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ORIGINAL RESEARCH

# Risk Factors for Heart Failure in Patients With Chronic Kidney Disease: The CRIC (Chronic Renal Insufficiency Cohort) Study

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***Background***—Heart failure is common in patients with chronic kidney disease. We studied risk factors for incident heart failure among 3557 participants in the CRIC (Chronic Renal Insufficiency Cohort) Study.

***Methods and Results***—Kidney function was assessed by estimated glomerular filtration rate (eGFR) using serum creatinine, cystatin C, or both, and 24-hour urine albumin excretion. During an average of 6.3 years of follow-up, 452 participants developed incident heart failure. After adjustment for age, sex, race, and clinical site, hazard ratio (95% CI) for heart failure associated with 1 SD lower creatinine-based eGFR was 1.67 (1.49, 1.89), 1 SD lower cystatin C-based-eGFR was 2.43 (2.10, 2.80), and 1 SD higher log-albuminuria was 1.65 (1.53, 1.78), all $P<0.001$. When all 3 kidney function measures were simultaneously included in the model, lower cystatin C-based eGFR and higher log-albuminuria remained significantly and directly associated with incidence of heart failure. After adjusting for eGFR, albuminuria, and other traditional cardiovascular risk factors, anemia (1.37, 95% CI 1.09, 1.72, $P=0.006$), insulin resistance (1.16, 95% CI 1.04, 1.28, $P=0.006$), hemoglobin A1c (1.27, 95% CI 1.14, 1.41, $P<0.001$), interleukin-6 (1.15, 95% CI 1.05, 1.25, $P=0.002$), and tumor necrosis factor-α (1.10, 95% CI 1.00, 1.21, $P=0.05$) were all significantly and directly associated with incidence of heart failure.

***Conclusions***—Our study indicates that cystatin C-based eGFR and albuminuria are better predictors for risk of heart failure compared to creatinine-based eGFR. Furthermore, anemia, insulin resistance, inflammation, and poor glycemic control are independent risk factors for the development of heart failure among patients with chronic kidney disease. **(*J Am Heart Assoc*. 2017;6:e005336. DOI: 10.1161/JAHA.116.005336.)**

**Key Words:** albuminuria • chronic kidney disease • glomerular filtration rate • heart failure • risk factor



Cardiovascular disease (CVD) is the major cause of premature death in patients with chronic kidney disease (CKD).[1] Several prospective cohort studies have documented an increased risk of CVD, including heart failure, in patients with CKD.[2–4] For example, Dhingra and colleagues reported that individuals with creatinine-based estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 $m^2$ had a 2-fold increased risk of heart failure compared with those with eGFR ≥60 in a cohort of 10 181 participants followed up for 10 years.[3] Reduced creatinine-based eGFR and increased proteinuria measured by dipstick were significantly associated with increased risk of heart failure in a population-based

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longitudinal study with 1 526 437 patients identified from province-wide laboratory data from Alberta, Canada.[4] However, the association of severity of CKD measured by creatinine-based eGFR, cystatin C-based eGFR, and 24-hour urine albumin with heart failure has not been well examined among patients with CKD. In addition, the contribution of novel CVD risk factors to the excess risk of heart failure among patients with CKD has not been well investigated.

We aimed to compare the strengths of associations among creatinine-based eGFR, cystatin C-based eGFR, and 24-hour urine albumin and incident heart failure. In addition, we investigated the association of traditional and novel CVD risk factors with heart failure in patients with CKD.

## Methods

### Study Participants

The CRIC (Chronic Renal Insufficiency Cohort) Study is an ongoing multicenter cohort study among 3939 participants who were enrolled between June 2003 and August 2008 from 7 clinical centers in the United States. The design of the study and baseline characteristics of participants have been previously published.[5] Briefly, men and women were eligible for the study if they were between 21 and 74 years of age with an eGFR between 20 and 70 mL/min per 1.73 $m^2$ depending upon age (age 21–44, eGFR 20–70; age 45–64, eGFR 20–60; and age 65–74, eGFR 20–50). Patients who previously received dialysis for ≥1 month or a kidney transplant, and those with glomerulonephritis requiring immunosuppression, cirrhosis, polycystic kidney disease, or severe heart failure, defined as New York Heart Association class III or IV, were excluded. For this analysis, we excluded 382 patients with a self-reported history of physician-diagnosed heart failure. Therefore, a total of 3557 participants were included in this analysis.

The investigation conforms with the principles outlined in the Declaration of Helsinki. Institutional review boards at all participating institutions approved the study protocol, and all participants provided written informed consent.

### Baseline Measurements

A baseline medical history questionnaire was administered to obtain information on demographic characteristics, lifestyle risk factors, previous history of CVD, and use of medications. Body weight, height, and waist circumference were measured according to standard methods. Three seated blood pressure (BP) measurements were obtained by trained and certified staff after at least 5 minutes of quiet rest. Hypertension was defined as mean BP ≥140/90 mm Hg or self-reported use of antihypertensive medication.

Serum creatinine was measured using an enzymatic method on an Ortho Vitros 950 and standardized to isotope-dilution mass spectrometry traceable values. Cystatin C, homocysteine, high-sensitive C-reactive protein, interleukin-6, and tumor necrosis factor (TNF)-α were measured by the particle-enhanced immunonephelometry method. Fibrinogen was measured using the immunochemical reaction method. eGFR was calculated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation, cystatin C equation, and creatinine-cystatin C equation.[6] A homeostasis model assessment (HOMA) was calculated to evaluate insulin resistance using fasting serum insulin and plasma glucose.[7] Diabetes mellitus was defined as a fasting plasma glucose ≥126 mg/dL, a nonfasting plasma glucose ≥200 mg/dL, or self-reported use of anti-diabetes mellitus medication. A 24-hour urine specimen was collected in all participants and urinary albumin was measured by radioimmunoassay. All laboratory measurements were conducted at the CRIC Study central laboratory at the University of Pennsylvania with stringent quality control.

### Assessment of Outcomes

CRIC Study participants were followed annually by clinic visits with interim telephone contact at 6 months. The primary study outcome was incident heart failure over the time from study entry to March 2012. Heart failure was identified by asking study participants every 6 months if they were hospitalized, and selected hospitals or healthcare systems were queried for qualifying encounters. The first 30 discharge codes were identified for all hospitalizations, and codes relevant to heart failure resulted in retrieval of medical records by study personnel for centralized adjudicated review. At least 2 study physicians reviewed all possible heart failure events using medical records and guidelines on clinical symptoms, radiographic evidence of pulmonary congestion, physical examination of the heart and lungs and, when available, central venous hemodynamic monitoring data, and echocardiographic imaging. Heart failure was confirmed when both reviewers agreed on a probable or definite occurrence of heart failure based on modified clinical Framingham criteria.[8] Patients' follow-up was censored at the time of heart failure, death, withdrawal, loss to follow-up, or the end of the follow-up period, whichever occurred first.

### Statistical Analysis

To compare the relative strengths in predicting incident heart failure, hazard ratios associated with 1 SD of creatinine-based eGFR, cystatin-C-based eGFR, or log-transformed albuminuria were assessed using Cox proportional hazards models after adjustment for age, sex, race, and clinical site.[9] In addition,

these CKD markers were included in the multivariable Cox proportional hazards models simultaneously. Age, sex, and race were only moderately correlated with eGFR ($r \leq 0.2$) in the CRIC participants. The assumption of proportionality was tested using Schoenfeld residuals and interaction terms with time for each exposure variable and covariate. No substantial deviations from proportionality were observed.

The associations of baseline traditional and novel risk factors with subsequent heart failure incidence were examined using multivariable Cox proportional hazards models. Initial models were adjusted for age, sex, race, and clinical site. For the multivariable analysis of traditional risk factors, the backward elimination method was used, and only covariates that were significant ($P<0.05$) were retained in the final model. For the multivariable analysis of novel risk factors, all variables retained in the final traditional risk factor model were included as covariates. The log-transformation was performed for risk factors that were not normally distributed. Hazard ratios and 95% CI of heart failure associated with categorical variables or 1 SD increase in continuous variables were presented. All analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, NC). All *P*-values were 2-sided, and statistical significance was defined as $P<0.05$.

## Results

Baseline characteristics of study participants by quartile of creatinine and cystatin C-based eGFR are presented in Table 1. Participants with lower creatinine and cystatin C-based eGFR were more likely to be older, female, and black or Hispanic; to have less than high school education and lower physical activity and alcohol consumption, but higher current smoking; to have higher prevalence of CVD, hypertension, diabetes mellitus, and anemia; to have higher levels of body mass index, waist circumference, systolic BP, HOMA-insulin resistance, hemoglobin A1c (HbA1c), homocysteine, fibrinogen, high-sensitive C-reactive protein, interleukin-6, TNF-α, and leukocyte count, and lower levels of high-density lipoprotein- and low-density lipoprotein-cholesterol, and hemoglobin.

