LVEF and LVESV worsened and were significantly associated with greater risk for postdialysis mortality. There may be opportunities for intervention during this transition period to improve outcomes.

Complete author and article information (including a list of the CRIC Study Investigators) provided before references.

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Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) have a substantial burden of cardiovascular disease (CVD), which is associated with high levels of morbidity and mortality.[1-3] In patients with CKD and ESRD, abnormalities in left ventricular structure and function are common and often precede the onset of clinical CVD, including heart failure, which is one of the most prevalent cardiovascular subtypes in CKD. The majority of incident maintenance dialysis patients have left ventricular hypertrophy,[4,5] which is an independent predictor of CVD and death.[6,7] In addition, low left ventricular ejection fraction (LVEF), even without clinical heart failure, has been shown to be a risk factor for cardiovascular and all-cause mortality among both patients with CKD and those with ESRD.[8,9]

Few studies have examined the evolution of subclinical CVD as CKD progresses to ESRD. Previously, we studied 190 participants from the Chronic Renal Insufficiency Cohort (CRIC) Study and noted a 3% decline in LVEF, but no statistically significant change in left ventricular mass (LVM) index (LVMI) between stage 4 CKD and ESRD (mean time gap was 2.0 ± 1.0 years).[10] In a subset of 182 Initiating Dialysis Early and Late (IDEAL) trial participants who had serial echocardiograms obtained 12 months apart[11] (the majority of participants had started dialysis therapy by the second echocardiogram), there was no change in LVMI, left atrial volume, diastolic dysfunction, or LVEF.[11] In contrast, substantial improvements in echocardiographic parameters have been reported after kidney transplantation.[12,13] Furthermore, other echocardiographic measures, such as left ventricular end-systolic volume (LVESV), a measure of contractility and ventricular remodeling,[14-16] and left ventricular end-diastolic volume (LVEDV), a measure of preload and diastolic function,[17,18] have not been well described in patients with kidney disease, and larger volumes have been shown to be associated with poor outcomes in the general population. Notably, no prior studies have related change in these measures of subclinical CVD as measured by echocardiography with clinical outcomes in patients with kidney disease.

In the current study, we expanded on our prior analysis[10] by increasing our sample size, examining change in echocardiographic parameters over a longer period, broadening our analyses to include additional echocardiographic parameters (such as left atrial volume, diastolic relaxation, and LVESV), and most importantly, testing the association of changes in echocardiographic parameters with mortality after progression to ESRD. We hypothesized that there is significant worsening in echocardiographic measures during the transition from CKD to ESRD, and that this worsening of subclinical CVD (assessed using echocardiograms) is associated with greater risk for post-ESRD mortality.

Methods

Study Participants

We analyzed data from the CRIC Study, an ongoing multicenter prospective cohort study of persons with CKD recruited from 7 clinical centers (with 13 enrolling sites). Eligibility criteria and baseline characteristics have been previously published.[19,20] The CRIC Study initially enrolled patients with CKD with estimated glomerular filtration rates (eGFRs) of 20 to 70 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) Study equation. Exclusion criteria included New York Heart Association class III or IV heart failure. Institutional review board approval was obtained from all participating institutions and informed consent to participate in CRIC was obtained from all participants.

CRIC participants have annual in-person visits and telephone contact every 6 months. At the annual in-person visits, participants complete questionnaires updating interim medical events and medication use and undergo laboratory testing.

Research echocardiograms were obtained at the following time points: follow-up visits 1 and 4 years after study entry, at the first study visit at which a participant's eGFR was <20 mL/min/1.73 m^2, and at the first follow-up visit after the start of maintenance dialysis therapy or receipt of a kidney transplant (defined as ESRD).[10,21]

For our primary analysis, we included CRIC participants who initiated maintenance hemodialysis (HD) or peritoneal dialysis (PD) therapy and had complete echocardiograms obtained before and after ESRD onset through March 2013 (Fig 1). We analyzed the first technically adequate echocardiogram during the pre-ESRD CKD phase of disease (referred to as the "CKD echocardiogram"), which for most participants was the year 1 echocardiogram. We also analyzed the first technically adequate echocardiogram after initiation of HD or PD therapy. Participants receiving HD (typically 3 times a week among CRIC enrollees) were targeted to have their echocardiograms performed 1 day after a dialysis session (which was achieved in ~80% of participants in our study). A total of 417 participants were included in our sample (Fig 1). In comparing participants who initiated dialysis therapy who were included versus those who were excluded from the analysis, there were few differences in baseline characteristics or year 1 echocardiographic measures (Table S1).

In secondary analyses, for comparison and because there are reports that kidney transplantation is associated with substantial improvements in echocardiographic parameters,[12,13] we examined the subset of 44 CRIC Study participants who received a preemptive kidney transplant (ie, underwent kidney transplantation before needing maintenance dialysis therapy) and had paired echocardiograms (pre- and posttransplantation) obtained as part

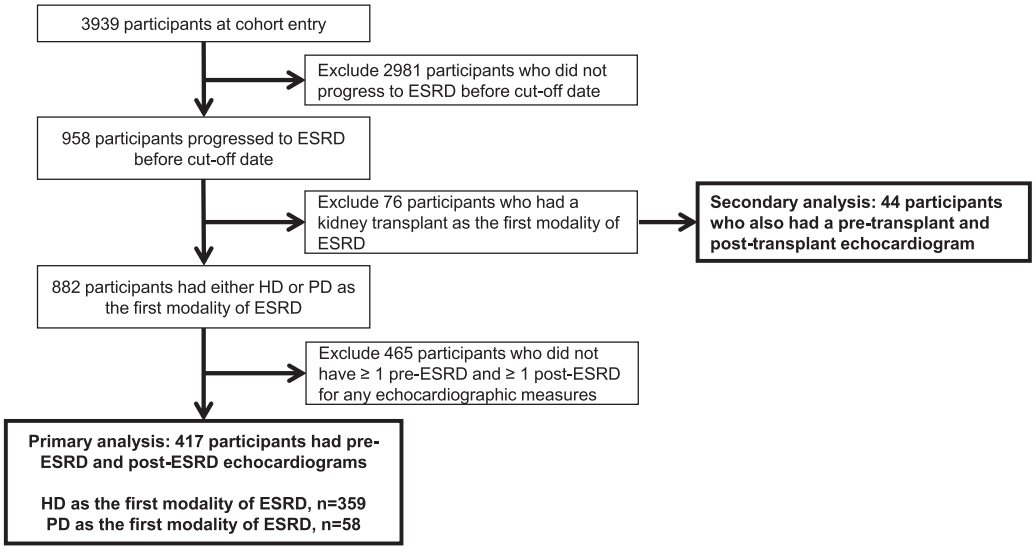

Figure 1. Flow chart of the study population. Abbreviations: ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis.