Patients with chronic kidney disease (CKD) are at high risk of heart failure (HF). However, there are currently no recommendations to screen for either early or increased risk of HF in patients with CKD. One simple strategy, yet untested, is to question patients with CKD about early symptoms of subclinical HF.

Background—Chronic kidney disease is a risk factor for heart failure (HF). Patients with chronic kidney disease without diagnosed HF have an increased burden of symptoms characteristic of HF. It is not known whether these symptoms are associated with occurrence of new onset HF.

Methods and Results—We studied the association of a modified Kansas City Cardiomyopathy Questionnaire with newly identified cases of hospitalized HF among 3093 participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study who did not report HF at baseline. The annually updated Kansas City Cardiomyopathy Questionnaire score was categorized into quartiles (Q1–4) with the lower scores representing the worse symptoms. Multivariable-adjusted repeated measure logistic regression models were adjusted for demographic characteristics, clinical risk factors for HF, N-terminal probrain natriuretic peptide level and left ventricular hypertrophy, left ventricular systolic and diastolic dysfunction. Over a mean (±SD) follow-up period of 4.3±1.6 years, there were 211 new cases of HF hospitalizations. The risk of HF hospitalization increased with increasing symptom quartiles; 2.62, 1.85, 1.14, and 0.74 events per 100 person-years, respectively. The median number of annual Kansas City Cardiomyopathy Questionnaire assessments per participant was 5 (interquartile range, 3–6). The annually updated Kansas City Cardiomyopathy Questionnaire score was independently associated with higher risk of incident HF hospitalization in multivariable-adjusted models (odds ratio, 3.30 [1.66–6.52]; P=0.001 for Q1 compared with Q4).

Conclusions—Symptoms characteristic of HF are common in patients with chronic kidney disease and are associated with higher short-term risk for new hospitalization for HF, independent of level of kidney function, and other known HF risk factors. (Circ Heart Fail. 2015;8:702-708. DOI: 10.1161/CIRCHEARTFAILURE.115.002097.)

Key Words: heart failure ■ hospitalization ■ renal insufficiency, chronic

© 2015 American Heart Association, Inc.

Circ Heart Fail is available at http://circheartfailure.ahajournals.org

DOI: 10.1161/CIRCHEARTFAILURE.115.002097
edema, determined by a modified version of the Kansas City Cardiomyopathy Questionnaire (KCCQ). The prevalence of these symptoms was greater in persons with poorer kidney function. However, it is not known whether these symptoms precede the development of clinically apparent HF or are the result of pathophysiologic changes because of CKD. To better understand the relationship of symptoms characteristic of HF with new onset of HF that required hospitalization in patients with CKD, we studied participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Methods

Participants

The CRIC Study was established in 2001 as a prospective observational cohort study to evaluate the determinants of progression to end-stage renal disease and occurrence of cardiovascular disease among persons with CKD. Participants were recruited from 7 clinical centers between June 2003 and August 2008. Inclusion criteria were an estimated GFR between 20 and 70 mL/min per 1.73 m² for persons aged 21 to 44 years, 20 to 60 mL/min per 1.73 m² for persons aged 45 to 64 years, and 20 to 50 mL/min per 1.73 m² for those aged 65 to 74 years. Exclusion criteria included previous transplantation, polycystic kidney disease, multiple myeloma, use of immunosuppression, and severe comorbid illnesses, such as cirrhosis, HIV disease, and severe HF, defined as New York Heart Association (NYHA) class III or IV HF at baseline. The study was reviewed and approved by the Institutional Review Board at each participating clinical center. HF at study entry was assessed by participant response to the question at baseline: have you ever been diagnosed with or has a doctor or other health professional ever told you that you have HF? Of 3520 participants who completed the year 1 visit, we excluded 404 participants who reported HF at baseline and 23 who were missing year 1 KCCQ score. For this analysis, we included 3093 participants who did not report a history of HF and who completed the KCCQ at year 1 of follow-up.

