ORIGINAL RESEARCH

Cardiac Biomarkers and Risk of Incident Heart Failure in Chronic Kidney Disease: The CRIC (Chronic Renal Insufficiency Cohort) Study

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***Background*—**Cardiac biomarkers may signal mechanistic pathways involved in heart failure (HF), a leading complication in chronic kidney disease. We tested the associations of NT-proBNP (N-terminal pro-B-type natriuretic peptide), high-sensitivity troponin T (hsTnT), galectin-3, growth differentiation factor-15 (GDF-15), and soluble ST2 (sST2) with incident HF in chronic kidney disease.

***Methods and Results*—**We examined adults with chronic kidney disease enrolled in a prospective, multicenter study. All biomarkers were measured at baseline. The primary outcome was incident HF. Secondary outcomes included HF with preserved ejection fraction (EF≥50%) and reduced ejection fraction (EF<50%). Cox models were used to test the association of each cardiac biomarker with HF, adjusting for demographics, kidney function, cardiovascular risk factors, and medication use. Among 3314 participants, all biomarkers, with the exception of galectin-3, were significantly associated with increased risk of incident HF (hazard ratio per SD higher concentration of log-transformed biomarker): NT-proBNP (hazard ratio, 2.07; 95% CI, 1.79–2.39); hsTnT (hazard ratio, 1.38; 95% CI, 1.21–1.56); GDF-15 (hazard ratio, 1.44; 95% CI, 1.26–1.66) and sST2 (hazard ratio, 1.19; 95% CI, 1.05–1.35). Higher NT-proBNP, hsTnT, and GDF-15 were also associated with a greater risk of HF with reduced EF; while higher NT-proBNP GDF-15 and sST2 were associated with HF with preserved EF. Galectin-3 was not associated with either HF with reduced EF or HF with preserved EF.

***Conclusions*—**In chronic kidney disease, elevations of NT-proBNP, hsTnT, GDF-15, sST2 were associated with incident HF. There was a borderline association of galectin-3 with incident HF. NT-proBNP and hsTnT were more strongly associated with HF with reduced EF, while the associations of the newer biomarkers GDF-15 and sST2 were stronger for HF with preserved EF. **(*J Am Heart Assoc*. 2019;8:e012336 DOI: 10.1161/JAHA.119.012336.)**

Key Words: cardiac biomarkers • chronic kidney disease • heart failure

Heart failure (HF) is a leading cardiovascular complication among patients with chronic kidney disease (CKD) and is associated with greater risks of death, recurrent hospitalizations, and worse health-related quality of life.[1–6] Mitigating the high risk of HF in the setting of CKD is thus a high priority and could be facilitated by identification of pathways involved in the pathogenesis of HF and by distinguishing high-risk patients early in the course of disease to guide implementation and development of new therapies.

Cardiac biomarkers have shown great promise to identify patients at high-risk for HF and could signal potential mechanistic pathways. Two clinically available cardiac biomarkers, high sensitivity troponin T (hsTnT) and NT-proBNP (N-terminal pro-B-type natriuretic peptide), have been shown to predict HF in the general population.[7,8] NT-proBNP is secreted from cardiac myocytes in response to myocardial stretch from pressure or volume overload,[9] and levels increase with increasing left ventricular mass.[10–12] Concentrations of hsTnT rise in response to myocardial injury or myocardial remodeling or left ventricular hypertrophy.[13,14]

In addition, inflammation, cardiac remodeling and fibrosis are potentially important pathways in the pathogenesis of HF.

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Accompanying Tables S1–S8 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012336

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Clinical Perspective

What Is New?

- In patients with moderate to severe chronic kidney disease, elevations of N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin T, growth differentiation factor-15, soluble ST2, and galectin-3 were associated with incident heart failure and the strengths of these associations differed by heart failure subtype and duration of follow-up.

What Are the Clinical Implications?

- Further investigation of pathways reflected by circulating biomarkers may help guide development of heart failure therapies in people with chronic kidney disease.

While there are numerous candidate biomarkers that may reflect alterations in these biological pathways, galectin-3, growth differentiation factor-15 (GDF-15), and soluble ST2 (sST2) have emerged as some of the strongest predictors of cardiovascular events in the general population, and 2 (galectin-3 and sST2) of these biomarkers have been approved by the US Food and Drug Administration for clinical use in risk-stratifying patients with established HF.[15] Galectin-3 belongs to the β-galactoside–binding protein family and is both proinflammatory and profibrotic in cardiomyocytes.[16,17] GDF-15 is a member of the transforming growth factor-β cytokine family[18,19] and plays a role in cardiomyocyte repair.[20] ST2 is a member of the interleukin-1 receptor family. It has 2 forms, sST2 and transmembrane ST-2 (ST2L). ST2 is a marker of cardiac stress that is upregulated with myocyte stretch similar to BNP. In the general population and in patients with known heart disease, higher concentrations of galectin-3, GDF-15, and sST2 have been strongly associated with all-cause death and cardiovascular events independent of traditional biomarkers and other risk factors.[21–36]

The pathophysiology of HF is unique in people with CKD in part due to novel CKD-specific risk factors and metabolic effects of decreased clearance[37–39]; thus, the association of these biomarkers with HF may differ in people with CKD. We previously observed strong associations of NT-proBNP, hsTnT, and GDF-15, but not galectin-3 and sST2, with risk of incident HF in populations of CKD patients.[37,40–44] However, these previous studies were limited by multiple factors that may influence the findings, including relatively small sample sizes, limited follow-up, inability to examine the cardiac biomarkers simultaneously, and no data on subtype of HF based on left ventricular ejection fraction (EF).

To address these limitations, we performed a prospective study of over 3000 well-characterized CKD patients to test the associations of 5 cardiac biomarkers measured concurrently (NT-proBNP, hsTnT, galectin-3, GDF-15, and sST2) with risk of incident HF, incident HF with preserved EF (HFpEF) and incident HF with reduced EF (HFrEF).

Methods

Study Population

We studied adults with mild to moderate CKD at entry in the CRIC (Chronic Renal Insufficiency Cohort) study.[45] A total of 3939 participants were enrolled into the CRIC study between June 2003 and August 2008 at 7 clinical centers across the United States (Ann Arbor/Detroit, MI; Baltimore, MD; Chicago, IL; Cleveland, OH; New Orleans, LA; Philadelphia, PA; and Oakland, CA). Details on study design and baseline characteristics of the participants were previously published.[46,47] All study participants provided written informed consent, and the study protocol was approved by institutional review boards at each of the participating sites. Inclusion and exclusion criteria have been previously described.[46] Institutional review board approval at each participating site was obtained.

For the present analysis, we excluded participants with diagnosed HF at study entry (on the basis of self-report), those without blood available at baseline to perform our biomarker measures of interest, and those who were not able to have all 5 cardiac biomarkers measured concurrently. After applying these exclusions, 3314 participants were eligible for analysis.

Data generated from this ancillary study will be made publicly available through the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository.[45]

Cardiac Biomarkers

Galectin-3, GDF-15, and sST2 were measured from EDTA plasma stored at −70°C from samples at baseline in batch at the University of Pennsylvania Laboratory. All assays were measured in duplicate. Galectin-3, GDF-15, and sST2 were measured using ELISA (R&D Systems, Minneapolis, MN) and had intra-assay coefficients of variation of 4.0%, 2.0%, and 2.6%, respectively.

HsTnT and NT-proBNP were measured at the University of Maryland at baseline in 2008 from EDTA plasma stored at −70°C using a chemilluminescent microparticle immunoassay (www.roche-diagnostics.us, Basel, Switzerland) on the ElecSys 2010. HsTnT was measured using the highly sensitive assay with a range of values from 3 to 10 000 ng/mL.[48] Any values below the lower limit of blank were characterized as "undetectable." The coefficient of variation was 6.0% at a level of 26 ng/mL and 5.4% at 2140 ng/mL. The value at the 99th percentile cutoff from a healthy reference population was 13 ng/mL for hsTnT with a 10% coefficient of variation.[48] The range of values for NT-proBNP was from 5 to 35 000 pg/mL, and the coefficient of variation was 9.3% at a level of 126 pg/mL and 5.5% at 4319 pg/mL.

In 2017, we remeasured a subset of 100 baseline NT-proBNP and hsTnT samples at the University of Maryland. The new measurements in 2017 were performed on the Roche

E601. We developed and applied a Deming regression to calibrate the 2008 baseline NT-proBNP measures with the 2017 NT-proBNP measures. Similarly, for hsTnT, we remeasured any baseline hsTnT measure with a value <3 ng/mL using a newer, more sensitive assay.

Incident Heart Failure

The primary outcome was incident HF from study entry through May 2014. HF was identified by asking study participants biannually if they were hospitalized and reviewing electronic health records from selected hospitals or healthcare delivery systems. 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 and deaths 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. Deaths were identified from report by next of kin, retrieval of death certificates or obituaries, review of hospital records, and through the Social Security Death Master File.