Over 6.3 years of follow-up, the overall incidence of heart failure was 21.7 per 1000 person-years. In general, the incidence of heart failure was higher among individuals with lower creatinine-based eGFR and cystatin C-based eGFR (Figure A). However, this association was more consistent with cystatin C-based eGFR, especially among those with a creatinine-based eGFR less than 60 mL/min per 1.73 $m^2$. Likewise, the incidence of heart failure was higher among individuals with lower creatinine-based eGFR and higher albuminuria (Figure B). This association was more consistent with albuminuria.

The descriptive statistics of creatinine-based eGFR, cystatin C-based eGFR, and urine albumin, as well as their correlation coefficients, are shown in Table 2. As anticipated, creatinine-based eGFR and cystatin C-based eGFR are highly correlated. All 3 measures of CKD were associated with incident heart failure after adjusting for age, sex, race, and clinical site (Table 3). In the multivariable model including both creatinine-based eGFR and cystatin C-based eGFR simultaneously, the association between lower cystatin C-based eGFR and heart failure became stronger, while the association between lower creatinine-based eGFR and heart failure became inverse. In multivariable models including both creatinine-based eGFR and albuminuria, or cystatin C-based eGFR and albuminuria, the associations of creatinine-based eGFR, cystatin C-based eGFR, and albuminuria with incident heart failure remained significant. In multivariable models including creatinine-based eGFR, cystatin C-based eGFR, and albuminuria simultaneously, the associations of cystatin C-based eGFR and albuminuria with incident heart failure remained significant, while the association between creatinine-based eGFR and heart failure became inverse.

After adjusting for age, sex, race, and clinical site, several risk factors (ie, <high school education, history of CVD, hypertension, and diabetes mellitus, higher levels of body mass index, waist girth, systolic BP, cystatin C, and urine albumin, and lower level of creatinine-cystatin C-based eGFR) were significantly associated with higher incidence of heart failure. Higher levels of physical activity, alcohol consumption, and high-density lipoprotein-cholesterol were significantly associated with lower incidence of heart failure (Table 4). In the backward selection model, lesss than high school education, history of CVD and diabetes mellitus, higher levels of waist circumference, systolic BP, cystatin C, and urine albumin remained significantly associated with higher risk of incident heart failure.

In the demographic-adjusted model, anemia, HOMA-insulin resistance, HbA1c, uric acid, homocysteine, fibrinogen, high-sensitive C-reactive protein, interleukin-6, TNF-α, and leukocyte count were significantly associated with increased risk of incident heart failure while blood hemoglobin was significantly associated with decreased risk of incident heart failure (Table 5). After further adjustment for the significant traditional risk factors listed above, the associations of anemia, hemoglobin, HOMA-insulin resistance, HbA1c, interleukin-6, and TNF-α remained significantly associated with higher risk of incident heart failure.

## Discussion

Our study indicated that the incidence of heart failure is high in patients with CKD. Incident heart failure was significantly

**Table 1.** Baseline Characteristics of Study Participants by Categories of Creatinine-Cystatin C-Based eGFR: the CRIC Study