Predictors

The predictor was the annually updated KCCQ score. The KCCQ is a validated instrument to assess health status among persons with HF. The self-administered questionnaire includes 23-items, which quantify the importance of dyspnea, fatigue, and edema on physical, social, and emotional functions. The responses are categorized under 3 subscales (symptom burden, physical limitation, and quality of life) with a range of possible subscale scores from 0 to 100, with 100 representing the least burden of symptoms. The total KCCQ score represents the mean of the 3 subscale scores. We modified the KCCQ by omitting reference to the participant having existing HF, thereby allowing administration of the instrument to persons with and without diagnosed HF; the scoring was not changed by this modification (Data Supplement). The KCCQ was administered as a written form in person during annual study visits to participants beginning 1 year after enrollment and each year thereafter. The questionnaire was read aloud to participants with poor literacy and their verbal re-

Outcomes

The primary study outcome was the first hospitalization for HF from study entry until the administrative censoring date of March 31, 2011. Study participants were queried 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 HF resulted in retrieval of medical records by study personnel for centralized adjudicated review. At least 2 study physicians reviewed all possible HF 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. HF was confirmed when both reviewers agreed on a probable or definite occurrence of HF based on modified clinical Framingham criteria.

Covariates

Covariates evaluated at baseline included demographic characteristics (age, sex, and race/ethnicity); clinical characteristics (body mass index, systolic and diastolic blood pressure, hypertension, diabetes mellitus, current smoking, alcohol use, and coronary artery disease [previous myocardial infarction or revascularization]); hemoglobin level, low- and high-density lipoprotein levels, cardiac troponin T (TnT), measured using the highly sensitive assay on the Elecsys 2010 analyzer, and N-terminal pro-B-type natriuretic peptide (NT-proBNP), measured using the Elecsys 2010 analyzer. 24-hour urine protein and estimated glomerular filtration rate (eGFR) using both creatinine and cystatin C was performed in all CRIC participants at year 1 of follow-up according to the American Society of Echocardiography guidelines and the data were sent to the CRIC core echocardiography laboratory for measurement and analysis. Left ventricular (LV) geometry, mass, and systolic and diastolic function, evaluated using M-mode, 2-dimensional and Doppler echocardiography, were included as covariates in cross-sectional analyses. LV mass was calculated using the area-length method and indexed to height².9 LV hypertrophy (LHV) was defined as LV mass/height² ≥47 g/m² in women and ≥50 g/m² in men.10 LV end-diastolic and end-systolic volumes were calculated using the modified biplane method and ejection fraction was calculated as: (end-diastolic volume−end-systolic volume)/end-diastolic volume. LV systolic dysfunction was defined as an ejection fraction <0.45,11,12 Mitral inflow E- and A-wave velocities, E-wave deceleration time and pulmonary venous reverse A-wave duration were used to categorize LV diastolic function into normal, mildly, moderately or severely abnormal.13 Because 1 center was unable to evaluate diastolic function, these measures were unavailable in 564 participants.

Statistical Analysis

We categorized KCCQ scores into quartiles to examine for any trends without imposing prespecified cut-points.1 In addition, KCCQ score was dichotomized at the clinically relevant cut-off value of 75 and was modeled as a continuous variable per 10 points and after log-transformation because of its skewed distribution. Baseline demographic and laboratory values and year 1 echocardiographic values were compared across categories of the first KCCQ score using the ANOVA or Kruskal–Wallis test for continuous variables and x² test for categorical variables. We also compared baseline characteristics of the participants who were included in this study and the participants without a history of HF who were not included. The incidence of HF was calculated for each quartile of the first KCCQ score. Before evaluating the association of the first KCCQ score with time to incident HF events, we tested the proportional hazards assumption and found that it was violated. We then proceeded to study the association between the annually updated KCCQ score and incident HF in the 1-year period after the last KCCQ administration using repeated measure logistic regression. For the annually updated KCCQ score, we began with a demographically adjusted model (age, sex, race/ethnicity, and site) and then created a clinically adjusted model (age, sex, race/ethnicity, site, diabetes mellitus status, history of cardiovascular disease, current smoking and alcohol use, body mass index, systolic blood pressure, low-density and high-density lipoprotein levels, 24-hour urine protein, and eGFR). We then further adjusted for baseline NT-proBNP concentrations. In a final step, we fully adjusted the model by including LHV and LV systolic dysfunction at baseline as covariates. We repeated these analyses with the annually updated KCCQ score dichotomized at a cut-point of 75. In a clinically stable population with advanced HF, a score >75 has been used to define good health status, and ≤75 as clinically significant HF.
symptoms. All covariates included in the multivariable-adjusted models, except NT-proBNP concentration, were also time-updated. We also evaluated the unadjusted time-updated association of each of the subscales of the KCCQ (symptom burden, physical limitation, and quality of life) with incident HF. Of the total number of participant visits, including the year 1 visit, follow-up KCCQ data were missing for 2.1%. Participants were censored on death or development of end-stage renal disease with initiation of hemodialysis. STATA version 11 (StataCorp, www.stata.com) was used for the analysis.

**Results**

The participants’ ages ranged from 22 to 76 years at the year 1 assessment. Participants in the lowest quartile of the first KCCQ scores were more likely to be female and black and had a higher prevalence of diabetes mellitus, current smoking, and cardiovascular disease, but a lower prevalence of alcohol use (Table 1). Participants in the lowest quartile of KCCQ scores also had higher body mass index, systolic blood pressure, urine protein, NT-proBNP and TnT concentrations, and lower eGFR, hemoglobin and high-density lipoprotein concentrations. The 427 participants who were not included in this study because of a history of HF or missing year 1 KCCQ data were more likely to be older and black had worse kidney health and had a higher prevalence of comorbidities (Table I in the Data Supplement).

Compared with those with the first KCCQ scores in the highest quartile, participants in the lowest quartile had a significantly higher mean LV mass index and a 2-fold greater prevalence of LVH (Table 2). The prevalence of LV systolic and diastolic dysfunction, however, did not differ significantly across quartiles of KCCQ scores.

Over a mean±SD (range) follow-up period of 4.3±1.6 years (0.7–6.7 years), 211 new HF hospitalizations were identified. The rate of new HF hospitalization decreased as the quartile of first KCCQ score increased (Table 3).

The median number of annual KCCQ assessments per participant was 5 (interquartile range, 3–6). Participants with annually updated KCCQ scores within the first and second quartiles were at significantly greater risk of incident HF hospitalization in the following year in demographically adjusted models (Table 4). In the fully adjusted model that included baseline NT-proBNP level, LVH and LV systolic dysfunction as covariates, participants within the lowest quartile were at 3.3-fold risk for incident HF hospitalization in the following year (Table 4). As a dichotomized variable, an annually updated KCCQ score ≤75 was associated with an increased risk of incident HF hospitalization in the following year in both the demographically adjusted (odds ratio [OR], 2.56 [1.92–3.44]; *P*<0.001) and fully adjusted models (1.88 [1.30–2.70];
When modeled as a linear variable, lower KCCQ score was associated with higher risk of incident HF hospitalization in the following year in the fully adjusted model (OR, 1.22 per 10 KCCQ point decrease [1.14–1.32]; \( P < 0.001 \)). The unadjusted associations for each of the annually updated subscales of the KCCQ with incident HF were similar to each other and to that of the total KCCQ score: symptom burden (OR, 1.23 per 10 KCCQ points [95% confidence interval, 1.17–1.29; \( P < 0.001 \)), physical limitation (OR, 1.26 per 10 KCCQ points [95% confidence interval, 1.21–1.32; \( P < 0.001 \)), and quality of life (OR, 1.20 per 10 KCCQ points [95% confidence interval, 1.14–1.26; \( P < 0.001 \)).

Discussion

In patients with CKD, we found that HF symptoms are associated with the initial hospitalization for HF within the upcoming year, independent of all covariates including NT-proBNP and with objective measures of subclinical cardiac disease, including LVH. Our study, therefore, takes the important step of linking common preclinical HF symptoms with near-term risk of HF hospitalization in the setting of CKD.

Although CKD is a strong and independent predictor of incident HF, there are currently no established strategies for identifying patients at high risk for HF or preventing the onset of HF in patients with CKD. We had previously reported a high prevalence of symptoms characteristic of HF—dyspnea, fatigue, and edema—as assessed by the modified KCCQ among patients with moderate-to-severe CKD without a previous self-reported diagnosis of HF. This study expands the literature by demonstrating that the KCCQ score independently predicts incident HF in the near-term in an at-risk population.

Previous studies have studied the KCCQ primarily in HF populations, comparing and correlating the KCCQ score with natriuretic peptide concentrations and left ventricular ejection fraction, and used it as an outcome. The KCCQ has recently been validated to monitor health-related quality of life in patients with severe aortic stenosis and NYHA class II–IV symptoms undergoing transcatheter aortic valve replacement. However, our study is the first to evaluate the association between KCCQ score and incident HF in a population without diagnosed HF and, thereby, extends the application of the KCCQ to the pre-HF setting.

