ORIGINAL RESEARCH

Cardiac Biomarkers and Risk of Atrial Fibrillation in Chronic Kidney Disease: The CRIC Study

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***Background*—**We tested associations of cardiac biomarkers of myocardial stretch, injury, inflammation, and fibrosis with the risk of incident atrial fibrillation (AF) in a prospective study of chronic kidney disease patients.

***Methods and Results*—**The study sample was 3053 participants with chronic kidney disease in the multicenter CRIC (Chronic Renal Insufficiency Cohort) study who were not identified as having AF at baseline. Cardiac biomarkers, measured at baseline, were NT-proBNP (N-terminal pro-B-type natriuretic peptide), high-sensitivity troponin T, galectin-3, growth differentiation factor-15, and soluble ST-2. Incident AF ("AF event") was defined as a hospitalization for AF. During a median follow-up of 8 years, 279 (9%) participants developed a new AF event. In adjusted models, higher baseline log-transformed NT-proBNP (N-terminal pro-B-type natriuretic peptide) was associated with incident AF (adjusted hazard ratio [HR] per SD higher concentration: 2.11; 95% CI, 1.75, 2.55), as was log-high-sensitivity troponin T (HR 1.42; 95% CI, 1.20, 1.68). These associations showed a dose–response relationship in categorical analyses. Although log-soluble ST-2 was associated with AF risk in continuous models (HR per SD higher concentration 1.35; 95% CI, 1.16, 1.58), this association was not consistent in categorical analyses. Log-galectin-3 (HR 1.05; 95% CI, 0.91, 1.22) and log-growth differentiation factor-15 (HR 1.16; 95% CI, 0.96, 1.40) were not significantly associated with incident AF.

***Conclusions*—**We found strong associations between higher NT-proBNP (N-terminal pro-B-type natriuretic peptide) and high-sensitivity troponin T concentrations, and the risk of incident AF in a large cohort of participants with chronic kidney disease. Increased atrial myocardial stretch and myocardial cell injury may be implicated in the high burden of AF in patients with chronic kidney disease. **(*J Am Heart Assoc*. 2019;8:e012200. DOI: 10.1161/JAHA.119.012200.)**

Key Words: atrial fibrillation • biomarker • chronic kidney disease

Atrial fibrillation (AF) is the second most common cardiac comorbidity in patients with chronic kidney disease (CKD) [1] observed in ≈18% of adult CKD patients, an estimate that is 3-fold higher than in the general population.[2] Evidence from epidemiological studies suggests that CKD is a strong, independent risk factor for incident AF.[3] Furthermore, the presence of CKD is associated with increased rates of stroke, bleeding, and death among patients with AF and CKD than

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Accompanying Tables S1 through S9 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012200

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Clinical Perspective

What Is New?

- The mechanism(s) responsible for the increased atrial fibrillation burden among people with chronic kidney disease are poorly understood.
- We evaluated associations of cardiac biomarkers of myocardial stretch, injury, inflammation, and fibrosis with risk of incident atrial fibrillation in a large multicenter cohort of men and women with chronic kidney disease.
- Cardiac biomarkers of myocardial stretch and injury were found to be the predominant markers of risk of atrial fibrillation in people with chronic kidney disease.

What Are the Clinical Implications?

- Our findings provide mechanistic insights into the strong associations between chronic kidney disease and atrial fibrillation and may inform future therapeutic trials aimed at reducing the risk of atrial fibrillation in people with chronic kidney disease.

among patients with normal kidney function.[4,5] However, the pathogenesis of AF in patients with CKD remains poorly understood.