| | Quartiles of $eGFR_{Cr—Cyst\ C}$ (mL/min Per 1.73 $m^2$) | | | | *P*-Values for Group Differences |
|---|---|---|---|---|---|
| | ≥60 (n=672) | 45 to 59 (n=1021) | 30 to 44 (n=1192) | <30 (n=672) | |
| Age, mean (SD), y | 53.2 (10.7) | 58.8 (10.6) | 59.6 (11.1) | 58.2 (11.2) | <0.001 |
| Male, n (%) | 373 (55.5) | 606 (59.4) | 629 (52.8) | 333 (49.6) | <0.001 |
| Race/ethnicity, n (%) | | | | | |
| White | 357 (53.1) | 471 (46.1) | 476 (39.9) | 217 (32.3) | <0.001 |
| Black | 239 (35.6) | 398 (39.0) | 505 (42.4) | 291 (43.3) | |
| Hispanic | 38 (5.7) | 110 (10.8) | 173 (14.5) | 139 (20.7) | |
| Other | 38 (5.7) | 42 (4.1) | 38 (3.2) | 25 (3.7) | |
| High school education, n (%) | 624 (93.0) | 850 (83.3) | 887 (74.4) | 463 (68.9) | <0.001 |
| Physical activity, mean (SD), MET/week | 242.3 (165.7) | 202.3 (129.9) | 193.9 (152.2) | 177.3 (136.9) | <0.001 |
| Current cigarette smoking, n (%) | 65 (9.7) | 115 (11.3) | 162 (13.6) | 121 (18.0) | <0.001 |
| Current alcohol consumption, n (%) | 515 (76.6) | 682 (66.8) | 720 (60.4) | 361 (53.7) | <0.001 |
| History of cardiovascular disease, n (%) | 92 (13.7) | 260 (25.5) | 360 (30.2) | 222 (33.0) | <0.001 |
| Hypertension, n (%) | 435 (64.7) | 904 (88.5) | 1083 (90.9) | 622 (92.6) | <0.001 |
| Diabetes mellitus, n (%) | 184 (27.4) | 447 (43.8) | 632 (53.0) | 382 (56.8) | <0.001 |
| Anemia*, n (%) | 139 (20.8) | 382 (37.6) | 653 (55.1) | 471 (70.4) | <0.001 |
| Body mass index, mean (SD), $kg/m^2$ | 30.2 (6.5) | 31.8 (7.6) | 32.6 (7.9) | 32.4 (8.5) | <0.001 |
| Waist circumference, mean (SD), cm | 100.9 (15.1) | 105.9 (17.4) | 106.8 (17.5) | 106.4 (18.7) | <0.001 |
| Systolic blood pressure, mean (SD), mm Hg | 121.6 (18.5) | 127.2 (20.6) | 130.6 (22.8) | 133.5 (24.0) | <0.001 |
| HDL-cholesterol, mean (SD), mg/dL | 50.9 (16.8) | 48.1 (15.2) | 47.4 (15.7) | 45.6 (14.4) | <0.001 |
| LDL-cholesterol, mean (SD), mg/dL | 108.4 (32.2) | 104.7 (34.6) | 101.7 (35.3) | 101.9 (39.4) | <0.001 |
| Hemoglobin, mean (SD), g/dL | 13.6 (1.5) | 13.0 (1.7) | 12.3 (1.6) | 11.7 (1.7) | <0.001 |
| HOMA-insulin resistance, median (IQR) | 3.17 (2.11, 5.39) | 4.12 (2.64, 7.02) | 4.22 (2.60, 7.45) | 4.40 (2.57, 7.60) | <0.001 |
| Hemoglobin A1c, mean (SD), % | 6.19 (1.38) | 6.57 (1.50) | 6.76 (1.54) | 6.73 (1.60) | <0.001 |
| Uric acid, mean (SD), mg/dL | 6.12 (1.61) | 7.06 (1.69) | 7.68 (1.73) | 8.28 (1.96) | <0.001 |
| Homocysteine, median (IQR), mg/dL | 10.2 (8.6, 12.6) | 12.8 (10.7, 15.3) | 15.0 (12.5, 18.3) | 17.8 (14.5, 22.0) | <0.001 |
| Fibrinogen, mean (SD), mg/dL | 3.51 (0.85) | 3.96 (1.03) | 4.29 (1.20) | 4.71 (1.37) | <0.001 |
| hsC-reactive protein, median (IQR), mg/L | 1.51 (0.79, 3.59) | 2.58 (1.10, 6.00) | 2.89 (1.16, 7.10) | 2.95 (1.11, 7.59) | <0.001 |
| Interleukin-6, median (IQR), pg/mL | 1.09 (0.71, 1.82) | 1.67 (1.10, 2.60) | 2.08 (1.34, 3.34) | 2.59 (1.64, 4.13) | <0.001 |
| Tumor necrosis factor-α, median (IQR), ng/mL | 1.4 (1.0, 2.0) | 1.9 (1.4, 2.7) | 2.4 (1.8, 3.4) | 3.2 (2.3, 4.2) | <0.001 |
| Leukocyte count, median (IQR), $10^9$ cells/L | 5.6 (4.7, 6.8) | 6.1 (5.1, 7.4) | 6.4 (5.3, 7.8) | 6.7 (5.6, 8.1) | <0.001 |
| Creatinine, mean (SD), mg/dL | 1.19 (0.21) | 1.44 (0.22) | 1.80 (0.33) | 2.55 (0.58) | <0.001 |
| Cystatin C, mean (SD), mg/L | 0.89 (0.14) | 1.20 (0.15) | 1.60 (0.22) | 2.31 (0.42) | <0.001 |
| Urine albumin, median (IQR), g/24 h | 0.01 (0.01, 0.05) | 0.03 (0.01, 0.27) | 0.11 (0.02, 0.80) | 0.39 (0.06, 1.54) | <0.001 |

Mean (SD), median (interquartile range), or number (percent). CRIC indicates Chronic Renal Insufficiency Cohort Study; $eGFR_{Cr—Cyst\ C}$, creatinine and cystatin C-based glomerular filtration rate; HDL, high-density lipoprotein; hsC-reactive protein, high-sensitive C-reactive protein; HOMA, homeostasis model assessment; IQR, interquartile range; LDL, low-density lipoprotein; MET, metabolic equivalent of task.