Symptom burden as assessed by the KCCQ is a known predictor of recurrent HF events and death in patients with chronic HF. In this study, the initial assessment of symptoms characteristic of HF was strongly associated with incidence of HF hospitalization during follow-up. However, the proportional hazards assumption was violated when the initial KCCQ score was evaluated in multivariable analyses. Therefore, we modeled KCCQ score as a time-updated variable and found that, when repeated annually, the KCCQ score had a strong association with incident HF hospitalization, independent of all time-updated covariates. In addition, the time-updated subscales of the KCCQ, including symptom burden, physical limitation, and quality of life, had similar associations with incident HF, suggesting that these symptoms heralding incipient HF in patients with CKD negatively impact multiple facets of daily life. Our findings suggest that these clinical symptoms in patients with CKD are a clear harbinger of risk for de novo HF hospitalization. Moreover, in the clinical setting, the association of the lowest quartile of KCCQ score with 7-fold risk of hospitalization for HF in unadjusted analyses may be more relevant to the evaluation of

<table>
<thead>
<tr>
<th>Quartile</th>
<th>I (n=779)</th>
<th>II (n=813)</th>
<th>III (n=766)</th>
<th>IV (n=735)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCCQ Score</td>
<td>( \leq 74.5 )</td>
<td>74.6–91.7</td>
<td>91.8–99.0</td>
<td>&gt;99.0</td>
<td>0.001</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>55 (14)</td>
<td>51 (13)</td>
<td>48 (12)</td>
<td>46 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVH†</td>
<td>66%</td>
<td>51%</td>
<td>41%</td>
<td>32%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>55 (7)</td>
<td>55 (8)</td>
<td>55 (7)</td>
<td>55 (7)</td>
<td>0.68</td>
</tr>
<tr>
<td>LV systolic dysfunction‡</td>
<td>7%</td>
<td>10%</td>
<td>6%</td>
<td>6%</td>
<td>0.11</td>
</tr>
<tr>
<td>LV diastolic dysfunction§</td>
<td>46%</td>
<td>42%</td>
<td>40%</td>
<td>39%</td>
<td>0.16</td>
</tr>
</tbody>
</table>

KCCQ indicates Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEF, LV ejection fraction; and LVH, LV hypertrophy.

*Mean (SD) reported for continuous variables and percentage for categorical variables. \( P \) values are obtained using ANOVA or Kruskal–Wallis tests for continuous variables and \( \chi^2 \) tests for categorical variables.

†LVH was defined as LV mass/height² >47 g/m² for women and ≥50 g/m² for men.
‡Systolic dysfunction was defined as ejection fraction <45%.
§Diastolic dysfunction was defined as mild to severely abnormal.

Table 3. Incidence of Heart Failure by Quartiles of Year 1 KCCQ Score

<table>
<thead>
<tr>
<th>Initial KCCQ Score Quartile</th>
<th>Person-Yr at Risk</th>
<th>Events (n)</th>
<th>Event Rate (per 100 person-yr)</th>
<th>95% CI of Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (≤74.5)</td>
<td>3083</td>
<td>81</td>
<td>2.63</td>
<td>2.12–3.26</td>
</tr>
<tr>
<td>II (74.6–91.7)</td>
<td>3395</td>
<td>63</td>
<td>1.86</td>
<td>1.45–2.36</td>
</tr>
<tr>
<td>III (91.8–99.0)</td>
<td>3421</td>
<td>39</td>
<td>1.14</td>
<td>0.83–1.56</td>
</tr>
<tr>
<td>IV (&gt;99.0)</td>
<td>3359</td>
<td>25</td>
<td>0.74</td>
<td>0.50–1.10</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and KCCQ, Kansas City Cardiomyopathy Questionnaire.
Table 4. Association of Time-Updated KCCQ Score With Incident Heart Failure in the Following Year