Atrial myocardial wall stretch and myocardial cell damage have been implicated in the pathogenesis of AF.[6] Cardiac biomarkers reflecting these pathophysiologic changes have advanced the understanding of determinants of AF in the general population. For instance, NT-proBNP (N-terminal pro-B-type natriuretic peptide), a marker of myocardial wall stretch, is a strong predictor of AF onset beyond traditional AF risk factors in the general population.[7] Similarly, high-sensitivity troponin T (hsTnT), a marker of myocardial cell damage, is also strongly and independently associated with incident AF in the general population.[8] It is possible that the sustained myocardial wall stress and damage that is common in CKD may render these patients more susceptible to developing sustained arrhythmias such as AF.[9,10]

In addition, myocardial inflammation, fibrosis, and remodeling have also been postulated to play a role in the pathogenesis and perpetuation of AF.[6] Consistent with these possible mechanisms, galectin-3, a beta-galactosidase-binding lecithin expressed by macrophages that induces fibrosis and adverse remodeling,[11] has been found to be an independent predictor of incident AF. In addition, growth-differentiation factor-15 (GDF-15), a growth-factor part of the transforming growth factor-β cytokine family that increases in response to myocyte ischemia, stretch, and inflammation,[12–14] and soluble ST2 (SST2), a member of the interleukin-1 receptor family that promotes cardiomyocyte hypertrophy and fibrosis,[15,16] have been shown, to a variable extent, to be independently associated with AF in the general population.[17,18] In CKD, animal models and human studies have suggested that even mild impairments in kidney function lead to accelerated myocardial fibrosis, and have shown a close link between inflammation and left atrial fibrosis.[19–21] The relative contribution of these biologic pathways to AF have not been well characterized in CKD, where the pathophysiology of cardiovascular disease is unique.

In this context, evaluation of cardiac biomarkers in patients with CKD may provide insight into specific mechanistic pathways by which CKD is associated with AF. In this study, we evaluated associations of 5 cardiac biomarkers (NT-proBNP, hsTnT, galectin-3, GDF-15, and SST2) with risk of incident AF in a large multicenter cohort of men and women with CKD.

Methods

Study Population

The CRIC (Chronic Renal Insufficiency Cohort) Study is an ongoing, prospective, multicenter, cohort study of 3939 participants established to examine risk factors for the progression of CKD and the development and worsening of cardiovascular disease in patients with CKD.[22,23] Adult male and female patients with CKD aged 21 to 74 years were eligible to participate if they met the following age-specific estimated glomerular filtration (eGFR) criteria: 20 to 70 mL/min per 1.73 m^2 for age 21 to 44 years, 20 to 60 mL/min per 1.73 m^2 for age 45 to 64 years, and 20 to 50 mL/min per 1.73 m^2 for age 65 to 74 years. Exclusion criteria included heart failure (HF) with New York Heart Association functional class III or IV and polycystic kidney disease.

For this study, we excluded participants who were identified as having AF at baseline (defined by either self-report or evidence of AF on a baseline study visit ECG) (N=666) and participants who were missing at least 1 of the 5 cardiac biomarkers of interest measured (N=220). The final study population consisted of 3053 participants.

CRIC was approved by the institutional review boards of all participating institutions. All participants gave written informed consent before the start of the study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Cardiac Biomarkers

All 5 biomarkers were measured at baseline and at year 2 after cohort entry in duplicate from baseline frozen serum or plasma samples. NT-proBNP and hsTnT were measured at baseline in 2008 from EDTA plasma stored at −70°C using a chemiluminescent microparticle immunoassay (www.roche-

diagnostics.us) on the ElecSys 2010 at the University of Maryland. The range of values for NT-proBNP was from 5 to 35 000 pg/mL and the coefficient of variation (CV) was 9.3% at a level of 126 pg/mL and 5.5% at 5319 pg/mL. hsTnT was measured using the highly sensitive assay with a range of values from 3 to 10 000 pg/mL. The CV was 6.0% at a level of 26 pg/mL and 5.4% at 2140 pg/mL. The value at the 99th percentile cutoff from a healthy reference population was 13 pg/mL for hsTnT with a 10% CV.[13]

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. Galectin-3, GDF-15, and SST2 were measured using ELISA and had intra-assay CVs of 4.0%, 2.0%, and 2.6%, respectively.