*Anemia was defined as hemoglobin <13 g/dL for men and <12 g/dL for women.

higher among patients with lower eGFR and higher albuminuria. Cystatin C-based eGFR and albuminuria were stronger predictors for subsequent risk of heart failure than creatinine-based eGFR among patients with CKD. In addition to traditional risk factors, anemia, HOMA-insulin resistance, HbA1c, interleukin-6, and TNF-α were significantly associated with increased risk of incident heart failure among patients with CKD.

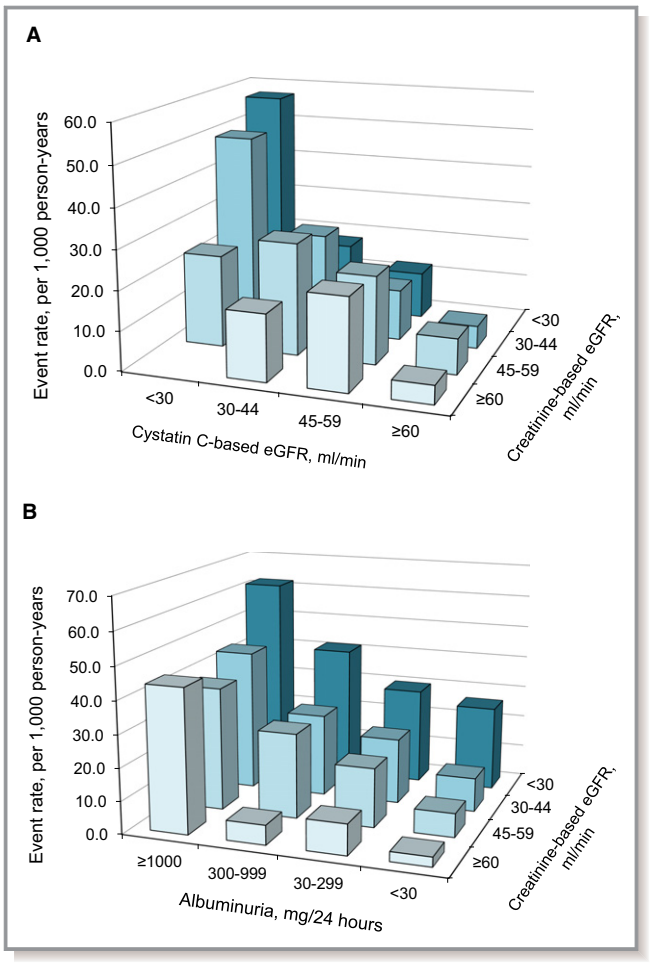


**Figure.** Incidence of heart failure among patients with chronic kidney disease by creatinine-based eGFR, cystatin C-based eGFR, and 24-hour urine albumin: the CRIC (Chronic Renal Insufficiency Cohort) Study. A, Incidence of heart failure by creatinine-based eGFR and cystatin C-based eGFR; (B) Incidence of heart failure by creatinine-based eGFR and albuminuria. eGFR indicates estimated glomerular filtration rate.

These findings have important clinical significance because CKD is highly prevalent in the general population and CVD, including heart failure, is the leading cause of death among patients with CKD.[1] In the Framingham Heart Study, the incidence of heart failure was 4.7 per 1000 person-years among 3757 men and 4472 women aged 40 to 94 years who were followed up from 1971 to 1996.[10] The Cardiovascular Lifetime Risk Pooling Project included 39 578 adults aged 45 years and older from 3 US cohort studies and reported a heart failure incidence of 8.3 per 1000 person-years.[11] In the Multi-Ethnic Study of Atherosclerosis study, the incidence of heart failure was 3.1 per 1000 person-years among 6814 participants aged 45 to 84 years.[12] The incidence of heart failure in our study participants is much higher than in these studies conducted in the general population but similar to studies in CKD populations.[13] For example, the incidence of heart failure was 23 per 1000 person-years in a community-based cohort of 114 900 adults with CKD stages 3 to 4 in Northern California.[13] Our study documented a several-fold increased incidence of heart failure among patients with CKD relative to the general population.