<table>
<thead>
<tr>
<th>KCCQ Score</th>
<th>≤74.5</th>
<th>74.6–91.7</th>
<th>91.8–99.0</th>
<th>&gt;99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>6.77 (3.75–12.23)</td>
<td>4.54 (2.49–8.28)</td>
<td>1.68 (0.86–3.30)</td>
<td>1.30 Ref</td>
</tr>
<tr>
<td>Demographic variables*</td>
<td>6.17 (3.40–11.18)</td>
<td>3.99 (2.18–7.31)</td>
<td>1.53 (0.78–3.01)</td>
<td>0.22 Ref</td>
</tr>
<tr>
<td>Clinical variables†</td>
<td>3.67 (1.90–7.10)</td>
<td>2.64 (1.37–5.07)</td>
<td>1.35 (0.66–2.77)</td>
<td>0.41 Ref</td>
</tr>
<tr>
<td>Clinical variables and NT-proBNP‡</td>
<td>3.69 (1.88–7.27)</td>
<td>2.67 (1.37–5.21)</td>
<td>1.42 (0.68–2.95)</td>
<td>0.35 Ref</td>
</tr>
<tr>
<td>Clinical variables, NT-proBNP, LVH, and LV systolic dysfunction§</td>
<td>3.30 (1.66–6.52)</td>
<td>2.18 (1.11–4.29)</td>
<td>1.23 (0.58–2.61)</td>
<td>0.58 Ref</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVH, LV hypertrophy; NT-proBNP, N-terminal probranxinatriuretic peptide; OR, odds ratio; and Ref, reference quartile.

*Adjusted for age, sex, ethnicity, and site.
†Adjusted for age, sex, ethnicity, site, diabetes mellitus status, history of cardiovascular disease, current smoking, alcohol use, 24-h urine protein, estimated glomerular filtration rate, systolic blood pressure, body mass index, low-density lipoprotein, and high-density lipoprotein levels.
‡Adjusted for above plus NT-proBNP level.
§Adjusted for above plus LVH and LV systolic dysfunction.

We had reported previously strong associations of NT-proBNP and TnT with LVH in the CRIC study.27,28 In this study, we determined that the KCCQ score was associated cross-sectionally with NT-proBNP and TnT concentrations, LV mass index and LVH prevalence. In contrast, there was no significant association between KCCQ score and LV systolic and diastolic dysfunction. Like NT-proBNP and TnT, symptoms characteristic of HF are linked with LVH. The associations of symptoms with increased LV mass and NT-proBNP suggest that increased LV mass and elevated LV filling pressures may contribute to the symptoms characteristic of HF among patients with CKD. However, the association between the lowest quartile of KCCQ score and incident HF hospitalization remained significant despite adjustment for baseline NT-proBNP level and LVH.

Although distinguishing HF from volume overload because of worsening kidney disease can be challenging, the adjudication process for HF hospitalization in the CRIC Study was designed to be as specific as possible. Moreover, only a small percentage of participants were hospitalized for HF, suggesting that CKD and HF were not necessarily coterminous in this cohort. Also, participants with worsening kidney disease, who eventually developed end-stage renal disease, were eliminated from the cohort on initiation of hemodialysis. Finally, in the fully adjusted repeated measure logistical regression model, the association between KCCQ score and HF hospitalization remained significant despite adjustment for measures of worsening kidney function, including time-updated 24-hour urine protein and eGFR.

Our study has several strengths. We studied a large, well-characterized cohort with CKD. The primary outcome of incident HF was adjudicated using established criteria.7 The KCCQ score and a large number of covariates of interest, including eGFR and 24-hour protein urine, were repeatedly assessed, permitting time-updated covariates to be included in our statistical models. Some limitations of our study should be considered. HF at study entry was assessed by self-report; it is possible that some participants may have been incorrectly classified as either having or not having HF. In addition, new cases of HF were identified initially by hospitalization. Therefore, participants who were diagnosed with HF in an ambulatory care setting would be missed. The modification of the KCCQ by the removal of reference to existing HF allowed us to administer the instrument to participants with and without diagnosed HF. However, it is possible that this modification may limit the translatability of our findings to the unmodified KCCQ. Finally, although the symptoms characteristic of HF were strongly associated with HF hospitalization, we could not evaluate whether they may be predictive of other types of hospitalization as well. It is possible that the symptoms reflect a global deconditioning rather than a specific predisposition to HF.

In conclusion, symptoms characteristic of HF independently predict the de novo hospitalization for HF within the following year in patients with CKD without a history of HF. They are also associated with subclinical manifestations of HF. Assessment of symptoms such as dyspnea, fatigue and edema may be a simple and low cost method of identifying patients at higher risk for HF to target for earlier intervention.

