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The Kansas City Cardiomyopathy Questionnaire Score Is Associated With Incident Heart Failure Hospitalization in Chronic Kidney Disease Patients Without Previously Diagnosed Heart Failure: The CRIC Study

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Abstract

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Disclosures

None.

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Background—Chronic kidney disease (CKD) is a risk factor for heart failure (HF). Patients with CKD 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 (KCCQ) with newly identified cases of hospitalized HF among 3,093 participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study who did not report HF at baseline. The yearly-updated KCCQ 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 pro-brain natriuretic peptide (NT-proBNP) level and left ventricular hypertrophy, left ventricular systolic and diastolic dysfunction. Over a mean (± standard deviation) 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 KCCQ assessments per participant was 5 (interquartile range 3 – 6). The annually updated KCCQ score was independently associated with higher risk of incident HF hospitalization in multivariable adjusted models (OR 3.30 (1.66 – 6.52); p=0.001 for Q1 compared with Q4).

Conclusions—Symptoms characteristic of HF are common in CKD patients 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.

Keywords

chronic kidney disease; heart failure; Kansas City Cardiomyopathy Questionnaire; hospitalization

Patients with chronic kidney disease (CKD) are at high risk of heart failure (HF) [1, 2]. 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 CKD patients about early symptoms of subclinical HF.

We have previously shown that patients with CKD without diagnosed HF report a significant burden of symptoms characteristic of HF, including dyspnea, fatigue and edema, determined by a modified version of the Kansas City Cardiomyopathy Questionnaire (KCCQ)[3]. 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 due to CKD. In order 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 Chronic Renal Insufficiency Cohort (CRIC) Study was established in 2001 as a prospective observational cohort study to evaluate the determinants of progression to ESRD

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and occurrence of CVD among persons with CKD.[4, 5] Participants were recruited from 7 clinical centers between June 2003 and August 2008. Inclusion criteria were an estimated GFR between 20–70 ml/min/1.73m^2 for persons aged 21–44, 20–60 ml/min/1.73m^2 for persons aged 45–64, and 20–50 ml/min/1.73m^2 for those aged 65–74. Exclusion criteria included prior transplantation, polycystic kidney disease, multiple myeloma, use of immunosuppression, and severe comorbid illnesses such as cirrhosis, HIV disease, and severe heart failure, defined as New York Heart Association 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 heart failure?” Of 3,520 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 3,093 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 heart failure[6]. 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 three 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 (Supplemental Material). The KCCQ was administered as a written form in person during annual study visits to participants beginning one year after enrollment and each year thereafter. The questionnaire was read aloud to participants with poor literacy and their verbal responses were recorded. The KCCQ scores were not forwarded to the participants’ clinical providers.

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 health care 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 two 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 upon a “probable” or “definite” occurrence of HF based on modified clinical Framingham criteria.[7]

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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, current smoking, alcohol use, coronary artery disease (prior myocardial infarction or revascularization)); hemoglobin level, low-density and high-density lipoprotein levels, cardiac troponin T (TnT), measured using the highly sensitive assay on the Elecsys 2010 analyzer (www.roche-diagnostics.us), and N-terminal pro-B-type natriuretic peptide (NT-proBNP), measured using the Elecsys 2010 analyzer (www.roche-diagnostics.us); 24-hour urine protein and estimated glomerular filtration rate using both creatinine and cystatin C (eGFR).[8] Trans-thoracic echocardiography (TTE) was performed in all CRIC participants at year 1 of follow-up according to the American Society of Echocardiography guidelines[9] 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, two-dimensional and Doppler echocardiography, were included as covariates in cross-sectional analyses. LV mass was calculated using the area-length method and indexed to height$^{2.7}$.[9] LVH was defined as LV mass/height$^{2.7}$ $\geq$ 47 g/m$^{2.7}$ in women and $\geq$ 50 g/m$^{2.7}$ in men.[10] LV end-diastolic and end-systolic volumes (EDV and ESV, respectively) were calculated using the modified biplane method and ejection fraction (EF) was calculated as: (EDV – ESV)/EDV. LV systolic dysfunction was defined as an EF < 0.45.[11–14] 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.[15] Since one 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 pre-specified cut-points[3]. In addition, KCCQ score was dichotomized at the clinically relevant cutoff 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 chi-square 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 one year period following 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 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

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adjusted the model by including LVH 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 heart failure, a score >75 has been used to define good health status, and ≤ 75 as clinically significant HF symptoms[16–18]. 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 1visit, follow-up KCCQ data were missing for 2.1%. Participants were censored upon 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, 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 due to 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 (Supplemental Table).