Incident AF

Incident AF was defined as a hospitalization for AF and confirmed by physician adjudication.[24] At each study visit, participants were asked if they had visited an emergency department or had been hospitalized. Medical records from corresponding hospitals or healthcare systems were queried for qualifying encounters. Diagnostic codes for AF (*International Classification of Diseases, Ninth Revision, Clinical Modification* 427.31 or 427.32) prompted retrieval of medical records and centralized review for the ascertainment of incident AF. Final adjudication of events was done after at least 2 study physicians reviewed all possible AF events by manual review of relevant medical records. Hospitalized ECGs (when available) were reviewed and were part of the adjudication process.

Baseline Assessments

Baseline information included sociodemographic characteristics, anthropometric measurements, self-reported medical history, current medications, and lifestyle behaviors. Diabetes mellitus was defined as a fasting glucose >126 mg/dL, a nonfasting glucose >200 mg/dL, or use of medications for diabetes mellitus including insulin. Additional measurements included 24-hour urine total protein, glucose, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Markers of abnormal mineral metabolism, including fibroblast growth factor-23, serum phosphorus, and total PTH, were used in multivariable models since prior studies have shown an independent association between these markers and AF risk.[24]

Echocardiograms were obtained in the entire study population 1 year after the baseline visit, and measures included left ventricular ejection fraction, left ventricular mass indexed to body surface area, and left atrial diameter.[25,26] Assessments were performed using 2-dimensional echocardiographic images and quantified at a central laboratory following a standard imaging protocol from the American Society of Echocardiography guidelines.[27]

Serum creatinine was measured using a standardized enzymatic method at the CRIC central laboratory.[28] Estimation of GFR was calculated from serum creatinine (www.roche-diagnostics.us; CV 1.1%) using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).[29]

Statistical Analysis

Descriptive statistics were used to summarize baseline demographic and clinical characteristics by quintile (except for hsTnT) of each cardiac biomarker, and crude-incident AF rates per 1000 person-years were calculated.

In time to event analyses, participants were followed for the first occurrence of an AF event. Censoring occurred at the last follow-up time (because of death, lost to follow-up, or administrative censoring). Separate Cox-regression methods were used to evaluate the associations of NT-proBNP, hsTnT, galectin-3, GDF-15, and SST2 continuously and categorically using quintiles with incident AF. An exception was hsTnT, which was analyzed in tertiles of the detectable range with the reference category corresponding to an undetectable range. The proportional hazards assumption was tested through examination of the time-dependency of the Schoenfeld partial residuals. Because of the skewed distribution of cardiac biomarkers, the hazard ratio estimates in continuous analyses were calculated assuming a log-log linear relationship with incident AF. The functional form of the association of incident AF and each cardiac biomarker was further evaluated with penalized regression spline models with 3 degrees of freedom using the *pspline* command in the R *survival* package.

Multivariable models were adjusted for covariates deemed a-priori to be possibly associated with AF including clinical center, age, sex, ethnicity, eGFR, 24-hour urinary protein, systolic blood cholesterol, history of self-reported cardiovascular disease including HF, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and diuretics.

Several sensitivity analyses were performed. To evaluate the independence between biomarkers in their association with AF, analyses were done with multivariable models including all 5 cardiac biomarkers. Since cardiac biomarkers may be surrogate markers of subclinical HF, analyses were done with further statistical adjustment for echocardiographic measures of left ventricular structure and function (left ventricular mass index, left ventricular ejection fraction) and left atrial diameter, and excluding participants with prevalent HF. Finally, these cardiac biomarkers were measured 2 years after enrollment in a random subset of

participants (N=790). We conducted a sensitivity analysis that used time-updated biomarkers for this subset (and baseline biomarkers only for the remaining participants) to investigate whether more proximal cardiac biomarkers were more strongly associated with incident AF.

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

Results

Baseline Characteristics

Among 3053 participants, the median eGFR at baseline was 43 mL/min per 1.73 m^2 and 24-hour urinary protein was 0.1 g/d. Compared with participants with NT-proBNP concentrations ≤32.7 pg/mL (lowest quintile-quintile used in Table 1), participants in the highest quintile (>423 pg/mL) were older (59 versus 53 years), more likely to be female (45% versus 35%), to have diabetes mellitus (66% versus 33%), prevalent HF (17% versus 2%), to be using diuretics (72% versus 42%), and less likely to report current alcohol use (54% versus 74%) (Table 1). Higher NT-proBNP concentrations were associated with lower eGFR, higher 24-hour urine protein, and higher blood pressure. These patterns were similar for hsTnT, galectin-3, GDF-15, and SST-2 (Tables S1 through S4). Demographic and clinical characteristics stratified by level of kidney function are presented in Table S5.