In secondary analyses, we separately evaluated incident HFpEF and HFrEF. HFpEF was defined as EF ≥50%, and HFrEF was defined as EF <50%. EF was ascertained from *clinical* echocardiograms performed during the index hospitalization for clinical purposes. If an echocardiogram was not performed during the index hospitalization, we used the EF quantified from an ambulatory CRIC research echocardiogram up to 1 year before or after the index HF hospitalization. Research echocardiograms in CRIC were performed at multiple time points including years 1, 4, and 7 as well as when the participant progressed to estimated glomerular filtration rate (eGFR) <20 mL/min per 1.73 m^2. Our previous work has shown that EF in CRIC is mostly stable over time.[49,50] Among participants with incident HF, 356 of 477 (75%) had EF available through either a clinical echocardiogram during the index hospitalization (261 participants [73%]) or a CRIC research echocardiogram (95 participants [27%]). When we compared participants who did versus did not have EF available, we found few differences (Table S1).

Covariates

At the baseline visit, participants provided information on their sociodemographic characteristics, medical history, medication usage, and lifestyle behaviors. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other. History of cardiovascular disease was determined by self-report. Alcohol use was dichotomized as none versus any in the past 12 months. Anthropometric measurements and blood pressure were assessed using standard protocols.[51] Body mass index was derived as weight in kilograms divided by height in meters squared. Serum creatinine was measured using an enzymatic method on an Ortho Vitros 950 (Raritan, NJ) at the CRIC Central Laboratory and standardized to isotope dilution mass spectrometry–traceable values.[52,53] Additional assays measured serum phosphorus, 24-hour urine total protein, glucose, low-density lipoprotein cholesterol (mathematically derived), high-density lipoprotein cholesterol, fibroblast growth factor-23, and total parathyroid hormone. The aforementioned assays were performed at the Central Laboratory with the exception of parathyroid hormone (measured at Scantibodies Laboratory Inc.), and hemoglobin (locally measured). Diabetes mellitus was defined as a fasting glucose >126 mg/dL, a nonfasting glucose >200 mg/dL, or use of insulin or other antidiabetic medication. eGFR was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.[54]

Research echocardiograms were performed 1 year and 4 years after enrollment and provided data on left ventricular EF, left ventricular mass index, and left ventricular hypertrophy.[55] Cardiac structure and function were assessed as previously described.[56,57] In brief, assessments were performed using 2-dimensional images and a standard imaging protocol according to American Society of Echocardiography guidelines,[58] and quantified centrally by a highly trained registered diagnostic cardiac sonographer.

Statistical Analysis

Summary statistics and distributions of galectin-3, NT-proBNP, hsTnT, GDF-15, and sST2 were generated. Study variables were described overall and across categories of hsTnT (category 1: undetectable values [≤10 ng/mL]; categories 2–5: tertiles of detectable values) and quintiles for galectin-3, NT-proBNP, GDF-15, and sST2 using standard measures.

Crude incident HF event rates were calculated across categories of each biomarker as specified above. Cumulative incidence curves for HF were generated across categories of each biomarker. Cox proportional hazards models were fit for HF, and follow-up was censored at the end of administrative follow-up, loss to follow-up, or death, whichever occurred first. We performed a series of nested Cox proportional hazard models with sequential adjustment for potential confounders as follows. Model 1 adjusted for demographic factors including age, sex, race/ethnicity, and traditional cardiovascular risk factors including diabetes mellitus status, self-reported cardiovascular disease at baseline, current smoking, 24-hour urine total protein excretion, eGFR, systolic blood pressure, body

mass index, low-density lipoprotein, and high-density lipoprotein levels. Model 2 included the factors in Model 1 as well as pertinent medication use and mineral metabolism markers: use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, and β-blockers; and serum phosphorus, parathyroid hormone, and fibroblast growth factor-23 levels. Missing covariates were multiply imputed using chained equations.[59] The multiple analyses over the imputations were combined using Rubin's rules to account for the variability in the imputation procedure.[60]

We tested the proportional hazards assumption[61]and found a significant violation of the assumption in unadjusted models of 2 of 5 cardiac biomarkers (GDF-15, P=0.02; and Galectin-3, P=0.0008) with incident HF. Therefore, in a sensitivity analysis, we examined the Schoenfeld residuals plots and chose to examine whether the association of the cardiac biomarkers and risk of HF differed during years 0 to 4 and after 4 years based on examination of these plots.

We tested for interaction by baseline eGFR in Model 2 for all 5 cardiac biomarkers. If the P value for interaction was <0.05, we performed stratified analyses by eGFR category.

Two exploratory analyses were performed. The first additional analysis adjusted for the other 4 cardiac biomarkers of interest to evaluate whether the observed associations were independent of each other or involved potentially shared biological pathways. The second analysis adjusted for year 1 EF and left ventricular mass index among the 2299 participants who had a year 1 echocardiogram performed. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

We also performed a secondary analysis in which we examined HFrEF and HFpEF as separate outcomes. EF was quantified either during the index HF hospitalization or a CRIC echocardiogram within 1 year of the index HF hospitalization in 75% of total incident HF participants. If EF was not available, participants were assumed to not have experienced the event and were censored at their follow-up time.

All analyses were performed using R 3.4.0 (R Foundation for Computing, Vienna, Austria).

Results

Characteristics of the Study Population

Overall, among 3314 eligible participants, the mean age was 58 years, 46% were women, and 39% were black. The mean eGFR was 45 mL/min per 1.73 m^2, with a median protein excretion of 0.1 g/24 h (Table 1). Across quintiles of baseline galectin-3, those with higher levels were more likely to be older, have lower eGFR and higher urine protein, have a higher burden of comorbidity including cardiovascular disease, and be using medications such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, and β-blockers (Table 1). Similar patterns were seen across levels of NT-proBNP, hsTnT, GDF-15, and sST2 (Tables S2 through S5).

Association of Cardiac Biomarkers With Risk of Incident HF

There were 477 incident HF events over a median (Q1–Q3) follow-up of 7.9 (5.0–9.3) years. The rate of incident HF increased across higher categories of each of the 5 cardiac biomarkers (Figure 1). The adjusted cumulative incidence of HF varied most across categories of NT-proBNP, hsTnT, and GDF-15 (Figure 2). In models adjusted for demographics, comorbidity, kidney function, blood pressure, body mass index, and cholesterol, all 5 cardiac biomarkers were significantly associated with risk of incident HF, with the strongest gradient in risk observed for NT-proBNP. When further adjusted for baseline receipt of cardiovascular medications and markers of mineral metabolism, galectin-3 was no longer significantly associated with incident HF (Table 2). The associations remained statistically significant and strong for log-transformed NT-proBNP (hazard ratio [HR], 2.07; 95% CI, 1.79–2.39), hsTnT (HR, 1.38; 95% CI, 1.21–1.56), GDF-15 (HR, 1.44; 95% CI, 1.26–1.66), and sST2 (HR, 1.19; 95% CI, 1.05–1.35) per SD higher concentration. The association of galectin-3 with incident HF showed a borderline association. When modeled in categories, there was a strong graded association between higher levels of NT-proBNP, hsTnT, GDF-15, and sST2 with incident HF, with the highest categories being associated with 2- to 8-fold higher risk of incident HF (Table 2).

Interaction by eGFR

The P values for interaction of each cardiac biomarker with continuous baseline eGFR were as follows: NT-proBNP (P=0.8), hsTnT (P=0.003), galectin-3 (P=0.98), sST2 (P=0.15), and GDF-15 (P=0.84). Since the interaction of hsTnT with eGFR was statistically significant, we performed stratified analyses to test the association of hsTnT with incident HF across eGFR categories (Table S6). In these analyses, the association of hsTnT with incident HF was stronger among participants with higher eGFR.

Analyses Combining All Biomarkers

In additional analyses, we adjusted for each of the alternative cardiac biomarkers to test whether the observed associations were independent of each other. In these analyses, neither galectin-3 nor sST2 were statistically significant. However, the associations of NT-proBNP, hsTnT, and GDF-15 were only mildly attenuated and remained statistically significant (Table 3).

