Associations of Conventional Echocardiographic Measures with Incident Heart Failure and Mortality: The Chronic Renal Insufficiency Cohort

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Abstract

Background and objectives Heart failure is the most frequent cardiac complication of CKD. Left ventricular hypertrophy is common and develops early in CKD, but studies have not adequately evaluated the association of left ventricular mass index with heart failure incidence among men and women with CKD.

Design, setting, participants, & measurements We evaluated echocardiograms of 2567 participants without self–reported heart failure enrolled in the Chronic Renal Insufficiency Cohort Study. Two-dimensional echocardiograms were performed at the year 1 study visit and interpreted at a central core laboratory. Left ventricular mass index was calculated using the linear method, indexed to height$^{2.7}$, and analyzed using sex-specific quartiles. The primary outcomes of incident heart failure and all-cause mortality were adjudicated over a median of 6.6 (interquartile range, 5.7–7.6) years.

Results Among 2567 participants, 45% were women, and 54% were nonwhite race; mean (SD) age was 59±11 years old, and mean eGFR was 44±17 ml/min per 1.73 m^2. During a median follow-up period of 6.6 years, 262 participants developed heart failure, and 470 participants died. Compared with participants in the first quartile of left ventricular mass index, those in the highest quartile had higher rates of incident heart failure (hazard ratio, 3.96; 95% confidence interval, 1.96 to 8.02) and mortality (hazard ratio, 1.86; 95% confidence interval, 1.22 to 2.85), even after adjustment for B–type natriuretic peptide, troponin T, mineral metabolism markers, and other cardiovascular disease risk factors. Those in the lowest quartile of ejection fraction had higher rates of incident heart failure (hazard ratio, 3.01; 95% confidence interval, 1.94 to 4.67) but similar mortality rates (hazard ratio, 1.18; 95% confidence interval, 0.89 to 1.57) compared with those in the highest quartile. Diastolic dysfunction was not significantly associated with heart failure or death.

Conclusions Among persons with CKD and without history of cardiovascular disease, left ventricular mass index is strongly associated with incident heart failure, even after adjustment for major cardiovascular risk factors and biomarkers.

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Introduction

Patients with predialysis CKD are more likely to be hospitalized for a cardiovascular event than proceed to ESRD (1), and heart failure (HF) is the most frequent cardiovascular event associated with CKD (2). A recent meta-analysis showed that eGFR, when added to traditional risk factors, improves risk prediction for HF more than it does for atherosclerotic disease (3).

Despite high rates of HF (4,5) in patients with predialysis CKD, we have a limited understanding of how to use echocardiographic parameters to risk stratify patients with CKD. Although the association of left ventricular mass index (LVMI) (6) and systolic function (7) with cardiovascular outcomes is well documented in the dialysis population, less is known about the importance of these parameters in the predialysis CKD population. The Chronic Renal Insufficiency Cohort (CRIC) provides a unique opportunity to evaluate the relative strengths of the association of conventional echocardiographic measures commonly used in clinical practice with risk for subsequent HF among the CKD population.

We hypothesized that, among the CRIC participants without baseline cardiovascular disease, conventional echo measures of systolic and diastolic function would have at most moderately strong associations with HF and mortality risk, whereas left ventricular (LV) mass would have stronger associations with both outcomes.

Materials and Methods

Study Population

The CRIC was designed to investigate risk factors for progression of CKD, cardiovascular disease, and overall mortality in persons with CKD. Participants were recruited between June of 2003 and March of 2007 at seven centers (Ann Arbor, MI; Baltimore, MD; Chicago, IL; Cleveland, OH; New Orleans, LA; Philadelphia, PA; and Oakland, CA). Investigators recruited 3939 racially and ethnically diverse individuals between the ages of 21–74 years old with eGFR between 20 and 70 ml/min per 1.73 m^2 by simplified Modification of Diet in Renal Disease equation (8). Exclusion criteria were as follows: polycystic kidney disease, use of immunosuppression within the last 6 months, institutionalization, inability to consent, enrollment in other studies, pregnancy, New York Heart Association classes 3–4 HF, HIV, cirrhosis, myeloma, renal cancer, recent chemotherapy, organ transplant, or dialysis treatment within the last month (9). The institutional review board at each study site approved the protocol, and participants gave written informed consent. Of 3939 CRIC participants, 2964 had echocardiograms. For this analysis, we included patients who had an initial echocardiogram as part of the study and did not self-report prior HF (final n=2567). Among these 2567 participants, missingness values of LVMI, diastolic function, and ejection fraction (EF) were n=0, n=340, and n=0, respectively.