In the Chronic Kidney Disease Prognosis Consortium cohorts, decreased creatinine-based eGFR and increased urinary albumin-to-creatinine ratio were independently associated with all-cause and CVD mortality.[1] Blecker and colleagues reported that albuminuria was associated with subsequent risk of heart failure in the Atherosclerosis Risk in Communities Study.[14] In addition, decreased cystatin C-based eGFR and albuminuria independently contributed to the risk of heart failure in the Atherosclerosis Risk in Communities study.[2] The independent associations of decreased creatinine-based eGFR and increased urinary albumin-to-creatinine ratio with incident heart failure were also observed in a large population-based longitudinal study in Alberta, Canada.[4] Our study indicated that creatinine-based eGFR, cystatin C-based eGFR, and albuminuria are all associated with incident heart failure. However, when all 3 CKD measures were included in the same model simultaneously, cystatin C-based eGFR and albuminuria provided better prediction of incident heart failure. It has been suggested in previous studies that cystatin C improves the prediction of CVD mortality beyond creatinine.[15] Our study also indicated that the association between lower creatinine-based eGFR and heart failure became inverse after adjustment for cystatin C-based eGFR. There are 2 alternate explanations for this finding. First, it is possible that high multicollinearity between cystatin C-based eGFR and creatinine-based eGFR results in a change of sign of the regression parameter estimate for the latter. Second, after adjustment for more precise GFR measurement (cystatin C-based eGFR), non-GFR determinants of serum creatinine (ie, muscle mass and nutritional status) were associated with lower all-cause mortality and heart failure incidence.[16,17]

Our study found that less than a high school education, history of CVD, diabetes mellitus, systolic BP, and waist circumference were significantly and independently associated with increased risk of heart failure. These traditional risk factors have been associated with increased risk of heart failure among the general population in previous cohort studies.[18]

Anemia is common among patients with CKD and is associated with increased risk of CVD in this population.[19,20] In addition, anemia is frequent among patients with heart failure and is associated with adverse outcomes and high mortality among these patients.[20] Our study indicated that baseline anemia is a significant and independent risk factor for subsequent risk of heart failure among patients with CKD. Furthermore, there is an inverse association between blood hemoglobin level and incidence of heart failure. However,

**Table 2.** Descriptive Statistics and Correlation Coefficients of Creatinine-Based eGFR, Cystatin C-Based eGFR, and 24-Hour Urine Albumin

| | Mean (SD) | Media (IQR) | Correlation Coefficients (*P*-Values) | | | |
|---|---|---|---|---|---|---|
| | | | Creatinine-Based eGFR | Cystatin C-Based eGFR | Albuminuria | Log-Albuminuria |
| Creatinine-based eGFR, mL/min per 1.73 $m^2$ | 44.9 (15.1) | 43.8 (33.5, 54.7) | 1.00 | 0.826 (<0.001) | −0.202 (<0.001) | −0.265 (<0.001) |
| Cystatin C-based eGFR, mL/min per 1.73 $m^2$ | 53.3 (23.7) | 48.9 (35.3, 67.5) | | 1.00 | −0.242 (<0.001) | −0.314 (<0.001) |
| Albuminuria, g/24 h | 0.68 (1.59) | 0.06 (0.01, 0.55) | | | 1.00 | 0.924 (<0.001) |
| Log-albuminuria, g/24 h* | 0.33 (0.52) | 0.06 (0.01, 0.44) | | | | 1.00 |

Creatinine-based eGFR ranged from 6.9 to 110.4 mL/min per 1.73 $m^2$; cystatin C-based eGFR ranged from 11.1 to 150.0 mL/min per 1.73 $m^2$; albuminuria ranged from 0 to 18.5 g/24 h; and log-albuminuria ranged from 0 to 2.97 g/24 h. eGFR indicates estimated glomerular filtration rate; IQR, interquartile range.
*Log-albuminuria=Log (urine albumin g/24 h+1).

several clinical trials have shown that treatment of anemia among patients with CKD does not reduce CVD outcomes, including heart failure.[21–23] Anemia could be a comorbid condition or common underlying cause of CKD and heart failure.[24,25] Future studies should examine whether the prevention of anemia in patients with CKD will reduce the risk of incident heart failure.

Inflammatory biomarkers have been associated with increased risk of heart failure in community-based cohort studies.[26,27] Our study provides novel findings on the association between systemic inflammation and risk of heart failure among patients with CKD. After adjustment for age, sex, and race, it was determined that multiple inflammatory biomarkers, including fibrinogen, high-sensitive C-reactive protein, interleukin-6, TNF-α, and leukocyte count, were all significantly associated with incident heart failure. After additional adjustment for established CVD risk factors, interleukin-6 and TNF-α were significantly and independently associated with risk of heart failure. These data suggest that inflammation might play an important role in the development of heart failure among patients with CKD.