Table 1. Baseline Characteristics by Quintile of Baseline Galectin-3 Level (N=3314)

	Overall	≤9.24	9.25–12.4	12.5–15.7	15.8–20.5	>20.5
N	3314	663	663	662	663	663
Age, y	57.5±11.1	55.6±11.4	57.3±11.8	57.4±10.8	58.4±11.0	59.0±10.4
Women	1520 (46)	228 (34)	275 (41)	308 (47)	331 (50)	378 (57)
Race/ethnicity						
Non-Hispanic white	1439 (43)	380 (57)	336 (51)	286 (43)	233 (35)	204 (31)
Non-Hispanic black	1304 (39)	215 (32)	234 (35)	264 (40)	290 (44)	301 (45)
Hispanic	433 (13)	40 (6)	64 (10)	85 (13)	112 (17)	132 (20)
Other	138 (4)	28 (4)	29 (4)	27 (4)	28 (4)	26 (4)
Estimated glomerular filtration rate, mL/min per 1.73 m^2	44.7±14.8	53.4±14.7	48.6±14.3	44.9±13.6	40.7±12.2	36.1±12.9
24-h urine protein (g/d), median (Q1–Q3)	0.1 (0.1-–0.7)	0.1 (0.0–0.3)	0.1 (0.0–0.5)	0.1 (0.1–0.7)	0.2 (0.1–0.9)	0.4 (0.1–1.8)
Diabetes mellitus	1542 (47)	223 (34)	234 (35)	311 (47)	352 (53)	422 (64)
History of cardiovascular disease	859 (26)	130 (20)	148 (22)	175 (26)	188 (28)	218 (33)
History of atrial fibrillation	443 (13)	76 (11)	99 (15)	77 (12)	97 (15)	94 (14)
Current smoker	416 (13)	57 (9)	72 (11)	104 (16)	84 (13)	99 (15)
Alcohol use	2134 (64)	502 (76)	462 (70)	419 (63)	383 (58)	368 (56)
Body mass index, kg/m^2	31.9±7.7	30.5±6.8	31.2±7.2	31.8±7.3	32.6±8.3	33.5±8.6
Systolic blood pressure, mm Hg	128.6±22.0	122.9±19.0	127.1±21.0	127.2±22.0	131.7±23.3	134.0±22.6
Diastolic blood pressure, mm Hg	71.9±12.6	72.8±12.1	71.8±12.1	71.9±12.3	72.0±13.6	70.9±12.8
Hemoglobin, g/dL	12.6±1.7	13.4±1.6	13.0±1.7	12.6±1.6	12.3±1.6	11.7±1.7
LDL cholesterol, mg/dL	104.1±35.1	104.5±32.7	106.0±33.8	104.6±33.7	102.4±37.0	102.7±38.0
HDL cholesterol, mg/dL	48.1±15.6	48.4±15.3	48.0±15.6	48.1±15.9	48.2±15.1	47.7±16.3
ACEi/ARB	2234 (67)	408 (62)	439 (66)	453 (68)	458 (69)	476 (72)
Diuretics	1859 (56)	286 (43)	345 (52)	367 (55)	405 (61)	456 (69)
β-blockers	1524 (46)	251 (38)	296 (45)	299 (45)	337 (51)	341 (51)
Fibroblast growth factor-23 (RU/mL), median (Q1–Q3)	138.8 (94.0–220.9)	100.4 (73.1–150.0)	125.0 (84.6–185.0)	138.7 (95.1–204.6)	156.8 (106.7–253.8)	202.0 (127.7–333.6)
Serum phosphorus, mg/dL	3.7±0.7	3.5±0.6	3.6±0.6	3.7±0.6	3.8±0.7	4.0±0.7
Total parathyroid hormone (pg/mL), median (Q1–Q3)	52.0 (34.0–84.7)	39.5 (29.0–60.0)	45.0 (31.4–71.5)	51.0 (34.2–81.0)	59.0 (38.7–92.4)	75.0 (46.0–131.2)

Entries are mean±SD or N (%), except as noted. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Association of Cardiac Biomarkers With Risk of Incident HF, Adjusted for Left Ventricular Structure and Function

In another analysis, we adjusted for echocardiographic measures of left ventricular mass index and left ventricular EF prior to an incident HF event. The associations of higher NT-proBNP, hsTnT, GDF-15, and sST2 remained strong and statistically significant (Table 3).

Sensitivity Analysis: Allowing for Difference Effects Before and After 4 Years of Follow-Up Time

In a sensitivity analysis, we examined whether the associations of the cardiac biomarkers differed by length of follow-up time. In this analysis, the adjusted association of galectin-3 with incident HF within 4 years was statistically significant (HR, 1.38; 95% CI, 1.18–1.61), while the association after 4

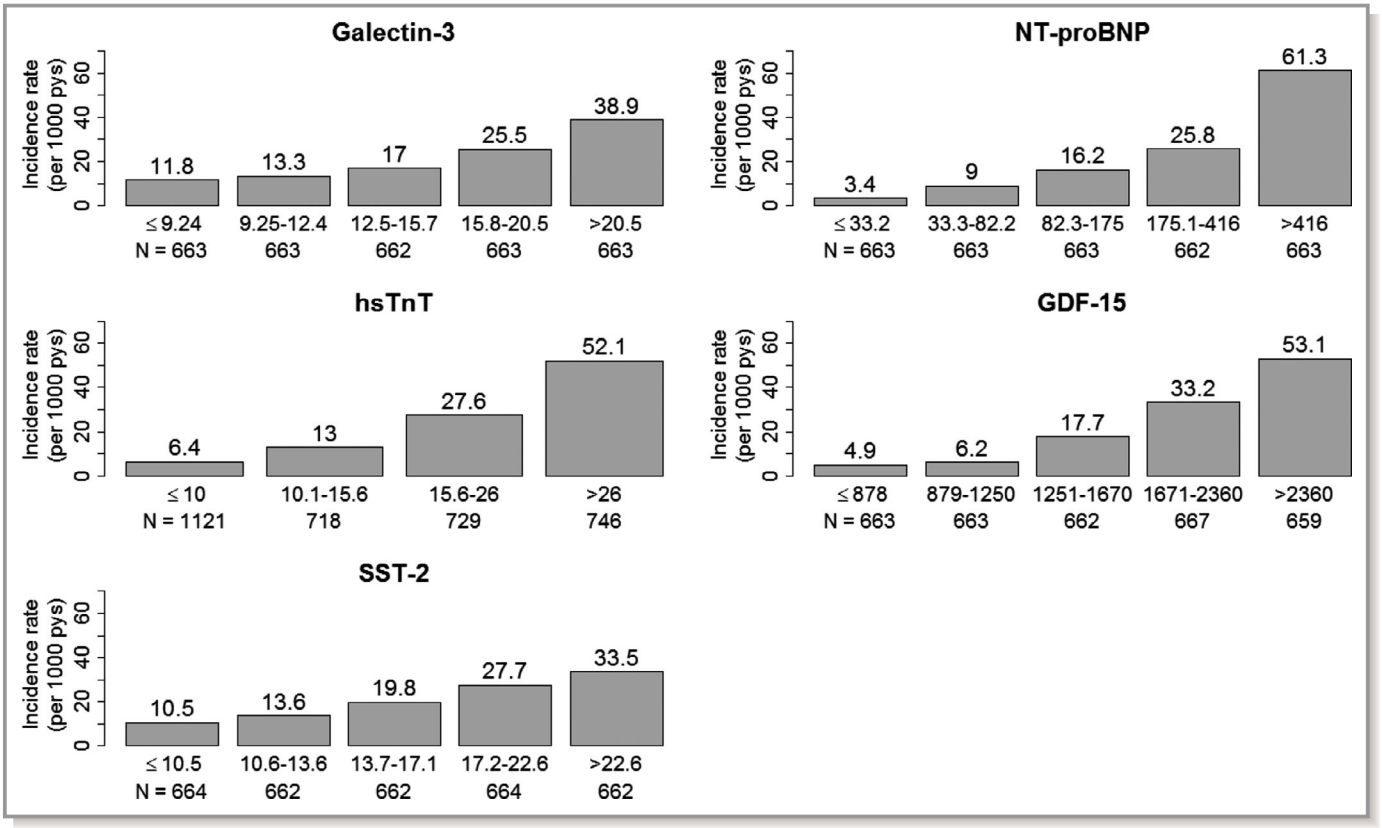

Figure 1. Unadjusted incidence rates of heart failure by category of cardiac biomarker in people with chronic kidney disease. GDF-15 indicates growth differentiation factor-15; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble ST2.

years of follow-up time was not significant (Table S7). The associations of the other cardiac biomarkers with incident HF ≤4 versus >4 years of follow-up time were all statistically significant but stronger for ≤4 years of follow-up time.

Secondary Analysis: Association of Cardiac Biomarkers With Risk of HFrEF and HFpEF

The overall incidence rate for HFrEF was 6.7 (95% CI, 5.6–7.8) per 1000 person-years. Higher NT-proBNP (HR, 3.01; 95% CI, 2.37–3.84), hsTnT (HR, 1.56; 95% CI, 1.26–1.93), and GDF-15 (HR, 1.34; 95% CI, 1.06–1.71) were significantly associated with greater risk of HFrEF in adjusted models (Table S8 and Figure 3). The strongest association was that seen with NT-proBNP. Neither galectin-3 nor sST2 were significantly associated with HFrEF.

The overall incidence rate of HFpEF was 8.6 (95% CI, 7.4–9.8) per 1000 person-years. Higher NT-proBNP (HR, 1.64; 95% CI, 1.32–2.04), GDF-15 (HR, 1.53; 95% CI, 1.24–1.89), and sST2 (HR, 1.27; 95% CI, 1.07–1.51) were significantly associated with greater risk of HFpEF (Table S8 and Figure 3). While the association of NT-proBNP was stronger for HFrEF compared with HFpEF, the associations of GDF-15 and sST2 were qualitatively stronger for HFpEF. Galectin-3 was not significantly associated with HFpEF.