Data Collection

Echocardiograms. Echocardiograms were performed at 1 year after enrollment using standard techniques to acquire optimal views of cardiac function. Images were transferred to the core echocardiography laboratory (University of Pennsylvania), where they were read by a Registered Diagnostic Cardiac Sonographer according to the guidelines (10) of the American Society of Echocardiography. Readers were blinded to participants' baseline eGFRs.

LVMI was derived by the area length method and indexed to height$^{2.7}$. LV systolic function was assessed as EF ([end diastolic volume] − [end systolic volume]/[end systolic volume]) ×100%. LV diastolic dysfunction was determined from the ratio of early to late ventricular filling velocities, mitral deceleration time, and the ratio of systolic to diastolic pulmonary vein flow.

Outcomes. Incident HF and overall mortality were adjudicated over a median of 6.6 years of follow-up through March 31, 2013. The CRIC Study personnel screened for hospitalizations by contacting participants and selected hospitals. For each hospitalization, the first 30 discharge codes were screened for cardiovascular events, including HF (International Classification of Diseases, 9th Revision codes 428.0–428.9), myocardial infarction, arrhythmia, or stroke. Potential cardiovascular hospitalizations were each reviewed by two physicians, with close attention to physical examination findings, chest x-ray, consultant notes, serologic markers, and if available, echocardiogram and/or invasive hemodynamic monitoring. The two reviewers were asked to come to a consensus regarding a diagnosis of no HF, probable HF, or definite HF on the basis of modified Framingham criteria (11). Patients were censored at death, loss to follow-up, or ESRD. Date and cause of death were collected from death certificates or obituaries, review of hospital records, and the Social Security Death Master File.

Covariates. Information on demographics and clinical history was obtained by self-report through questionnaires administered at the baseline visit. Diabetes was defined as documented medical history, current or previous use of diabetic medications, or elevated fasting blood glucose. Participants reported whether they currently used tobacco; they graded their own frequency of alcohol use on a zero to eight scale, ranging from zero (never) and one (not in the past 12 months) up to eight (every day or almost every day). BP was averaged over three measurements performed in a standardized fashion in a seated position at rest using a calibrated sphygmomanometer. Samples for cystatin C were processed using a Siemens BNII Nephelometer at the CRIC Central Laboratory, with an intra–assay coefficient of variation of 4.9%. eGFR was calculated from serum cystatin and creatinine using the CRIC Study equation (12), and eGFR was categorized as <30, 30–44, 45–59, and ≥60 ml/min per 1.73 m^2. Urine samples were collected for spot albumin-to-creatinine ratios, and albumin-to-creatinine ratio was categorized as <30, 30–299, 300–999, and ≥1000 mg/g. Biomarker assays for lipids, phosphate, B–type natriuretic peptide (BNP), and troponin T were performed at the CRIC Central Laboratory at the University of Pennsylvania, with the exception of total parathyroid hormone (PTH), which was measured at Scantibodies Laboratory, Inc.

Statistical Analyses

We first explored the distributions of EF, categorical diastolic function, and LVMI among the CRIC participants. The cohort was divided into LVMI quartiles, and characteristics across LVMI quartiles were compared using ANOVA, chi-squared test, or Wilcoxon rank sum test. Because of their skewed distributions, PTH, fibroblast growth factor-23 (FGF23), BNP, and troponin T were log transformed. Crude incident HF and overall death rates were calculated across quartiles of LVMI, EF, and categories of diastolic function. For the analysis of incident HF, censoring occurred at ESRD (n=608), loss to follow-up (n=310), or death (n=251).