**Table 3.** Multivariable-Adjusted Hazard Ratios (95% CI) of Congestive Heart Failure Associated With 1 SD of Creatinine-Based eGFR, Cystatin C-Based eGFR, and Log-Transformed 24-Hour Urine Albumin

| | Hazard Ratio (95% CI) | *P*-Value |
|---|---|---|
| 1 SD decrease in creatinine-based eGFR (−15.1 mL/min 1.73 $m^2$) | | |
| Age, sex, and race adjusted | 1.67 (1.49, 1.89) | <0.001 |
| Age, sex, race, and cystatin C-based eGFR adjusted | 0.78 (0.65, 0.93) | 0.006 |
| Age, sex, race, and urine albumin adjusted | 1.40 (1.23, 1.59) | <0.001 |
| Age, sex, race, cystatin C-based eGFR, and urine albumin adjusted | 0.77 (0.65, 0.92) | 0.005 |
| 1 SD decrease in cystatin C-based eGFR (−23.8 mL/min) | | |
| Age, sex, and race adjusted | 2.43 (2.10, 2.80) | <0.001 |
| Age, sex, race, and creatinine-based eGFR adjusted | 3.04 (2.45, 3.78) | <0.001 |
| Age, sex, race, and urine albumin adjusted | 2.01 (1.73, 2.34) | <0.001 |
| Age, sex, race, creatinine-based eGFR, and urine albumin adjusted | 2.52 (2.02, 3.15) | <0.001 |
| 1 SD increase in log-albuminuria (0.5 g/24 h) | | |
| Age, sex, and race adjusted | 1.65 (1.53, 1.78) | <0.001 |
| Age, sex, race, and creatinine-based eGFR adjusted | 1.56 (1.44, 1.69) | <0.001 |
| Age, sex, race, and cystatin C-based eGFR adjusted | 1.45 (1.34, 1.58) | <0.001 |
| Age, sex, race, creatinine-based eGFR, and cystatin C-based eGFR adjusted | 1.45 (1.34, 1.58) | <0.001 |

All analyses stratified by clinical site. eGFR indicates estimated glomerular filtration rate; log-albuminuria, log (urine albumin g/24 h+1).

**Table 4.** Multivariable-Adjusted Hazard Ratios (95% CI) of Congestive Heart Failure Associated With Established CVD Risk Factors

| | Age-Sex-Race-Adjusted | | Multivariable-Adjusted† | |
|---|---|---|---|---|
| Variables* | Hazard Ratio (95% CI) | *P*-Value | Hazard Ratio (95% CI) | *P*-Value |
| <High-school education | 1.75 (1.39, 2.19) | <0.001 | 1.47 (1.15, 1.87) | 0.002 |
| Physical activity, 147.5 MET/week | 0.80 (0.71, 0.90) | <0.001 | | |
| Current cigarette smoking | 1.24 (0.95, 1.62) | 0.11 | | |
| Current alcohol consumption | 0.75 (0.61, 0.91) | 0.003 | | |
| History of cardiovascular disease | 4.72 (3.89, 5.73) | <0.001 | 3.28 (2.67, 4.04) | <0.001 |
| Hypertension | 2.85 (1.80, 4.50) | <0.001 | | |
| Diabetes mellitus | 3.04 (2.46, 3.76) | <0.001 | 1.71 (1.35, 2.16) | <0.001 |
| Body mass index, 7.7 kg/m$^2$ | 1.35 (1.24, 1.47) | <0.001 | | |
| Waist circumference, 17.4 cm | 1.42 (1.30, 1.56) | <0.001 | 1.28 (1.16, 1.42) | <0.001 |
| Systolic blood pressure, 22 mm Hg | 1.45 (1.33, 1.58) | <0.001 | 1.23 (1.10, 1.36) | <0.001 |
| HDL-cholesterol, 15.6 mg/dL | 0.81 (0.72, 0.91) | <0.001 | | |
| LDL-cholesterol, 35.5 mg/dL | 0.96 (0.87, 1.05) | 0.36 | | |
| Cystatin C, 0.5 mg/dL | 1.73 (1.60, 1.88) | <0.001 | 1.42 (1.29, 1.56) | <0.001 |
| Log urine albumin, 0.5 g/24 h | 1.65 (1.53, 1.78) | <0.001 | 1.22 (1.11, 1.34) | <0.001 |
| $eGFR_{Cr—Cyst\ C}$, −16.9 mL/min 1.73 m$^2$ | 2.08 (1.83, 2.37) | <0.001 | | |

All analyses stratified by clinical site. CVD indicates cardiovascular disease; $eGFR_{Cr—Cyst\ C}$, creatinine and cystatin C-based glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent of task.
*Binary variable or 1 SD.
†Multivariable model was selected by the backward selection method.