Discussion

Among a large, well-characterized cohort of CKD participants, we found that elevated concentrations of circulating NT-proBNP, hsTnT, GDF-15, and sST2 were significantly associated with a greater risk of incident HF and remained robust with adjustment for traditional and mineral metabolism markers. Galectin-3 was significantly associated with incident HF within 4 years of follow-up time only. When we stratified by HF subtype, we found that NT-proBNP, GDF-15, and sST2 were associated with HFpEF; however, only NT-proBNP, hsTnT, and GDF-15 were associated with HFrEF. There was no association of galectin-3 with incident HF, HFrEF, or HFpEF. Our findings both support and differ from prior studies in patients with and without CKD and may identify promising pathways involved in the development of HF overall and in HFpEF and HFrEF.

Participants in the highest quartile of NT-proBNP and hsTnT had a 7-fold and 2-fold higher risk of incident HF, respectively, in this large cohort of patients with CKD. These associations were independent of cardiovascular risk factors (including

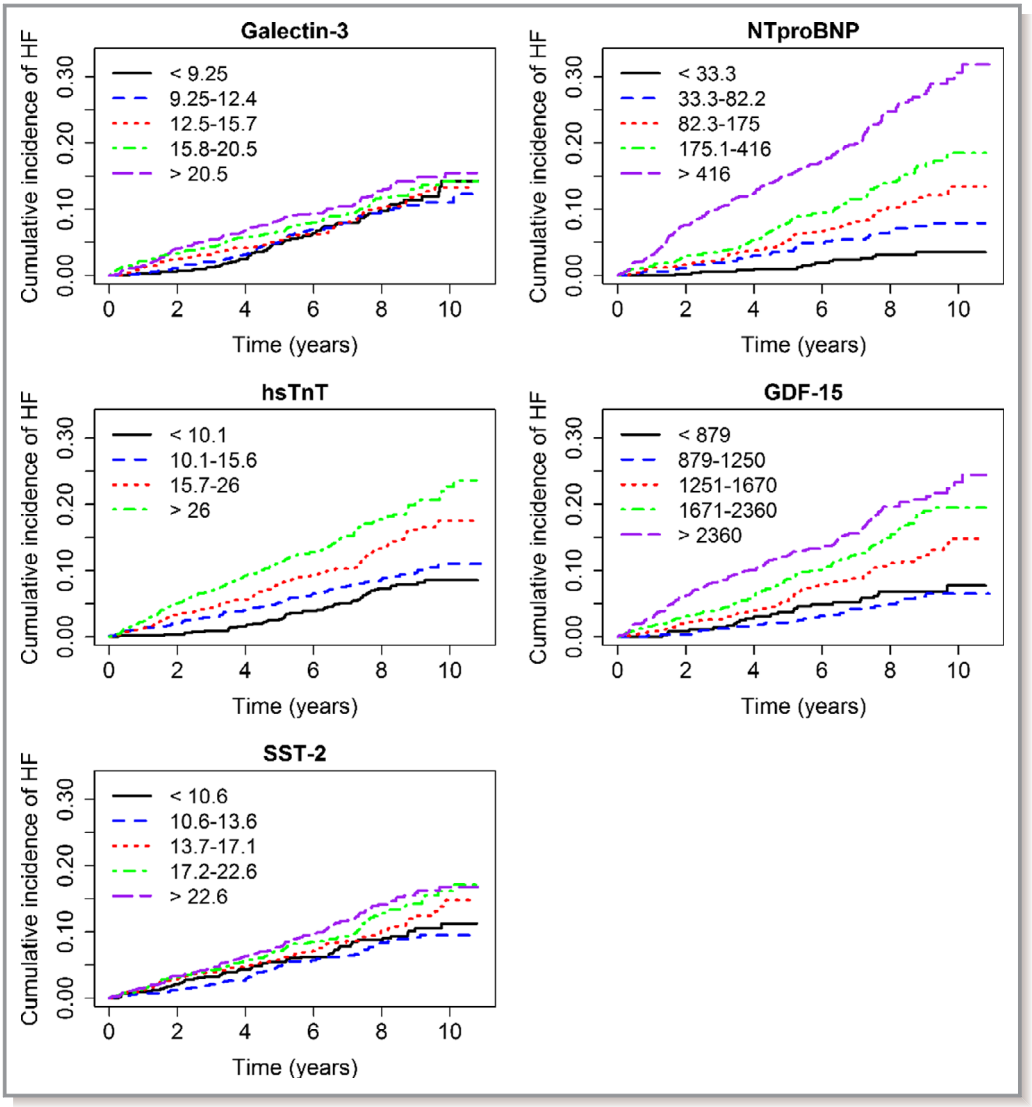

Figure 2. Cumulative incidence of heart failure in people with chronic kidney disease stratified by cardiac biomarker. Figure shows cumulative incidence for a person with mean values of all adjustment variables (age, sex, race, diabetes mellitus, cardiovascular disease, smoking, 24-hour urinary protein, estimated glomerular filtration rate, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. GDF-15 indicates growth differentiation factor-15; HF, heart failure; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble ST2.

measures of mineral metabolism) and left ventricular mass index and left ventricular EF. Patients with kidney disease often have increased NT-proBNP and hsTnT levels even in the absence of clinical heart disease, which has led to speculation on whether elevated levels are simply a reflection of decreased kidney clearance.[10,62–64] There are several possible mechanisms that may explain elevated NT-proBNP and hsTnT levels in patients with CKD including (but not limited to) previous myocardial infarction/unrecognized coronary ischemia, cardiac stress from increased filling pressures (eg, volume), ventricular fibrosis, left ventricular hypertrophy, left ventricular dilation, inflammation, endothelial dysfunction, and other (eg, nonischemic) cardiac injury.[65–68] Work from our group and others has shown that even after accounting for level of kidney function, elevations in these cardiac biomarkers likely signal early HF pathophysiology in patients with CKD.[69–73] The present study is one of the first to examine the associations of NT-proBNP and hsTnT with incident HF events while also adjusting for concurrent measurements of newer cardiac biomarkers, galectin-3, GDF-15, and sST2. In these additional analyses, the observed association of NT-proBNP and hsTnT remained strong (with NT-proBNP being the strongest of the 5 biomarkers). These findings may suggest that the pathways represented by these biomarkers are independent and complementary in early HF pathophysiology.

Table 2. Associations of Cardiac Biomarkers and Incident HF in People With CKD

Cardiac Biomarker	N at Risk (N events)	Model 1		Model 2	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value*
Continuous predictors					
Log(Galectin-3) per 1 SD (0.50) increase	3314 (477)	1.17 (1.05–1.30)	0.005	1.12 (1.00–1.24)	0.05
Log(NT-proBNP) per 1 SD (1.66) increase	3314 (477)	2.21 (1.92–2.54)	<0.0001	2.07 (1.79–2.39)	<0.0001
Log(hsTnT) per 1 SD (0.80) increase	3314 (477)	1.48 (1.31–1.68)	<0.0001	1.38 (1.21–1.56)	<0.0001
Log(GDF-15) per 1 SD (0.60) increase	3314 (477)	1.62 (1.42–1.84)	<0.0001	1.44 (1.26–1.66)	<0.0001
Log(sST2) per 1 SD (0.56) increase	3314 (477)	1.24 (1.09–1.42)	0.001	1.19 (1.05–1.35)	0.008
Categorical predictors					
Galectin-3					
Reference: ≤9.24	663 (60)				
9.25–12.4	663 (66)	0.93 (0.65–1.32)	0.06	0.89 (0.63–1.27)	0.28
12.5–15.7	662 (79)	0.97 (0.69–1.37)		0.94 (0.66–1.32)	
15.8–20.5	663 (115)	1.21 (0.87–1.67)		1.11 (0.80–1.53)	
>20.5	663 (157)	1.36 (0.98–1.88)		1.20 (0.87–1.66)	
NT-proBNP, pg/mL					
Reference: ≤33.2	663 (18)				
33.3–82.2	663 (45)	2.05 (1.19–3.54)	<0.0001	1.99 (1.15–3.43)	<0.0001
82.3–175	663 (79)	3.38 (2.02–5.67)		3.19 (1.90–5.37)	
175.1–416	662 (116)	4.67 (2.80–7.79)		4.37 (2.60–7.34)	
>416	663 (219)	8.75 (5.23–14.65)		7.61 (4.49–12.90)	
hsTnT, pg/mL					
Reference: <10	1121 (57)				
10.1–15.6	718 (70)	1.38 (0.97–1.97)	<0.0001	1.31 (0.92–1.87)	<0.0001
15.7–26	729 (135)	2.24 (1.59–3.15)		2.13 (1.52–2.99)	
>26	746 (215)	3.11 (2.16–4.48)		2.66 (1.83–3.87)	
GDF-15					
Reference: ≤878	663 (26)				
879–1250	663 (32)	0.81 (0.47–1.38)	<0.0001	0.74 (0.43–1.27)	<0.0001
1251–1670	662 (87)	1.76 (1.08–2.85)		1.54 (0.95–2.48)	
1671–2360	667 (140)	2.66 (1.61–4.40)		2.17 (1.32–3.57)	
>2360	659 (192)	3.55 (2.12–5.94)		2.71 (1.61–4.54)	
sST2					
Reference: ≤10.5	664 (53)				
10.6–13.6	662 (67)	0.98 (0.68–1.41)	0.0009	0.95 (0.66–1.38)	0.01
13.7–17.1	662 (92)	1.30 (0.91–1.84)		1.26 (0.89–1.79)	
17.2–22.6	664 (123)	1.51 (1.07–2.12)		1.43 (1.02–2.03)	
>22.6	662 (142)	1.76 (1.25–2.49)		1.57 (1.11–2.22)	

CKD indicates chronic kidney disease; GDF-15, growth differentiation factor-15; HF, heart failure; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble ST2. M1: age, sex, race, diabetes mellitus, cardiovascular disease, smoking, 24-h urinary protein, estimated glomerular filtration rate, systolic blood pressure, body mass index, LDL cholesterol, HDL cholesterol. M2: M1+use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, β-blockers, phosphate, parathyroid hormone, fibroblast growth factor-23.