Multivariable regression was performed using Cox proportional hazards models for the outcomes of HF and overall death. Model 1 was adjusted for demographic factors (age, sex, and race/ethnicity), clinical site, and traditional cardiovascular risk factors, including diabetes, current smoking, alcohol use, log(24-hour urine total protein excretion), eGFR, systolic and diastolic BP, body mass index, and lipoprotein concentrations. Model 1 also included phosphate, hemoglobin, and use of medications, including aldosterone antagonists, angiotensin–converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and β-blockers. Model 2 included the previously listed covariates as well as PTH, FGF23, use of aspirin, and statins. Model 3 added BNP and troponin T to model 2. We *a priori* explored effect modification of the following baseline characteristics: age <60 years old, sex, race, diabetes, eGFR<45, and hemoglobin <12.

Results

Among 2567 participants, 45% were women, and 54% were nonwhite race; mean (SD) age was 59±11 years old, and mean (SD) eGFR was 44±17 ml/min per 1.73 m^2 at baseline. Median LVMI was 49 $g/m^{2.7}$. Over a median follow-up of 6.6 (interquartile range, 5.7–7.6) years, 262 participants developed incident HF, and 470 participants died. Higher LVMI was associated with older age, black race, Hispanic ethnicity, diabetes, hypertension, higher systolic BP, and higher body mass index. Higher LVMI was also associated with lower eGFR, LDL, and HDL as well as higher proteinuria, calcium, phosphorus, PTH, FGF23, BNP, and troponin T (Table 1).

Among all participants, LVMI in the third (48.5 to <57.5 $g/m^{2.7}$) or fourth quartile (≥57.5 $g/m^{2.7}$) was associated with HF independent of comorbidities, eGFR, FGF23, BNP, and troponin T. These associations were consistent for both men and women using sex-specific quartiles (Table 2). There were no significant interactions by age, sex, race, eGFR, or hemoglobin for the association of LVMI (as linear variable) with HF incidence. However, the association seemed significantly stronger in nonpatients with diabetes (2.15; 95% confidence interval [95% CI], 1.64 to 2.82) than patients with diabetes (1.33; 95% CI, 1.10 to 1.61; P=0.01). Similarly, participants in the third and fourth quartiles of LVMI had higher rates of overall mortality after full adjustment (Table 3); modeled as a linear variable, this risk again seemed stronger in nonpatients with diabetes (1.57; 95% CI, 1.31 to 1.88) than patients with diabetes (1.23; 95% CI, 1.04 to 1.45; P<0.01). An interaction of age and LVMI was also present for this association with mortality, with a stronger association apparent in those younger than 60 years of age (1.55; 95% CI, 1.25 to 1.91) than older participants ≥60 years of age (hazard ratio [HR], 1.27; 95% CI, 1.09 to 1.48; P=0.04). There were no significant interactions of race, eGFR, or hemoglobin in the association of LVMI with mortality. We performed an alternative analysis of LVMI divided into sex–specific clinical cut points according to American Society of Echocardiography guidelines (10) and found that men with mildly abnormal LVMI (49–56 $g/m^{2.7}$) were at higher risk of HF (HR, 2.05; 95% CI, 1.10 to 3.8) as were men at higher cut points: 56–64 $g/m^{2.7}$ (HR, 2.07; 95% CI, 1.05 to 4.07) and ≥64 $g/m^{2.7}$ (HR, 2.68; 95% CI, 1.37 to 5.28). Men with mildly abnormal LVMI were at slightly higher risk of death (HR, 1.55; 95% CI, 1.05 to 2.27), but this association was not significant at higher cut points. Among women, only those above the highest cut point (59 $g/m^{2.7}$) were at significantly higher risk for these outcomes (HR for HF, 4.77; 95% CI, 2.15 to 10.57; HR for death, 2.47; 95% CI, 1.37 to 4.45).

When EF was modeled in categories by clinical cut points, using EF=50%–65% as the referent, each of the two lower EF categories (EF=25%–50% and EF<35%) showed higher risk of HF than the referent category. However, only the lowest category, EF<35%, had a significant association with mortality (Table 4). When EF was modeled in quartiles, using EF≥59.2% as the referent category, quartiles 2–4 (the patients with lower EF) had higher risk of HF compared with the referent. EF quartiles 2–4 did not have significantly higher HRs for mortality (Supplemental Table 1).