Sources of Funding

This project was supported by R01 DK066488 award (principal investigator Dr Shlipak). Funding for the Chronic Renal Insufficiency Cohort (CRIC) Study was obtained under a cooperative agreement from National Institute of Diabetes and Digestive and Kidney Diseases (U01DK060990, U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060963, and U01DK060902). In addition, this work was supported in part by the Perelman School of Medicine at the University of Pennsylvania Clinical and Translational Science Award National Institutes of Health (NIH)/National Center for Advancing Translational Sciences (NCATS) UL1TR000003, Johns Hopkins University UL1 TR-000424, University of Maryland GCRC M01 RR-16500, Clinical and Translational Science Collaborative of Cleveland, UL1TR000439 from the NCATS component of the National Institutes of Health and NIH roadmap for Medical Research, Michigan Institute for
Clinical and Research Health UL1TR000433, University of Illinois at Chicago Clinical and Translational Science Award UL1RR029879, Tulane University Translational Research in Hypertension and Renal Biology P30GM103337, and Kaiser Permanente NIH/NCRR UCSF-CTSUL1 UL RR-024131.

Disclosures

None.

References


9. Lang RM, Beirig M, Devereux RB, Flachskampf FA, Foster E, Pelikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–1463. doi: 10.1016/j.echo.2005.10.005.


CLINICAL PERSPECTIVE
The Kanas City Cardiomyopathy Questionnaire is a validated instrument designed to measure symptom burden and its impact on physical limitation and quality of life in patients with heart failure (HF). In this study, we administered a modified version of the Kanas City Cardiomyopathy Questionnaire to a large cohort of patients with chronic kidney disease. We found that, in patients with chronic kidney disease without a history of HF, symptom burden, as measured by the modified Kanas City Cardiomyopathy Questionnaire, predicts incident hospitalization for HF, independent of level of kidney function and other known HF risk factors. Our findings extend the application of the Kanas City Cardiomyopathy Questionnaire to the pre-HF setting and suggest that routine assessment of patients with chronic kidney disease for symptoms characteristic of HF, including dyspnea, fatigue, and edema, might identify those at greatest risk for incident HF, who may benefit from further evaluation.
Kansas City Cardiomyopathy Questionnaire Score Is Associated With Incident Heart Failure Hospitalization in Patients With Chronic Kidney Disease Without Previously Diagnosed Heart Failure: Chronic Renal Insufficiency Cohort Study

CRIC Study Investigators

*Circ Heart Fail,* 2015;8:702-708; originally published online May 18, 2015;
doi: 10.1161/CIRCHEARTFAILURE.115.002097

*Circulation: Heart Failure* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/8/4/702

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2015/05/20/CIRCHEARTFAILURE.115.002097.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Heart Failure* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation: Heart Failure* is online at:
http://circheartfailure.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL
**Supplemental Table: Baseline Characteristics of Chronic Renal Insufficiency Cohort Participants Included and Not Included in the Study.**

<table>
<thead>
<tr>
<th></th>
<th>Included (N=3,093)</th>
<th>Not Included (N=427)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>59 (11)</td>
<td>61 (10)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>45%</td>
<td>46%</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>45%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>39%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>12%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>46%</td>
<td>73%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>46%</td>
<td>73%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Current Smoker</strong></td>
<td>12%</td>
<td>13%</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Current Alcohol Use</strong></td>
<td>59%</td>
<td>45%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular Disease</strong></td>
<td>28%</td>
<td>68%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td>31.8 (7.6)</td>
<td>34.3 (8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure (mmHg)</strong></td>
<td>126 (21)</td>
<td>132 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure (mmHg)</strong></td>
<td>70 (13)</td>
<td>68 (14)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73m²)</strong></td>
<td>43.5 (16.9)</td>
<td>34.5 (14.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>24-hour Urine Protein (g/24 hrs.)</strong></td>
<td>0.9 (1.8)</td>
<td>1.6 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/dL)</strong></td>
<td>12.9 (1.8)</td>
<td>12.2 (1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Low-density lipoprotein (mg/dL)</strong></td>
<td>100 (35)</td>
<td>91 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>High-density lipoprotein (mg/dL)</strong></td>
<td>49 (16)</td>
<td>45 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>NT-proBNP (pg/mL)†</strong></td>
<td>124 (55, 299)</td>
<td>510 (221, 1441)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Troponin T (pg/mL)†</strong></td>
<td>11 (5, 20)</td>
<td>24 (14, 43)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Note: Mean (Standard Deviation) reported for continuous variables and percentage for categorical variables. P values are obtained using Kruskal-Wallis tests for continuous variables and Chi-square tests for categorical variables.