**P* values for categorical exposures come from a Wald test of the null hypothesis that all categories have a hazard ratio of 1 vs at least 1 hazard ratio different from 1.

We observed an association of higher GDF-15 with risk of incident HF. The mechanisms of inflammation marked by GDF-15 have not been fully elucidated, but its expression is upregulated in tissue injury. It is unknown whether GDF-15 expression is a compensatory or putative response to injury. Recent in vivo mouse studies have shown that GDF-15 interferes with chemokine-triggered integrin activation, preventing inflammatory cell extravasation at sites of cardiac injury and subsequent inflammatory damage.[74,75] In another study, GDF-15–deficient mice developed greater infarct sizes

Table 3. Associations of Cardiac Biomarkers and Incident HF in People With CKD, Adjusted for Possible Mediators

	Adjusted Model*		Adjusted Model + Alternative Cardiac Biomarkers†		Adjusted Model + Left Ventricular Structure and Function‡	
Cardiac Biomarker	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Continuous predictors						
Log(Galectin-3) per 1 SD (0.50) increase	1.12 (1.00–1.24)	0.047	1.09 (0.98–1.21)	0.11	1.11 (1.00–1.24)	0.06
Log(NT-proBNP) per 1 SD (1.66) increase	2.07 (1.79–2.39)	<0.0001	1.99 (1.71–2.31)	<0.0001	1.88 (1.63–2.16)	<0.0001
Log(hsTnT) per 1 SD (0.80) increase	1.38 (1.21–1.56)	<0.0001	1.30 (1.14–1.48)	0.0001	1.31 (1.16–1.49)	<0.0001
Log(GDF-15) per 1 SD (0.60) increase	1.44 (1.26–1.66)	<0.0001	1.35 (1.17–1.56)	<0.0001	1.43 (1.25–1.64)	<0.0001
Log(sST2) per 1 SD (0.56) increase	1.19 (1.05–1.35)	0.008	1.13 (1.00–1.27)	0.06	1.20 (1.05–1.36)	0.006
Categorical predictors						
Galectin-3						
Reference: ≤9.24						
9.25–12.4	0.89 (0.63–1.27)	0.28	0.93 (0.66–1.31)	0.57	0.88 (0.63–1.25)	0.25
12.5–15.7	0.94 (0.66–1.32)		0.94 (0.67–1.32)		0.92 (0.66–1.29)	
15.8–20.5	1.11 (0.80–1.53)		1.10 (0.80–1.52)		1.09 (0.79–1.50)	
>20.5	1.20 (0.87–1.66)		1.15 (0.83–1.59)		1.21 (0.88–1.66)	
NT-proBNP, pg/mL						
Reference: ≤33.2						
33.3–82.2	1.99 (1.15–3.43)	<0.0001	1.99 (1.16–3.44)	<0.0001	1.89 (1.10–3.27)	<0.0001
82.3–175	3.19 (1.90–5.37)		3.15 (1.88–5.3)		2.95 (1.75–4.96)	
175.1–416	4.37 (2.60–7.34)		4.15 (2.47–6.99)		3.89 (2.31–6.54)	
>416	7.61 (4.49–12.9)		7.03 (4.12–12.00)		6.11 (3.60–10.38)	
hsTnT, pg/mL						
Reference: <10						
10.1–15.6	1.31 (0.92–1.87)	<0.0001	1.29 (0.90–1.84)	<0.0001	1.24 (0.87–1.77)	0.0001
15.7–26	2.13 (1.52–2.99)		2.05 (1.46–2.89)		1.88 (1.33–2.65)	
>26	2.66 (1.83–3.87)		2.36 (1.61–3.46)		2.24 (1.54–3.25)	
GDF-15						
Reference: ≤878						
879–1250	0.74 (0.43–1.27)	<0.0001	0.74 (0.43–1.27)	<0.0001	0.78 (0.46–1.32)	<0.0001
1251–1670	1.54 (0.95–2.48)		1.51 (0.93–2.45)		1.51 (0.94–2.42)	
1671–2360	2.17 (1.32–3.57)		2.14 (1.29–3.54)		2.16 (1.32–3.53)	
>2360	2.71 (1.61–4.54)		2.43 (1.43–4.13)		2.74 (1.65–4.54)	
sST2						
Reference: ≤10.5						
10.6–13.6	0.95 (0.66–1.38)	0.01	0.96 (0.66–1.39)	0.06	0.97 (0.67–1.41)	0.004
13.7–17.1	1.26 (0.89–1.79)		1.23 (0.86–1.76)		1.29 (0.91–1.83)	
17.2–22.6	1.43 (1.02–2.03)		1.41 (0.99–1.99)		1.53 (1.08–2.16)	
>22.6	1.57 (1.11–2.22)		1.43 (1.00–2.05)		1.63 (1.16–2.30)	

CKD indicates chronic kidney disease; GDF-15, growth differentiation factor-15; HF, heart failure; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble ST2.

*Adjusted model: age, sex, race, diabetes mellitus, cardiovascular disease, smoking, 24-h urinary protein, estimated glomerular filtration rate, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, β-blockers, phosphate, parathyroid hormone, fibroblast growth factor-23.

†Adjusted model+other biomarkers (NT proBNP, galectin-3, hsTnT, GDF-15, sST2).

‡Adjusted model+left ventricular mass index+left ventricular ejection fraction (N=2306 due to missing data).

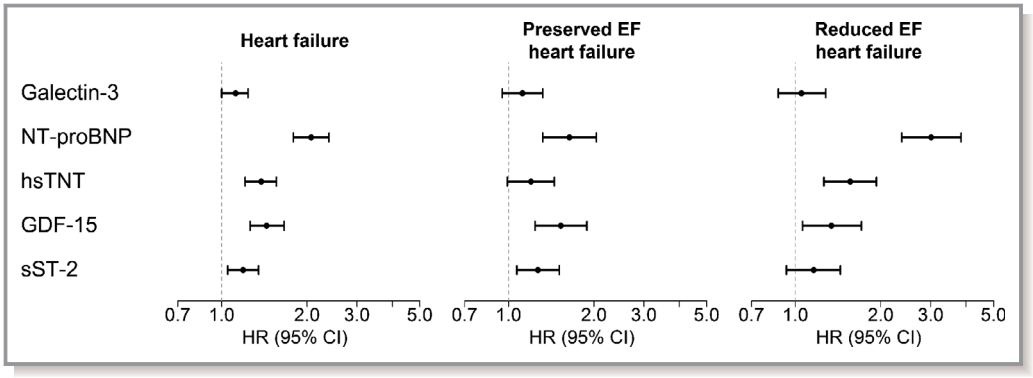

Figure 3. Multivariable associations of baseline cardiac biomarkers with any incident heart failure, heart failure with preserved ejection fraction, and heart failure with reduced ejection fraction in people with chronic kidney disease. Associations come from a model of continuous biomarkers that adjusted for age, sex, race/ethnicity, diabetes mellitus, cardiovascular disease, smoking, 24-hour urinary protein, estimated glomerular filtration rate, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, β-blockers, phosphate, parathyroid hormone, fibroblast growth factor-23. Associations are per SD of the log-transformed biomarker. EF indicates ejection fraction; GDF-15, growth differentiation factor-15; HR, hazard ratio; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble ST2.

and displayed more cardiomyocyte apoptosis in the infarct border zone, suggesting that endogenous GDF-15 limits myocardial damage in vivo.[20] Clinical studies of patients without CKD have reported associations of higher GDF-15 with HF and HF severity as measured by New York Heart Association class and recurrent hospitalizations.[21,23,25–28] Our previous study of 2 CKD cohorts also reported a similar association of elevated GDF-15 with risk of HF[41]; however, in that previous study, we were not able to specifically examine incident HF as in the present analyses. The other limitation of the prior study was its smaller sample size and inability to control for potential important confounders such as left ventricular mass and systolic function, and mineral metabolism measures. Also, in the present study, adjustment for other important cardiac biomarkers such as NT-proBNP and hsTnT did not attenuate the observed associations of GDF-15 with excess HF risk. Thus, elevations of GDF-15 may signal early HF physiology and help identify patients with CKD at highest risk for HF, particularly for HFpEF.