To account for the potential of informative censoring of participants due to ESRD or death, we performed a Fine–Gray analysis for the associations of LVMI and EF with incident HF. The associations were somewhat attenuated using this approach but qualitatively similar to the Cox analyses: participants in LVMI quartiles 3 and 4 remained at significantly higher risk of HF compared with those in quartile 1. Fully adjusted HRs for LVMI quartiles compared with referent quartile 1 were as follows: quartile 2 HR, 1.16; 95% CI, 0.78 to 1.73; quartile 3 HR, 1.73; 95% CI, 1.18 to 2.53; and quartile 4 HR, 2.07; 95% CI, 1.38 to 3.11. Fine–Gray analyses for EF categories showed that only participants in the lowest category of EF had significantly higher risk of HF; HRs for EF cut points compared with referent group EF=50%–65% were as follows: EF>65% HR, 0.71; 95% CI, 0.44 to 1.16; EF=35%–50% HR, 1.04; 95% CI, 0.79 to 1.37; and EF<35% HR, 2.42; 95% CI, 1.49 to 3.95. We also performed a sensitivity analysis using the Chronic Kidney Disease Epidemiology Collaboration equation for eGFR, and it did not change the results.

As previously reported, the vast majority of the CRIC participants had either normal diastolic function (n=771; 30%) or mildly abnormal diastolic function (n=1663; 60%). In unadjusted analyses, mildly abnormal diastolic function was associated with higher risk of HF (HR, 1.41; 95% CI, 1.04 to 1.90) and death (HR, 1.46; 95% CI, 1.17 to 1.84) compared with normal diastolic function. However, these associations lost statistical significance after adjustment. Moderately and severely abnormal diastolic dysfunctions were not significantly associated with HF, regardless of model selection, and severely abnormal diastolic dysfunction was only marginally associated with death after full adjustment (Supplemental Table 2).

Discussion

In this study of individuals with CKD and without baseline HF, we evaluated associations of LV mass and systolic and diastolic function with longitudinal risk for HF and mortality. LVMI was a strong, independent risk factor for incident HF and death; these associations were independent of known cardiac risk factors in CKD, including eGFR, troponin T, BNP, and FGF23. EF was a strong risk factor for incident HF, but only the lowest EF (<35%) was associated with mortality. Categories of diastolic function did not predict HF or death.

Left ventricular hypertrophy (LVH) has been recognized as a key feature of uremic cardiomyopathy for over a century (13). The median LVMI in the CRIC is virtually equivalent to the definition of hypertrophy by current guidelines (10), showing the high prevalence of LVH in patients with CKD. LVH in this setting has traditionally been understood as a physiologic adaptation to reduce ventricular wall stress in response to increased workload (13) that results from anemia and hypertension (13,14). However, we now know there are several additional factors that lead to LV remodeling and LVH. Wolf and colleagues (14,15) have identified the phosphaturic hormone FGF23 as a kidney-specific mediator of LVH (14) that is associated with HF in CKD (15). Fibrosis, mediated by inflammation and possibly resulting from "organ crosstalk" in cardiorenal syndrome, has also been increasingly recognized as a key factor involved in LV remodeling in CKD (16).

Table 1. Characteristics of the Chronic Renal Insufficiency Cohort Study participants without heart failure by quartile of left ventricular mass index