Cardiac Biomarkers and Risk of Incident AF

NT-proBNP and hsTnT

During a median follow-up time of 8 years (interquartile range 5.4–9.4 years), an incident AF event was identified in 279 (9%) participants. There were strong unadjusted associations between all evaluated cardiac biomarkers and incident AF with spline models suggestive of log-linear associations between NT-proBNP and incident AF (Figure).

In multivariable Cox-regression models, NT-proBNP and hsTnT were each strongly and independently associated with incident AF (Table 2). These associations were largely unchanged when adding HF medication use and markers of abnormal mineral metabolism (model 2) to multivariable models that included clinical center, demographics, comorbidities, and level of kidney function. The hazard ratio (per 1 SD) for the association of higher baseline log-transformed NT-proBNP with incident AF was 2.11 (95% CI, 1.75, 2.55), and 1.42 (95% CI, 1.20, 1.68) for log-transformed hsTnT. In categorical analyses, we found a dose–response relationship with a 7-fold hazard ratio for the highest NT-proBNP category, and >2-fold for hsTnT, comparing the highest category with the lowest (Table 2).

Galectin-3, GDF-15, and sST-2

In multivariable models, SST-2 was independently associated with incident AF as a continuous predictor (Table 2). However, this association was not observed in categorical analyses. Galectin-3 and GDF-15 were not independently associated with AF risk in continuous or in categorical analyses.

Sensitivity Analyses

Results from models that included all cardiac biomarkers were consistent with results presented in the main analysis (Table S6). Results were also consistent when adjusting for echocardiographic measurements that included left ventricular ejection fraction, left ventricular mass index, and left atrial diameter (Table S3). Similarly, time-variable analyses with repeated measurements of cardiac biomarkers were consistent with the primary results (Table S7). There were no significant differences in the results when excluding 182 participants with prevalent HF (Table S8). Finally, results were similar across 2 strata of eGFR using a cutoff of 45 mL/min per 1.73 m^2 (Table S9).

Discussion

In this prospective cohort study, we found strong, graded associations between level of NT-proBNP and hsTnT with risk of incident AF in a large population of participants with CKD. These associations were independent of covariates known to be predictive of AF in the general population and in people with CKD, including measures of level of kidney function, alterations in mineral metabolism, and left ventricular structure and function. Associations with incident AF were modest and inconsistent for SST2 (only significant when SST2 was modeled continuously) and not significant for galectin-3 and GDF-15. Our findings suggest that increased atrial myocardial stretch and myocardial cell injury are important factors contributing to the high burden of AF in patients with CKD.

Our findings of strong associations of NT-proBNP and incident AF are consistent with observations in the general population.[7] Both HF and hypertension have been shown to increase the hemodynamic load to the atria causing myocardial stretch, increasing the susceptibility to developing AF.[6,30,31] This mechanism may be particularly important in patients with CKD where subclinical volume overload is highly prevalent and strongly correlated with NT-proBNP levels.[32] Despite the strong overlap between AF and HF, our results were consistent when excluding participants with HF at baseline. It is therefore possible that elevations in NT-proBNP are manifestations of subclinical HF. Previously, we found that incident AF in people with CKD is associated with a nearly 6-fold risk of developing HF, an estimate higher than most recognized risk factors for

Table 1. Demographic and Clinical Characteristics by Quintile of Baseline NT-proBNP (N=3053)