There was a modest but statistically significant association of sST2 with risk of incident HF in our cohort. ST-2 has 2 forms, sST2 and ST2L. Mechanistically, ST2L binds ligand interleukin-33 and provides cardioprotection in vivo. The interaction of ST2L/interleukin-33 reduces cardiomyocyte apoptosis and prevents the adverse cardiac remodeling seen after cardiac ischemia.[76] The soluble form of ST2, however, acts as a decoy and disrupts binding of ST2L and interleukin-33, preventing its cardioprotective effects.[77] sST2 has been approved by the US Food and Drug Administration for use clinically for risk stratification in patients with known HF.[78] sST2 has also been previously studied in the general population, where it is associated with all-cause death, HF severity, and adverse HF-related outcomes.[41,79–86] Our previous study of CKD patients did not find an association of sST2 with HF; however, it may have been underpowered to detect an association in contrast to the current study. In this study, we did find that the association of sST2 with incident HF was attenuated when adjusted for the other cardiac biomarkers of interest, suggesting that there may be shared biological pathways as represented by sST2 and the other biomarkers of interest.

We found only a borderline association of galectin-3 with incident HF overall and a statistically significant association with HF within 4 years of follow-up time. At the molecular level, galectin-3 crosslinks with glycoproteins to promote cell-cell and cell-matrix interactions, ultimately leading to fibrosis and extracellular matrix stiffening.[87] In the heart, galectin-3 is highly expressed by cardiac macrophages and promotes cardiac fibrosis.[88] Similarly, galectin-3 is also present in the kidney, where it promotes tubulointerstitial fibrosis,[87] and its levels rise with advancing CKD.[36] Previous studies of galectin-3 in patients with normal kidney function have shown that higher galectin-3 levels strongly predict all-cause mortality[89,90] and HF.[91–95] In response to these studies, the US Food and Drug Administration approved clinical galectin-3 testing to aid in prognosis for patients with HF in 2010.[96] However, few studies have examined the association of galectin-3 with clinical outcomes in patients with CKD, where the pathophysiology of cardiovascular complications may differ. Our previous study of patients with CKD reported an association of galectin-3 with death.[41] Similarly, a study of the LURIC (Ludwigshafen Risk and Cardiovascular Health study) and 4D (Die Deutsche Diabetes Dialyse Studie) cohorts found

a statistically significant increase in combined cardiovascular end points (sudden cardiac death, myocardial infarction, stroke, and death attributable to HF in hospitalized patients) among those with CKD and end-stage renal disease and elevated galectin-3.[36] Similar to the findings of the present analysis, another study reported that the prognostic value of galectin-3 for cardiovascular disease was attenuated after adjusting for eGFR.[97] Our findings are interesting, particularly in the context of the strong body of literature that supports the use of galectin-3 to risk stratify HF risk in the general population. Our data suggest that elevations in galectin-3 may better reflect short-term risk of HF. Our findings may lend further support to the framework that mechanisms for HF development in the setting of CKD are more distinct than those seen in other populations.

We stratified by subtype of HF and found that the associations of the traditional cardiac biomarkers (NT-proBNP and hsTnT) were stronger for HFrEF, while those observed for the newer cardiac biomarkers (sST2 and GDF-15) were stronger for HFpEF. Galectin-3 was not significantly associated with either HFpEF or HFrEF. Prior studies of the general population have reported similar findings, where NT-proBNP more strongly predicts HFrEF while GDF-15 predicts HFpEF.[98,99] However, in contrast to our findings, previous work has reported that galectin-3 and not sST2 predicted HFpEF.[100] Our findings support that HFpEF and HFrEF likely involve different mechanisms, which is also evidenced by differing responses to "standard" HF therapies in previous clinical trials. The mechanisms contributing to the development HFpEF remain more elusive, particularly in patients with certain comorbidities such as CKD. Thus, further investigation of novel pathways that may lead to elevations in GDF-15 and sST2 may guide development of novel therapeutics to reduce the incidence of HFpEF in people with CKD.

Our study had numerous strengths. We prospectively followed a racially/ethnically diverse, large population of well-characterized individuals with CKD but without known clinical HF. We adjusted for multiple possible confounding factors, including mineral metabolism markers and left ventricular hypertrophy and EF quantified from research echocardiograms. Study participants experienced a relatively large number of incident HF events. These outcomes were carefully adjudicated using a centralized process with accepted standardized clinical criteria. Our study had limitations as well. We determined HF and cardiovascular disease at baseline on the basis of self-report. Incident HF was based only on HF hospitalizations; we were not able to adjudicate incident HF diagnosed and managed only on an outpatient basis. As an observational study, we were not able to determine causality. Finally, we studied research volunteers, so our results may not be generalizable to all patients with CKD in usual clinical care.

In conclusion, among patients with CKD, elevated levels of NT-proBNP, hsTnT, GDF-15, sST2, and galectin-3 were strongly associated with incident HF; these biomarkers may indicate early, subclinical changes in cardiac structure and function that subsequently contribute to clinical HF. Many of these associations remained robust after adjustment for the alternative biomarkers, suggesting that while these biomarkers are complementary, they may represent distinct biological pathways associated with HF development. Further studies are needed to determine the potential role of these biomarkers in a comprehensive HF risk prediction and prevention strategy.

Appendix

CRIC Study Investigators

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of participants who developed incident heart failure with vs. without ejection fraction quantification (N = 477).

	Ejection fraction missing	Ejection fraction available
N	121	356
Age (years)	59.5 (10.2)	60.3 (9.6)
Women	55 (45)	150 (42)
Race/ethnicity		
Non-Hispanic white	32 (26)	127 (36)
Non-Hispanic black	57 (47)	169 (47)
Hispanic	26 (21)	50 (14)
Other	6 (5)	10 (3)
Estimated glomerular filtration rate, mL/min/1.73m^2	40.9 (14.5)	37.5 (12.6)
24-hour urine protein (g/d), median (Q1-Q3)	0.4 (0.1-2.0)	0.6 (0.1-2.3)
Diabetes mellitus	81 (67)	254 (71)
History of cardiovascular disease	49 (40)	161 (45)
History of atrial fibrillation	23 (19)	84 (24)
Current smoker	15 (12)	54 (15)
Alcohol use	57 (47)	201 (56)
Body mass index (kg/m^2)	34.2 (7.9)	33.9 (8.1)
Systolic blood pressure (mmHg)	136.1 (21.3)	137.5 (23.8)
Diastolic blood pressure (mmHg)	71.2 (13.7)	70.8 (13.9)
Hemoglobin (g/dL)	12.0 (1.9)	11.8 (1.8)
LDL cholesterol (mg/dL)	101.7 (39.2)	103.1 (37.5)
HDL cholesterol (mg/dL)	46.6 (13.7)	45.5 (13.9)

angiotensin converting enzyme inhibitors/aldosterone receptor blockers	87 (72)	267 (75)
Diuretics	83 (69)	269 (76)
Beta blockers	76 (63)	224 (63)
Fibroblast growth factor-23 (RU/mL), median (Q1-Q3)	193.2 (126.3-317.2)	197.6 (132.6-314.8)
Serum phosphorus, mg/dL	3.9 (0.7)	3.9 (0.8)
Total parathyroid hormone (pg/mL), median (Q1-Q3)	69.4 (43.5-100.6)	70.0 (43.9-120.0)

Entries are mean (SD) or N (%), except as noted.

Table S2. Baseline characteristics by quintile of baseline NTproBNP level (N = 3314).