Characteristic	LVMI Quartiles (N, g/m$^{2.7}$)					
	641 (<41.3)	643 (41.3 to <48.5)	642 (48.5 to <57.5)	641 (≥57.5)	*P* Value	Linear Trend *P* Value
Age, yr	58.0 [46.0, 64.0]	60.0 [52.0, 66.0]	61.0 [54.0, 67.0]	62.0 [56.0, 67.0]	<0.001	<0.001
Sex						
Men	327 (51.0%)	345 (53.7%)	365 (57%)	341 (53.2)	0.21	0.31
Women	314 (49%)	298 (46.4%)	277 (43.2%)	300 (46.8%)		
Race						
Non-Hispanic white	393 (61.3%)	305 (47.4%)	255 (39.7%)	164 (25.6%)	<0.001	<0.001
Non-Hispanic black	188 (29.3%)	238 (37.%)	267 (41.6%)	314 (49%)		
Hispanic	35 (5.5%)	70 (10.9%)	95 (14.8%)	140 (21.8%)		
Other	25 (3.9%)	30 (4.7%)	25 (3.9%)	23 (3.6%)		
Diabetes	186 (29%)	262 (40.8%)	327 (50.9%)	410 (64%)	<0.001	<0.001
History of hypertension	480 (74.9%)	548 (85.2%)	591 (92.1%)	624 (97.4%)	<0.001	<0.001
History of cardiovascular disease[a]	101 (15.8%)	137 (21.3%)	190 (29.6%)	254 (39.6%)	<0.001	<0.001
Tobacco use	74 (11.5%)	69 (10.7%)	76 (11.8%)	81 (12.6%)	0.76	0.27
Alcohol use	457 (71.3%)	396 (61.6%)	383 (59.7%)	310 (48.4%)	<0.001	<0.001
Systolic BP, mmHg	117.2 (16.4)	124.3 (19.1)	128.8 (20.5)	137.5 (24.6)	<0.001	<0.001
Diastolic BP, mmHg	69.8 (10.9)	70.2 (11.8)	70.7 (12.9)	71.8 (14.1)	0.03	<0.001
Body mass index, kg/m^2	27.3 (5.1)	30.1 (6.1)	32.6 (6.4)	35.6 (7.9)	<0.001	<0.001
Angiotensin–converting enzyme inhibitor or ARB	414 (64.6%)	431 (67%)	460 (71.7%)	455 (71.2%)	0.02	0.01
Diuretics	253 (39.5%)	317 (49.3%)	387 (60.3%)	458 (71.7%)	<0.001	<0.001
β-Blockers	196 (30.6%)	266 (41.4%)	314 (48.9%)	398 (62.3%)	<0.001	<0.001
Aldosterone antagonists	16 (2.50%)	12 (1.9%)	23 (3.6%)	23 (3.6%)	0.17	0.08
Aspirin	220 (34%)	267 (42%)	297 (46%)	315 (49%)	<0.001	<0.001
Statin	322 (50%)	355 (55%)	374 (58%)	422 (66%)	<0.001	0.08
Ejection fraction, %	55.9 (6.1)	55.8 (6.8)	55.3 (7.0)	53.6 (9.0)	<0.001	<0.001
Ln(24-h proteinuria)	0.1 [0.1, 0.3]	0.1 [0.1, 0.4]	0.1 [0.1, 0.6]	0.4 [0.1, 1.1]	<0.001	<0.001
eGFR, ml/min per 1.73 m^2	49.9 (16.9)	46.6 (17.1)	41.8 (16.5)	37.3 (14.5)	<0.001	<0.001
LDL, mg/dl	103.9 (34.3)	104.0 (35.4)	101.0 (34.3)	97.2 (35.1)	0.001	<0.001
HDL, mg/dl	53.2 (17.9)	50.0 (15.1)	47.3 (15.6)	45.1 (13.0)	<0.001	<0.001
Calcium, mg/dl	9.4 (0.5)	9.4 (0.5)	9.3 (0.5)	9.2 (0.6)	<0.001	<0.001
Phosphate, mg/dl	3.6 (0.6)	3.7 (0.6)	3.7 (0.6)	3.9 (0.7)	<0.001	<0.001
Hemoglobin, mg/dl	13.5 (1.6)	13.0 (1.7)	12.8 (1.7)	12.1 (1.8)	<0.001	<0.001
PTH, pg/ml	48.0 [33.7, 70.3]	54.1 [36.0, 85.0]	58.0 [39.5, 97.0]	74.7 [47.9, 120.0]	<0.001	<0.001
FGF23, RU/ml	107.0 [75.6, 164.6]	124.0 [84.7, 194.3]	134.5 [92.7, 208.3]	167.7 [109.9, 280.0]	<0.001	<0.001
BNP, pg/ml	23.6 [7.6, 51.5]	30.5 [12.8, 65.3]	38.1 [16.4, 85.9]	59.5 [22.4, 125.2]	<0.001	<0.001
Troponin T, pg/ml	6.3 [1.5, 11.5]	8.6 [4.4, 16.1]	12.2 [6.1, 21.1]	17.5 [9.7, 32.6]	<0.001	<0.001

Entries in first four columns are number (percent) or mean [range]. *P* value by chi-squared test for categorical variables or ANOVA for continuous variables. LVMI, left ventricular mass index; ARB, angiotensin receptor blocker; PTH, parathyroid hormone; FGF23, fibroblast growth factor-23; BNP, B–type natriuretic peptide.

[a]Coronary artery disease, peripheral vascular disease, or stroke.