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±standard deviation (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 (OR 2.56 (1.92 – 3.44); p<0.001) and fully adjusted models (1.88 (1.30 – 2.70); p=0.001). 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 and 2.27 per log KCCQ decrease (1.67 – 3.22); p<0.001). The unadjusted associations for each

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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% C.I. 1.17 – 1.29; p<0.001); physical limitation (OR 1.26 per 10 KCCQ points (95% C.I. 1.21 – 1.32; p<0.001); quality of life (OR 1.20 per 10 KCCQ points (95% C.I. 1.14 – 1.26; p<0.001).

Discussion

In patients with CKD, we found that heart failure 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 pre-clinical HF symptoms with near-term risk of HF hospitalization in the setting of CKD.

While CKD is a strong and independent predictor of incident HF[19], 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 prior self-reported diagnosis of HF[3]. 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[18, 20], comparing and correlating the KCCQ score with natriuretic peptide concentrations and left ventricular ejection fraction, [21, 22] and used it as an outcome [23]. The KCCQ has recently been validated to monitor health-related quality of life in patients with severe aortic stenosis and New York Heart Association (NYHA) class II-IV symptoms undergoing transcatheter aortic valve replacement[24, 25]. 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[18, 26]. 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 CKD patients 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 an approximately 7-fold risk of hospitalization for HF in unadjusted analyses may be more relevant to the evaluation of risk than the epidemiologic finding of a 3.3-fold risk in the fully adjusted model. Therefore, in this high-risk population, screening for symptoms characteristic of HF

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may provide an opportunity for early diagnostic and therapeutic interventions to prevent acute HF leading to hospitalization.

We had reported previously strong associations of NT-proBNP and TnT with LVH in the CRIC study [27, 28]. In the current 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 CKD patients. 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.

Though distinguishing heart failure from volume overload due to 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 ESRD, were eliminated from the cohort upon 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 or may not 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 CKD patients 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.

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Supplementary Material

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Table 1

Baseline characteristics of Chronic Renal Insufficiency Cohort participants without chronic heart failure by quartile of Initial Kansas City Cardiomyopathy Questionnaire (KCCQ) Score*

Quartile	I (N=779)	II (N=813)	III (N=766)	IV (N=735)	P Value
KCCQ Score	**≤74.5**	**74.6–91.7**	**91.8–99.0**	**>99**	
Age (years)	60 (10)	60 (10)	60 (12)	58 (11)	0.001
Female	55%	47%	42%	35%	<0.001
Race					<0.001
Non-Hispanic White	32%	40%	53%	56%	
Non-Hispanic Black	51%	45%	32%	29%	
Hispanic	13%	12%	10%	10%	
Other	4%	3%	5%	6%	
Diabetes mellitus	61%	52%	39%	33%	<0.001
Current Smoker	18%	13%	10%	8%	<0.001
Current Alcohol Use	42%	56%	67%	70%	<0.001
Cardiovascular Disease**	41%	32%	22%	16%	<0.001
Body Mass Index (kg/m^2)	35.4 (8.9)	32.2 (7.4)	30.2 (6.3)	29.2 (5.6)	<0.001
Systolic Blood Pressure (mmHg)	130 (23)	129 (22)	125 (20)	122 (19)	<0.001
Diastolic Blood Pressure (mmHg)	70 (14)	70 (14)	70 (12)	71 (11)	0.60
eGFR ($mL/min/1.73m^2$)	39.2 (16.0)	40.9 (16.4)	44.3(16.3)	50.1 (16.8)	<0.001
24-hour Urine Protein (g/24hrs.)	1.2 (2.2)	1.0 (2.1)	0.7 (1.5)	0.6(1.4)	<0.001
Hemoglobin (g/dL)	12.3 (1.8)	12.6 (1.8)	13.1 (1.7)	13.5 (1.6)	<0.001
Low-density lipoprotein (mg/dL)	100 (37)	100 (35)	100 (34)	102 (32)	0.36
High-density lipoprotein (mg/dL)	47 (15)	49 (16)	50 (16)	50 (16)	<0.001
NT-proBNP (pg/mL)†	163 (71, 415)	152 (69, 375)	119 (58, 273)	79 (36, 179)	<0.001
Troponin T (pg/mL)†	13 (6, 24)	12 (6, 23)	10 (5, 19)	8 (4, 16)	<0.001

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

**Cardiovascular disease was defined as a self-reported history of coronary artery disease, myocardial infarction or stroke.