	≤ 33.2	**33.3 – 82.2**	**82.3 – 175**	**175.1 – 416**	**> 416**
N	663	663	663	662	663
Age (years)	52.9 (11.7)	56.8 (10.7)	58.5 (11.2)	59.3 (10.6)	60.1 (10.0)
Women	236 (36)	311 (47)	322 (49)	348 (53)	303 (46)
Race/ethnicity					
Non-Hispanic white	291 (44)	290 (44)	312 (47)	302 (46)	244 (37)
Non-Hispanic black	296 (45)	277 (42)	250 (38)	232 (35)	249 (38)
Hispanic	43 (6)	62 (9)	83 (13)	99 (15)	146 (22)
Other	33 (5)	34 (5)	18 (3)	29 (4)	24 (4)
Estimated glomerular filtration rate, mL/min/1.73m^2	54.3 (14.2)	47.9 (14.0)	44.2 (14.2)	40.8 (12.8)	36.4 (12.2)
24-hour urine protein (g/d), median (Q1-Q3)	0.1 (0.0-0.2)	0.1 (0.0-0.5)	0.1 (0.1-0.5)	0.2 (0.1-0.9)	0.6 (0.1-2.6)
Diabetes mellitus	213 (32)	282 (43)	296 (45)	343 (52)	408 (62)
History of cardiovascular disease	73 (11)	123 (19)	161 (24)	197 (30)	305 (46)
History of atrial fibrillation	51 (8)	70 (11)	81 (12)	93 (14)	148 (22)
Current smoker	61 (9)	71 (11)	77 (12)	90 (14)	117 (18)

	≤ 33.2	33.3 – 82.2	82.3 – 175	175.1 – 416	> 416
Alcohol use	486 (73)	473 (71)	413 (62)	402 (61)	360 (54)
Body mass index (kg/m^2)	31.8 (6.8)	32.2 (7.4)	32.0 (8.4)	31.9 (8.4)	31.8 (7.6)
Systolic blood pressure (mmHg)	119.4 (15.7)	124.1 (18.3)	125.1 (18.9)	132.1 (21.9)	142.2 (26.1)
Diastolic blood pressure (mmHg)	72.8 (11.2)	72.4 (11.5)	69.9 (11.7)	71.6 (13.1)	72.7 (15.0)
Hemoglobin (g/dL)	13.5 (1.6)	12.9 (1.5)	12.6 (1.6)	12.3 (1.7)	11.8 (1.9)
LDL cholesterol (mg/dL)	107.7 (33.8)	104.5 (35.0)	104.2 (35.3)	102.0 (33.9)	101.8 (37.3)
HDL cholesterol (mg/dL)	47.6 (14.4)	48.2 (15.6)	49.0 (15.8)	48.7 (16.6)	46.9 (15.7)
Angiotensin converting enzyme inhibitors/aldosterone receptor blockers	439 (66)	444 (67)	458 (69)	453 (68)	440 (66)
Diuretics	277 (42)	358 (54)	382 (58)	382 (58)	460 (69)
Beta blockers	147 (22)	235 (35)	296 (45)	386 (58)	460 (69)
Fibroblast growth factor-23 (RU/mL), median (Q1-Q3)	101.2 (74.4-146.1)	124.1 (86.0-186.9)	132.8 (95.4-205.8)	158.9 (107.2-244.1)	203.6 (135.7-336.8)
Serum phosphorus, mg/dL	3.5 (0.6)	3.6 (0.6)	3.7 (0.7)	3.8 (0.7)	3.9 (0.7)
Total parathyroid hormone (pg/mL), median (Q1-Q3)	41.0 (29.7-56.3)	48.0 (33.0-77.4)	52.0 (32.0-80.5)	56.8 (37.0-93.2)	74.5 (47.0-126.0)

Entries are mean (SD) or N (%), except as noted.

Table S3. Baseline characteristics by quartile of baseline hsTnT level (N = 3314).

	< 10	**10.1 – 15.6**	**15.7 – 26**	**> 26**
N	1121	718	729	746
Age (years)	53.6 (11.7)	58.9 (10.7)	60.5 (9.7)	59.2 (10.3)
Women	736 (66)	329 (46)	259 (36)	196 (26)
Race/ethnicity				
Non-Hispanic white	567 (51)	360 (50)	294 (40)	218 (29)
Non-Hispanic black	388 (35)	256 (36)	306 (42)	354 (47)
Hispanic	103 (9)	78 (11)	102 (14)	150 (20)
Other	63 (6)	24 (3)	27 (4)	24 (3)
Estimated glomerular filtration rate, mL/min/1.73m^2	52.1 (15.5)	44.8 (12.6)	41.8 (12.6)	36.5 (12.3)
24-hour urine protein (g/d), median (Q1-Q3)	0.1 (0.0-0.3)	0.1 (0.1-0.4)	0.2 (0.1-0.9)	0.6 (0.1-2.6)
Diabetes mellitus	272 (24)	302 (42)	393 (54)	575 (77)
History of cardiovascular disease	170 (15)	164 (23)	237 (33)	288 (39)
History of atrial fibrillation	119 (11)	84 (12)	124 (17)	116 (16)
Current smoker	142 (13)	90 (13)	89 (12)	95 (13)

Alcohol use	795 (71)	464 (65)	465 (64)	410 (55)
Body mass index (kg/m^2)	30.8 (7.6)	31.8 (7.9)	32.8 (8.0)	32.8 (7.3)
Systolic blood pressure (mmHg)	120.9 (18.0)	127.3 (20.2)	131.6 (22.4)	138.4 (24.0)
Diastolic blood pressure (mmHg)	72.0 (11.5)	71.4 (12.3)	71.6 (13.4)	72.4 (13.7)
Hemoglobin (g/dL)	13.0 (1.6)	12.8 (1.8)	12.6 (1.8)	11.8 (1.7)
LDL cholesterol (mg/dL)	108.2 (33.5)	103.0 (33.8)	100.5 (34.9)	102.3 (38.3)
HDL cholesterol (mg/dL)	51.7 (16.0)	47.8 (15.6)	45.7 (15.1)	45.3 (14.5)
Angiotensin converting enzyme inhibitors/aldosterone receptor blockers	637 (57)	500 (70)	544 (75)	553 (74)
Diuretics	460 (41)	393 (55)	466 (64)	540 (72)
Beta blockers	380 (34)	339 (47)	387 (53)	418 (56)
Fibroblast growth factor-23 (RU/mL), median (Q1-Q3)	111.8 (77.3-170.8)	134.8 (94.3-209.9)	148.5 (101.0-219.7)	192.6 (126.4-318.9)
Serum phosphorus, mg/dL	3.6 (0.6)	3.6 (0.6)	3.7 (0.6)	4.0 (0.8)
Total parathyroid hormone (pg/mL), median (Q1-Q3)	42.9 (30.8-65.4)	46.0 (32.0-74.0)	58.8 (37.9-89.0)	76.0 (46.2-132.2)

Entries are mean (SD) or N (%), except as noted.

Table S4. Baseline characteristics by quintile of baseline GDF-15 level (N = 3314).

	≤ 878	**879 – 1250**	**1251 – 1670**	**1671 – 2360**	**> 2360**
N	663	663	662	667	659
Age (years)	51.1 (11.7)	56.7 (10.9)	58.9 (10.7)	60.6 (9.8)	60.5 (9.6)
Women	343 (52)	311 (47)	294 (44)	295 (44)	277 (42)
Race/ethnicity					
Non-Hispanic white	372 (56)	303 (46)	296 (45)	267 (40)	201 (31)
Non-Hispanic black	223 (34)	260 (39)	261 (39)	274 (41)	286 (43)
Hispanic	39 (6)	65 (10)	88 (13)	97 (15)	144 (22)
Other	29 (4)	35 (5)	17 (3)	29 (4)	28 (4)
Estimated glomerular filtration rate, mL/min/1.73m^2	59.1 (13.4)	48.6 (11.5)	43.0 (11.5)	38.8 (12.2)	34.2 (11.8)
24-hour urine protein (g/d), median (Q1-Q3)	0.1 (0.0-0.1)	0.1 (0.0-0.4)	0.1 (0.1-0.5)	0.3 (0.1-1.2)	0.6 (0.1-2.8)
Diabetes mellitus	104 (16)	242 (37)	328 (50)	405 (61)	463 (70)
History of cardiovascular disease	64 (10)	130 (20)	183 (28)	244 (37)	238 (36)
History of atrial fibrillation	72 (11)	76 (11)	83 (13)	104 (16)	108 (16)
Current smoker	40 (6)	54 (8)	81 (12)	116 (17)	125 (19)

Alcohol use	527 (79)	460 (69)	413 (62)	373 (56)	361 (55)
Body mass index (kg/m^2)	30.9 (7.2)	32.0 (7.9)	32.7 (7.8)	32.2 (7.6)	31.8 (8.0)
Systolic blood pressure (mmHg)	119.9 (17.9)	125.0 (19.1)	127.6 (20.7)	132.9 (22.8)	137.5 (24.4)
Diastolic blood pressure (mmHg)	73.7 (11.6)	73.1 (12.5)	70.8 (12.3)	71.2 (12.9)	70.6 (13.3)
Hemoglobin (g/dL)	13.6 (1.5)	13.1 (1.6)	12.6 (1.6)	12.2 (1.6)	11.6 (1.8)
LDL cholesterol (mg/dL)	111.7 (33.2)	105.5 (34.6)	102.4 (34.9)	102.6 (35.6)	98.0 (35.8)
HDL cholesterol (mg/dL)	50.6 (16.2)	48.7 (15.3)	46.7 (14.5)	47.7 (16.3)	46.6 (15.4)
Angiotensin converting enzyme inhibitors/aldosterone receptor blockers	350 (53)	461 (70)	480 (73)	495 (74)	448 (68)
Diuretics	229 (35)	340 (51)	402 (61)	431 (65)	457 (69)
Beta blockers	192 (29)	287 (43)	312 (47)	365 (55)	368 (56)
Fibroblast growth factor-23 (RU/mL), median (Q1-Q3)	90.7 (67.0-124.8)	116.8 (84.2-171.6)	141.3 (102.9-199.7)	173.4 (121.2-267.9)	217.9 (139.6-368.7)
Serum phosphorus, mg/dL	3.5 (0.5)	3.6 (0.6)	3.7 (0.6)	3.8 (0.7)	4.0 (0.8)
Total parathyroid hormone (pg/mL), median (Q1-Q3)	38.0 (29.0-53.6)	45.0 (32.0-66.5)	52.0 (34.0-80.7)	65.5 (40.3-103.0)	81.2 (46.0-146.0)

Table S5. Baseline characteristics by quintile of baseline SST-2 level (N = 3314).