Table 2. Associations of left ventricular mass index quartiles with incident heart failure in the Chronic Renal Insufficiency Cohort participants without heart failure

LVMI Q (g/m$^{2.7}$)	*N* (Events)	*N* (Participants)	Rate (Events/1000 person-yr)	HR (95% CI)		
				Model 1	Model 2	Model 3
All						
Q1 (<41.3)	11	641	2.8	Reference	Reference	Reference
Q2 (41.3 to <48.5)	29	643	8.0	1.82 (0.9 to 3.7)	1.73 (0.85 to 3.52)	1.55 (0.76 to 3.17)
Q3 (48.5 to <57.5)	55	642	16.7	3.19 (1.62 to 6.3)	3.05 (1.54 to 6.04)	2.71 (1.36 to 5.4)
Q4 (≥57.5)	119	641	43.2	5.23 (2.63 to 10.41)	4.89 (2.45 to 9.75)	3.96 (1.96 to 8.02)
Linear trend *P* value				<0.001	<0.001	<0.001
Men						
Q1 (<41.7)	5	345	2.4	Reference	Reference	Reference
Q2 (41.7 to <48.8)	17	344	9.1	2.25 (0.81 to 6.23)	2.21 (0.8 to 6.14)	1.89 (0.67 to 5.32)
Q3 (48.8 to <57.4)	33	345	19.2	3.77 (1.42 to 10.01)	3.57 (1.34 to 9.49)	3.06 (1.14 to 8.23)
Q4 (≥57.4)	59	344	42.2	4.61 (1.7 to 12.5)	4.38 (1.61 to 11.89)	3.52 (1.28 to 9.71)
Linear trend *P* value				<0.01	<0.01	0.05
Women						
Q1 (<40.8)	6	297	3.3	Reference	Reference	Reference
Q2 (40.8 to <47.9)	12	297	6.9	1.43 (0.52 to 3.9)	1.23 (0.45 to 3.39)	1.2 (0.43 to 3.35)
Q3 (47.9 to <57.7)	23	298	14.6	2.91 (1.11 to 7.65)	2.8 (1.06 to 7.41)	2.64 (0.97 to 7.19)
Q4 (≥57.7)	59	297	43.7	6.41 (2.41 to 17.04)	5.27 (1.97 to 14.12)	4.96 (1.78 to 13.81)
Linear trend *P* value				<0.001	<0.001	<0.001

Model 1: age, race, study site, diabetes, cardiovascular disease, tobacco, alcohol use, log(24-hour proteinuria), eGFR (Chronic Renal Insufficiency Cohort equation), systolic BP, diastolic BP, body mass index, LDL, HDL, aldosterone antagonists, angiotensin–converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers, phosphate, and hemoglobin. Model 2: model 1 plus log(parathyroid hormone), log(fibroblast growth factor-23), aspirin, and statin. Model 3: model 2 plus log(B–type natriuretic peptide) and log(high–sensitivity troponin T). LVMI, left ventricular mass index; Q, quartile; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 3. Associations of left ventricular mass index quartiles with death in the Chronic Renal Insufficiency Cohort participants without heart failure

LVMI Q ($g/m^{2.7}$)	*N* (Events)	*N* (Participants)	Rate	HR (95% CI)		
				Model 1	Model 2	Model 3
All						
Q1 (<41.3)	46	641	10.8	Reference	Reference	Reference
Q2 (41.3 to <48.5)	67	643	16.0	1.21 (0.82 to 1.79)	1.19 (0.8 to 1.76)	1.19 (0.79 to 1.78)
Q3 (48.5 to <57.5)	110	642	27.4	1.86 (1.27 to 2.71)	1.8 (1.23 to 2.64)	1.7 (1.14 to 2.52)
Q4 (≥57.5)	159	641	41.8	2.22 (1.49 to 3.32)	2.14 (1.43 to 3.21)	1.86 (1.22 to 2.85)
Linear trend *P* value				<0.001	<0.001	0.003
Men						
Q1 (<41.7)	26	345	11.4	Reference	Reference	Reference
Q2 (41.7 to <48.8)	41	344	18.6	1.31 (0.78 to 2.18)	1.27 (0.76 to 2.12)	1.25 (0.74 to 2.11)
Q3 (48.8 to <57.4)	70	345	32.7	1.88 (1.15 to 3.08)	1.83 (1.11 to 2.99)	1.69 (1.02 to 2.8)
Q4 (≥57.4)	88	344	43.8	2.06 (1.21 to 3.5)	1.98 (1.17 to 3.36)	1.7 (0.98 to 2.95)
Linear trend *P* value				0.003	<0.01	0.07
Women						
Q1 (<40.8)	18	297	9.1	Reference	Reference	Reference
Q2 (40.8 to <47.9)	25	297	12.6	1.19 (0.63 to 2.24)	1.2 (0.62 to 2.3)	1.27 (0.64 to 2.51)
Q3 (47.9 to <57.7)	43	298	22.9	2.23 (1.21 to 4.13)	2.14 (1.13 to 4.06)	2.21 (1.12 to 4.36)
Q4 (≥57.7)	71	297	39.5	3.33 (1.74 to 6.36)	3.2 (1.63 to 6.29)	3.08 (1.5 to 6.32)
Linear trend *P* value				<0.001	0.001	<0.01