The association between diabetes mellitus and heart failure has been well described, with diabetes mellitus increasing the risk of heart failure by 2- to 6-fold.[28] Recent population-based cohort studies reported that insulin resistance, calculated from insulin and glucose, was associated with increased risk of heart failure.[29,30] Our study indicates

**Table 5.** Multivariable-Adjusted Hazard Ratios (95% CI) of Congestive Heart Failure Associated With Novel CVD Risk Factors

| | Age-Sex-Race Adjusted | | Multivariable-Adjusted† | |
|---|---|---|---|---|
| Variables* | Hazard Ratio (95% CI) | *P*-Value | Hazard Ratio (95% CI) | *P*-Value |
| Anemia | 2.19 (1.79, 2.69) | <0.001 | 1.37 (1.09, 1.72) | 0.006 |
| Blood hemoglobin, 1.8 g/dL | 0.61 (0.55, 0.68) | <0.001 | 0.85 (0.75, 0.96) | 0.007 |
| Log HOMA-insulin resistance, 0.67 unit | 1.41 (1.29, 1.53) | <0.001 | 1.16 (1.04, 1.28) | 0.006 |
| Hemoglobin A1c, 1.5% | 1.54 (1.43, 1.65) | <0.001 | 1.27 (1.14, 1.41) | <0.001 |
| Uric acid, 1.9 mg/dL | 1.21 (1.09, 1.33) | <0.001 | 1.05 (0.94, 1.17) | 0.37 |
| Log homocysteine, 0.33 mg/dL | 1.23 (1.11, 1.36) | <0.001 | 0.90 (0.79, 1.03) | 0.11 |
| Fibrinogen, 1.2 mg/dL | 1.55 (1.42, 1.68) | <0.001 | 1.06 (0.95, 1.18) | 0.30 |
| Log hsC-reactive protein, 0.87 mg/L | 1.18 (1.08, 1.29) | <0.001 | 1.07 (0.97, 1.18) | 0.20 |
| Log interleukin-6, 0.66 pg/mL | 1.30 (1.22, 1.39) | <0.001 | 1.15 (1.05, 1.25) | 0.002 |
| Log tumor necrosis factor-α, 0.50 ng/mL | 1.27 (1.18, 1.36) | <0.001 | 1.10 (1.00, 1.21) | 0.05 |
| Log leukocyte count, $0.26\times10^9$ cells/L | 1.28 (1.17, 1.40) | <0.001 | 1.07 (0.97, 1.19) | 0.17 |

All analyses stratified by clinical site. CVD indicates cardiovascular disease; $eGFR_{Cr—Cyst\ C}$, creatinine and cystatin C-based glomerular filtration rate; HOMA, homeostasis model assessment; hsC-reactive protein, high-sensitive C-reactive protein.
*Binary variable or 1 SD.
†Adjusted for age, sex, race, education, history of cardiovascular disease, diabetes mellitus, systolic blood pressure, waist circumference, serum cystatin C, log-urine albumin, and $eGFR_{Cr—Cyst\ C}$.

that baseline HOMA-insulin resistance is significantly and directly associated with increased risk of heart failure, independent of multiple CVD risk factors including diabetes mellitus and central obesity. In addition, our study indicates that HbA1c, an index of long-term glycemic control, is significantly associated with incident heart failure, independent of diabetes mellitus. These data suggest that diabetes mellitus and metabolic risk factors played an important role in the risk of heart failure among patients with CKD.

A few limitations of our study should be considered when making conclusions. This is an observational study, which prevents us from making any causal inference. Since heart failure at baseline was assessed by self-report, it is possible that some participants may have been incorrectly classified as either having or not having heart failure. In addition, new cases of heart failure were identified initially by hospitalization. Therefore, participants who were diagnosed with heart failure in an ambulatory care setting would be missed. Furthermore, the diagnosis of heart failure was made using standard algorithms based on clinical, imaging, and laboratory data that are validated in the general population, but not for heart failure in the setting of CKD. Finally, the CRIC Study did not further classify patients into systolic or diastolic heart failure, which have different underlying mechanisms and treatments.[31,32]

In conclusion, our study indicated that cystatin C-based eGFR and albuminuria are better predictors for risk of heart failure compared with creatinine-based eGFR among patients with CKD. Furthermore, anemia, insulin resistance, inflammation, and poor glycemic control are independent risk factors for the development of heart failure among patients with CKD.

## Appendix

### Contributors

CRIC Study Investigators include Lawrence J. Appel, MD, MPH; Harold I. Feldman, MD, MSCE; Alan S. Go, MD; Jiang He, MD, PhD; John W. Kusek, PhD; James P. Lash, MD; Akinlolu Ojo, MD, PhD; Mahboob Rahman, MD; and Raymond R. Townsend, MD.

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## Disclosures

None.

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# Risk Factors for Heart Failure in Patients With Chronic Kidney Disease: The CRIC (Chronic Renal Insufficiency Cohort) Study

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