	≤ 10.5	**10.6 – 13.6**	**13.7 – 17.1**	**17.2 – 22.6**	**> 22.6**
N	664	662	662	664	662
Age (years)	55.2 (12.0)	58.1 (10.2)	58.4 (10.8)	58.9 (10.7)	57.2 (11.6)
Women	409 (62)	357 (54)	304 (46)	248 (37)	202 (31)
Race/ethnicity					
Non-Hispanic white	263 (40)	296 (45)	284 (43)	303 (46)	293 (44)
Non-Hispanic black	297 (45)	281 (42)	264 (40)	238 (36)	224 (34)
Hispanic	66 (10)	63 (10)	86 (13)	97 (15)	121 (18)
Other	38 (6)	22 (3)	28 (4)	26 (4)	24 (4)
Estimated glomerular filtration rate, mL/min/1.73m^2	47.8 (15.5)	45.2 (14.8)	45.3 (14.6)	43.4 (14.7)	42.1 (14.1)
24-hour urine protein (g/d), median (Q1-Q3)	0.1 (0.0-0.3)	0.1 (0.0-0.4)	0.1 (0.1-0.7)	0.2 (0.1-1.1)	0.4 (0.1-1.7)
Diabetes mellitus	201 (30)	273 (41)	296 (45)	374 (56)	398 (60)
History of cardiovascular disease	115 (17)	167 (25)	165 (25)	206 (31)	206 (31)
History of atrial fibrillation	72 (11)	93 (14)	92 (14)	94 (14)	92 (14)
Current smoker	95 (14)	83 (13)	85 (13)	77 (12)	76 (11)

Alcohol use	460 (69)	411 (62)	432 (65)	405 (61)	426 (64)
Body mass index (kg/m^2)	31.4 (7.7)	32.6 (7.5)	32.4 (7.4)	32.2 (8.2)	31.1 (7.7)
Systolic blood pressure (mmHg)	123.2 (20.6)	126.7 (20.1)	128.6 (21.5)	132.1 (23.4)	132.3 (22.7)
Diastolic blood pressure (mmHg)	72.6 (12.2)	71.7 (12.3)	71.7 (12.5)	71.3 (13.4)	72.1 (12.6)
Hemoglobin (g/dL)	12.8 (1.6)	12.7 (1.7)	12.6 (1.7)	12.6 (1.8)	12.3 (1.8)
LDL cholesterol (mg/dL)	107.3 (34.3)	104.5 (32.6)	103.3 (34.3)	103.1 (35.8)	102.0 (38.2)
HDL cholesterol (mg/dL)	48.9 (15.1)	48.1 (15.0)	48.3 (15.4)	46.5 (14.5)	48.5 (17.9)
Angiotensin converting enzyme inhibitors/aldosterone receptor blockers	391 (59)	445 (67)	463 (70)	474 (71)	461 (70)
Diuretics	315 (47)	369 (56)	360 (54)	404 (61)	411 (62)
Beta blockers	259 (39)	277 (42)	298 (45)	347 (52)	343 (52)
Fibroblast growth factor-23 (RU/mL), median (Q1-Q3)	124.3 (83.7-201.9)	137.4 (95.4-210.5)	132.4 (93.2-202.8)	147.9 (95.6-235.7)	159.5 (103.5-254.2)
Serum phosphorus, mg/dL	3.7 (0.6)	3.7 (0.6)	3.7 (0.6)	3.7 (0.7)	3.8 (0.8)
Total parathyroid hormone (pg/mL), median (Q1-Q3)	49.3 (32.5-76.8)	49.5 (33.7-78.8)	49.0 (33.0-79.5)	55.0 (35.9-87.0)	58.0 (37.0-102.8)

Entries are mean (SD) or N (%), except as noted.

Table S6. Association of hsTnT with risk of incident heart failure, stratified by category of estimated glomerular filtration rate.

Log(hsTnT) per 1 SD (0.80) increase			**Model 1**	**Model 2**
eGFR category (ml/min/1.73m2)	**N at risk**	**N events**	**HR (95% CI)**	
< 30	570	147	1.33 (1.09, 1.61)	1.22 (1.02, 1.47)
30-44	1202	187	1.38 (1.17, 1.64)	1.28 (1.08, 1.53)
45-59	1045	117	1.85 (1.51, 2.27)	1.75 (1.44, 2.14)
≥ 60	497	26	2.15 (1.40, 3.29)	1.97 (1.25, 3.09)

Model 1 was adjusted for age, sex, race, diabetes, cardiovascular disease, smoking, 24h urinary protein, estimated glomerular filtration rate, systolic blood pressure, body mass index, LDL cholesterol, HDL cholesterol

Model 2 was adjusted for covariates in Model 1 + angiotensin converting enzyme inhibitors/aldosterone receptor blockers, diuretics, beta blockers, phosphate, parathyroid hormone, fibroblast growth factor-23

Table S7. Associations of Galectin-3 and GDF-15 with incident HF in people with CKD, allowing for different effects before and after 4 years follow-up.

	Adjusted model	
	HR (95% CI)	p-value
≤ 4 years:		
Log(Galectin-3) per 1 SD (0.50) increase	1.38 (1.18, 1.61)	< 0.0001
Log (NT-proBNP) per 1 SD (1.66) increase	2.24 (1.89, 2.65)	< 0.0001
Log (hsTNT) per 1 SD (0.80) increase	1.53 (1.33, 1.76)	< 0.0001
Log(GDF-15) per 1 SD (0.60) increase	1.58 (1.34, 1.88)	< 0.0001
Log (sST-2) per 1 SD (0.56) increase	1.20 (1.04, 1.39)	0.01
> 4 years:		
Log(Galectin-3) per 1 SD (0.50) increase	0.93 (0.81, 1.06)	0.27
Log (NT-proBNP) per 1 SD (1.66) increase	1.89 (1.59, 2.25)	< 0.0001
Log (hsTNT) per 1 SD (0.80) increase	1.19 (1.01, 1.40)	0.03
Log(GDF-15) per 1 SD (0.60) increase	1.32 (1.11, 1.56)	0.001
Log (sST-2) per 1 SD (0.56) increase	1.17 (1.01, 1.35)	0.03

Adjusted model: age, sex, race, diabetes, CVD, smoking, 24h urinary protein, estimated glomerular filtration rate, systolic blood pressure, body mass index, LDL cholesterol, HDL cholesterol, angiotensin converting enzyme inhibitors/aldosterone receptor blockers, diuretics, beta blockers, phosphate, parathyroid hormone, fibroblast growth factor-23

Table S8. Associations of cardiac biomarkers and incident heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).

	HFrEF (156 events/3314 N at risk)				HFpEF (200 events; 3314 N at risk)			
Cardiac Biomarker	**Model 1**		**Model 2**		**Model 1**		**Model 2**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Log(Galectin-3) per 1 SD (0.50) increase	1.08 (0.89, 1.31)	0.45	1.05 (0.87, 1.28)	0.60	1.18 (1.00, 1.40)	0.05	1.12 (0.95, 1.32)	0.18
Log(NT-proBNP) per 1 SD (1.66) increase	3.15 (2.49, 3.97)	< 0.0001	3.01 (2.37, 3.84)	< 0.0001	1.72 (1.39, 2.12)	< 0.0001	1.64 (1.32, 2.04)	< 0.0001
Log(hsTnT) per 1 SD (0.80) increase	1.61 (1.32, 1.97)	< 0.0001	1.56 (1.26, 1.93)	< 0.0001	1.32 (1.10, 1.59)	0.003	1.20 (0.99, 1.45)	0.06
Log(GDF-15) per 1 SD (0.60) increase	1.46 (1.16, 1.84)	0.001	1.34 (1.06, 1.71)	0.02	1.71 (1.40, 2.10)	< 0.0001	1.53 (1.24, 1.89)	< 0.0001
Log(SST-2) per 1 SD (0.56) increase	1.21 (0.96, 1.52)	0.11	1.16 (0.93, 1.44)	0.20	1.33 (1.12, 1.59)	0.002	1.27 (1.07, 1.51)	0.006

Model 1 was adjusted for age, sex, race, diabetes, cardiovascular disease, smoking, 24h urinary protein, estimated glomerular filtration rate, systolic blood pressure, body mass index, LDL cholesterol, HDL cholesterol

Model 2 was adjusted for covariates in Model 1 + angiotensin converting enzyme inhibitors/aldosterone receptor blockers, diuretics, beta blockers, phosphate, parathyroid hormone, fibroblast growth factor-23