Model 1: age, race, study site, diabetes, cardiovascular disease, tobacco, alcohol use, log(24-hour proteinuria), eGFR (Chronic Renal Insufficiency Cohort equation), systolic BP, diastolic BP, body mass index, LDL, HDL, aldosterone antagonists, angiotensin–converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers, phosphate, and hemoglobin. Model 2: model 1 plus log(parathyroid hormone), log(fibroblast growth factor-23), aspirin, and statin. Model 3: model 2 plus log(B–type natriuretic peptide) and log(high–sensitivity troponin T). LVMI, left ventricular mass index; Q, quartile; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 4. Associations of ejection fraction clinical cut points with incident heart failure and death in the Chronic Renal Insufficiency Cohort participants without baseline heart failure

Ejection Fraction, %	*N* (Events)	*N* (Participants)	Rate	HR (95% CI)		
				Model 1	Model 2	Model 3
Heart failure						
>65	6	193	5.4	0.39 (0.17 to 0.89)	0.41 (0.18 to 0.94)	0.38 (0.16 to 0.94)
50–65	177	2205	15.1	Reference	Reference	Reference
35–50	52	433	24.3	1.52 (1.09 to 2.13)	1.59 (1.14 to 2.24)	1.57 (1.12 to 2.21)
<35	13	48	66.5	5.02 (2.76 to 9.14)	5.2 (2.78 to 9.72)	3.67 (1.93 to 6.99)
Linear trend *P* value				<0.001	<0.001	<0.001
Death						
>65	18	193	14.4	0.7 (0.43 to 1.13)	0.72 (0.45 to 1.17)	0.63 (0.37 to 1.07)
50–65	336	2205	24.0	Reference	Reference	Reference
35–50	73	433	26.9	1.02 (0.77 to 1.34)	1.03 (0.78 to 1.36)	0.94 (0.71 to 1.24)
<35	20	48	76.8	2.38 (1.48 to 3.84)	2.49 (1.53 to 4.07)	0.94 (0.71 to 1.24)
Linear trend *P* value				0.004	<0.01	0.04

Model 1: age, race, study site, diabetes, cardiovascular disease, tobacco, alcohol use, log(24-hour proteinuria), eGFR (Chronic Renal Insufficiency Cohort equation), systolic BP, diastolic BP, body mass index, LDL, HDL, aldosterone antagonists, angiotensin–converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers, phosphate, and hemoglobin. Model 2: model 1 plus log(parathyroid hormone), log(fibroblast growth factor-23), aspirin, and statin. Model 3: model 2 plus log(B-type natriuretic peptide) and log(high–sensitivity troponin T). HR, hazard ratio; 95% CI, 95% confidence interval.