†Reported as Median (Interquartile Range)

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

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Table 2

Left ventricular structure and function of Chronic Renal Insufficiency Cohort participants without chronic heart failure by quartile of Kansas City Cardiomyopathy Questionnaire (KCCQ)*

Quartile	I (N=779)	II (N=813)	III (N=766)	IV (N=735)	P Value
KCCQ Score	**≤74.5**	**74.6–91.7**	**91.8–99.0**	**>99.0**	
LV mass index ($g/m^{2.7}$)	55 (14)	51 (13)	48 (12)	46 (12)	<0.001
LVH**	66%	51%	41%	32%	<0.001
LVEF (%)	55 (7)	55 (8)	55 (7)	55 (7)	0.68
LV systolic dysfunction***	7%	10%	6%	6%	0.11
LV diastolic dysfunction****	46%	42%	40%	39%	0.16

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

** Left ventricular hypertrophy was defined as LV mass/height$^{2.7}$ ≥ 47 $g/m^{2.7}$ for women and ≥ 50 $g/m^{2.7}$ for men

*** Systolic dysfunction was defined as ejection fraction <45%.

**** Diastolic dysfunction was defined as mild to severely abnormal.

Abbreviations: KCCQ: Kansas City Cardiomyopathy Questionnaire; LV: left ventricular; LVH: left ventricular hypertrophy; LVEF: left ventricular ejection fraction.

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Table 3

Incidence of Heart Failure by Quartiles of Year 1 KCCQ Score

Initial KCCQ Score Quartile	Person-Years at Risk	Events (N)	Event Rate (per 100 person-years)	95% C.I. of Event Rate
I (≤74.5)	3083	81	2.63	2.12 – 3.26
II (74.6–91.7)	3395	63	1.86	1.45 – 2.36
III (91.8–99.0)	3421	39	1.14	0.83 – 1.56
IV (>99.0)	3359	25	0.74	0.50 – 1.10

Abbreviations: KCCQ: Kansas City Cardiomyopathy Questionnaire; C.I.: confidence interval

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Table 4

Association of time-updated Kansas City Cardiomyopathy Questionnaire (KCCQ) score with incident heart failure in the following year

KCCQ Score	≤74.5		74.6–91.7		91.8–99.0		>99
	OR (95% CI)	p	OR (95% CI)	P	OR (95% CI)	P	
Unadjusted	6.77 (3.75 – 12.23)	<0.001	4.54 (2.49 – 8.28)	<0.001	1.68 (0.86 – 3.30)	0.13	ref
Demographic Variables*	6.17 (3.40 – 11.18)	<0.001	3.99 (2.18 – 7.31)	<0.001	1.53 (0.78 – 3.01)	0.22	ref
Clinical Variables**	3.67 (1.90 – 7.10)	<0.001	2.64 (1.37 – 5.07)	0.004	1.35 (0.66 – 2.77)	0.41	ref
Clinical Variables and NTproBNP***	3.69 (1.88 – 7.27)	<0.001	2.67 (1.37 – 5.21)	0.004	1.42 (0.68 – 2.95)	0.35	ref
Clinical Variables, NT-proBNP, LVH, and LV systolic dysfunction****	3.30 (1.66 – 6.52)	0.001	2.18 (1.11 – 4.29)	0.02	1.23 (0.58 – 2.61)	0.58	ref

* Adjusted for age, sex, ethnicity and site.

** Adjusted for age, sex, ethnicity, site, diabetes status, history of cardiovascular disease, current smoking, alcohol use, 24-hour 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

Abbreviations: KCCQ: Kansas City Cardiomyopathy Questionnaire; NT-proBNP: *N*-terminal pro-brain natriuretic peptide; OR: odds ratio; CI: confidence interval; LVH: left ventricular hypertrophy; ref.: reference quartile.