†Reported as Median (Interquartile Range)

**Abbreviations:** estimated glomerular filtration rate (eGFR); N-terminal pro b-type natriuretic peptide (NT-proBNP)
THE KANSAS CITY QUESTIONNAIRE:

The following questions refer to symptoms of shortness of breath, fatigue (weariness), or ankle swelling that some people with kidney disease have, and how they might affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Shortness of breath and fatigue** affect different people in different ways. Please indicate how much you have been limited by shortness of breath or fatigue in your ability to do the following activities over the past 2 weeks. If you do NOT have either shortness of breath or fatigue, please mark “Not at all limited”.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Extremely Limited</th>
<th>Quite a bit Limited</th>
<th>Moderately Limited</th>
<th>Slightly Limited</th>
<th>Not at all Limited</th>
<th>Limited for other reasons or did not do the activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dressing yourself</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Showering/Bathing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking 1 block on level ground</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doing yardwork, housework or carrying groceries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing a flight of stairs without stopping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hurrying or jogging (as if to catch a bus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Compared with 2 weeks ago**, have there been changes in the amount of shortness of breath, fatigue or ankle swelling that you have? If you never have these symptoms, please mark “I’ve had no symptoms over the last 2 weeks”.

   My symptoms have become…

   - Much worse
   - Slightly worse
   - Not changed
   - Slightly better
   - Much better
   - I’ve had no symptoms over the last 2 weeks

3. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted? If you have no shortness of breath, please mark “Never over the past 2 weeks”.

   - All of the time
   - Several times per day
   - At least once a day
   - 3 or more times per week, but not every day
   - 1-2 times per week
   - Less than once a week
   - Never over the past 2 weeks

4. Over the past 2 weeks, how much has shortness of breath bothered you? It has been . . .

   - Extremely bothersome
   - Quite a bit bothersome
   - Moderately bothersome
   - Slightly bothersome
   - Not at all bothersome
   - I’ve had no shortness of breath

5. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?

   - Every night
   - 3 or more times per week, but not every night
   - 1-2 times a week
   - Less than once a week
   - Never over the past 2 weeks

6. Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you want?

   - All of the time
   - Several times a day
   - At least once a day
   - 3 or more times per week, but not every day
   - 1-2 times a week
   - Less than once a week
   - Never over the past 2 weeks

   - Extremely bothersome
   - Quite a bit bothersome
   - Moderately bothersome
   - Slightly bothersome
   - Not at all bothersome
   - I’ve had no fatigue

This questionnaire was ____ self-administered ____ administered by study personnel
7. Over the past 2 weeks, how much has **fatigue** bothered you? It has been . . .

8. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

- Every morning
- 3 or more times per week, but not every morning
- 1-2 times a week
- Less than once a week
- Never over the past 2 weeks

9. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you? It has been . . .

10. **Shortness of breath** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if **shortness of breath** develops or becomes worse?

- Not at all sure
- Not very sure
- Somewhat sure
- Mostly sure
- Completely sure

11. How well do you understand what things you are able to do to keep **shortness of breath** from getting worse?

- Do not understand at all
- Understand a little
- Somewhat understand
- Mostly understand
- Completely understand
- Not applicable

12. Over the past 2 weeks, how much has **shortness of breath** limited your enjoyment of life?

- It has **extremely** limited my enjoyment of life
- It has **quite a bit** limited my enjoyment of life
- It has **moderately** limited my enjoyment of life
- It has **slightly** limited my enjoyment of life
- It has **not** limited my enjoyment of life at all

13. If you had to spend the rest of your life with the amount of **shortness of breath** that you have **right now**, how would you feel about this?

- Completely dissatisfied
- Mostly dissatisfied
- Somewhat satisfied
- Mostly satisfied
- Completely satisfied
- I do not have shortness of breath

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of **shortness of breath**?

- I felt that way all of the time
- I felt that way most of the time
- I occasionally felt that way
- I rarely felt that way
- I never felt that way

15. How much does **shortness of breath** affect your lifestyle? Please indicate how these symptoms may have limited your participation in the following activities over the past 2 weeks.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Extremely Limited</th>
<th>Quite a bit Limited</th>
<th>Moderately Limited</th>
<th>Slightly Limited</th>
<th>Not at all Limited</th>
<th>Limited for other reasons or does not apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hobbies, recreational activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working or doing household chores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visiting family or friends out of your home</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Intimate relationships with loved ones</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

This questionnaire was ____ self-administered ____ administered by study personnel