LVH is a known risk factor for arrhythmic and nonarrhythmic cardiovascular events in the general population. In the Framingham cohort, LVH was associated with sudden cardiac death, which was thought to result primarily from arrhythmia (17). In a pooled analysis of the Atherosclerotic Risk in Communities Study, the Cardiovascular Health Study, and the Framingham cohort, LVH was associated with cardiovascular and composite outcomes, including mortality (18). In the dialysis population, baseline LVH (19,20) and increase in LV mass (6) were associated with cardiovascular events and mortality. There have been relatively few prior studies of LVH in predialysis CKD (21), and none of those studies have specifically addressed incident HF in patients without HF at baseline. In the African American Study of Kidney Disease and Hypertension (AASK) cohort, LVH and diastolic dysfunction were found to predict outcomes, including HF hospitalization. This cohort differed from our cohort and investigation in several aspects. The CRIC was designed to be an ethnically diverse cohort. Additionally, in the AASK, diabetes was an exclusion criteria (22), and 50% of participants in the AASK had a history of prior cardiovascular disease (23). In contrast, these analyses include patients with diabetes but exclude those who self-reported HF.

Our results indicate that, in patients with CKD who have not experienced HF, higher LVMI is associated with incident HF and overall mortality in a graded fashion. We adjusted for several known direct or indirect mediators of HF, including anemia, BP, FGF23, and eGFR. Thus, our results suggest that, in addition to these factors, there are additional unknown factors inherent to or related to LVH that cause HF in these patients. LVH is likely a multifactorial process including known or unknown inflammatory and fibrotic mediators that were not measured in this investigation. We also adjusted for two markers of end organ damage, BNP and troponin T, and found that LVMI predicted HF independently of these powerfully prognostic biomarkers in CKD (24).

The associations of LVMI with both HF and mortality seemed stronger in persons without diabetes compared with LVMI associations in persons with diabetes. There are several potential explanations. Nonpatients with diabetes in the CRIC are more likely to have purely hypertensive renal disease and may have developed hypertrophy over a longer period of time; thus, they may have more severe histologic remodeling that predisposes to HF or sudden cardiac death. The patients with diabetes might have been more likely to have occult large artery or microvascular coronary artery disease, and it is possible that LVH is less important than burden of atherosclerotic disease as a determinant of adverse outcomes in these patients.

Although we did not find associations between categorical LV diastolic function and HF or mortality, the parameters used to determine diastolic function in the CRIC were limited to pulse wave Doppler at the mitral valve and did not include tissue Doppler imaging (*i.e.*, e′ or a′). The E-to-e′ ratio is now a standard component of diastolic assessment (25) and particularly useful in differentiating normal from pseudonormal diastolic function. Additionally, recent studies have illustrated the prognostic utility of using speckle tracking echocardiography to quantify systolic function in patients with predialysis CKD (26) and ESRD

(27,28). Thus, the less striking associations observed for EF could be interpreted as a limitation of the conventional evaluation of systolic function in patients with normal EF.

Strengths and Limitations

Our study has numerous strengths, including the adjudication of HF by physician review. The CRIC is a highly diverse, well characterized CKD cohort recruited from multiple centers across the United States. We adjusted for a broad range of known cardiovascular risk factors, including BNP and troponin T. We also faced certain limitations. Some participants did not have available echocardiograms, and this theoretically could have introduced selection bias. Evaluation of diastolic dysfunction did not include tissue Doppler imaging, which may have contributed to the weak findings related to categorical diastolic function. Medical record review was limited to hospitalizations that were suspected of HF on the basis of discharge codes, an approach that prioritizes specificity of diagnosis rather than sensitivity. Therefore, some HF hospitalizations may have been missed. Additionally, HF adjudications in the CRIC before 2003 did not distinguish between HF with preserved EF and HF with reduced EF, which could have reduced our ability to detect associations between diastolic function and HF.

Implications for Future Research

Despite these limitations, we present a strong, independent association of LVMI with HF and mortality that is independent of known cardiovascular risk factors. These results suggest that efforts to prevent the development of LVH in patients with CKD without known HF might help reduce the incidence of HF. Although regression of LVH in non-CKD populations is known to improve outcomes (29,30), it is not yet known whether regression of LV mass should be a treatment target in CKD. Treating anemia does improve LVH in CKD (31), but the Trial to Reduce Cardiovascular Events with Aranesp Therapy Trial (32) and the Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial (33) have shown that using erythropoietin-stimulating agents to raise hemoglobin over 11–12 mg/dl may have deleterious effects. However, recent studies in the CRIC and other cohorts show that LVH is a multifactorial process. As new determinants of LVH are discovered, developing strategies to target these novel pathways may be useful in causing regression of LVH and/or preventing HF in CKD.

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Disclosures

None.

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