	≤32.7 pg/mL (N=611)	32.8 to 81 pg/mL (N=610)	81.1 to 176 pg/mL (N=611)	176.1 to 423 pg/mL (N=610)	>423 pg/mL (N=611)
Demographics					
Age, y	52.7 (11.8)	56.8 (10.7)	58.2 (11.2)	59.0 (10.6)	59.1 (10.4)
Women	211 (35)	284 (47)	288 (47)	324 (53)	274 (45)
Race/ethnicity					
Non-Hispanic white	269 (44)	269 (44)	281 (46)	274 (45)	202 (33)
Non-Hispanic black	271 (44)	250 (41)	235 (38)	211 (35)	241 (39)
Hispanic	40 (7)	59 (10)	80 (13)	99 (16)	143 (23)
Other	31 (5)	32 (5)	15 (2)	26 (4)	25 (4)
Medical history					
Diabetes mellitus	202 (33)	260 (43)	277 (45)	325 (53)	406 (66)
History of CVD	73 (12)	115 (19)	152 (25)	199 (33)	316 (52)
History of heart failure	13 (2)	12 (2)	16 (3)	39 (6)	102 (17)
Current smoker	54 (9)	64 (10)	77 (13)	90 (15)	104 (17)
Alcohol use	451 (74)	430 (70)	382 (63)	376 (62)	327 (54)
Markers of kidney function					
eGFR (CKD-EPI), mL/min per 1.73 m^2	54.5 (14.1)	47.9 (13.7)	43.8 (13.8)	40.7 (12.8)	36.2 (12.6)
24-h urine protein, g/d, median (IQR)	0.1 (0.0–0.2)	0.1 (0.0–0.5)	0.1 (0.1–0.6)	0.2 (0.1–0.9)	0.8 (0.1–3.3)
Clinical characteristics and laboratory measurements					
BMI, kg/m^2	31.8 (6.7)	32.1 (7.6)	32.0 (8.5)	32.1 (8.5)	31.9 (7.5)
SBP, mm Hg	119.4 (15.7)	124.1 (18.5)	125.4 (19.0)	131.8 (22.3)	142.8 (25.7)
DBP, mm Hg	73.1 (11.3)	72.5 (11.5)	70.1 (11.8)	71.4 (13.3)	73.0 (15.6)
Hemoglobin, g/dL	13.6 (1.6)	12.9 (1.5)	12.6 (1.6)	12.3 (1.6)	11.7 (1.9)
LDL cholesterol, mg/dL	107.5 (33.5)	104.3 (34.9)	104.2 (35.0)	101.0 (33.9)	101.6 (37.8)
HDL cholesterol, mg/dL	47.3 (14.4)	47.9 (15.6)	49.2 (16.2)	48.5 (16.4)	46.4 (16.0)
FGF-23, RU/mL, median (IQR)	101.0 (74.1–145.4)	122.7 (85.9–182.6)	132.8 (97.2–208.3)	159.5 (108.8–244.6)	207.2 (131.4–341.6)
Serum phosphorus, mg/dL	3.5 (0.6)	3.6 (0.6)	3.7 (0.7)	3.8 (0.7)	4.0 (0.7)
Total PTH, pg/mL, median (IQR)	40.7 (29.4–56.2)	48.0 (33.0–78.8)	51.1 (32.0–82.4)	58.9 (37.9–95.2)	78.0 (47.2–127.0)
Medications					
ACEi/ARBs	410 (67)	407 (67)	425 (70)	424 (70)	405 (66)
Diuretics	254 (42)	325 (53)	347 (57)	357 (59)	442 (72)
β-Blockers	142 (23)	212 (35)	263 (43)	362 (59)	418 (68)
Echocardiographic measurements					
LVEF from echocardiogram	55.5 (6.4)	56.1 (6.0)	56.0 (6.9)	54.5 (8.3)	52.0 (9.4)
LVMI, g/m^2	54.9 (18.0)	58.9 (19.5)	61.5 (21.8)	65.4 (21.8)	79.0 (25.8)

Data are mean (SD) or N (%), except as noted. ACEi/ARBs indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor-23; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PTH, parathyroid hormone; SBP, systolic blood pressure.

HF.[10] In CKD, therefore, AF and HF may be interrelated through shared mechanistic pathways related to volume status, cardiac filling pressures, and myocardial stress.

We also observed a strong association of the level of hsTnT with the risk of incident AF. This finding is consistent with a mechanism of high myocardial wall stress with secondary subclinical myocardial ischemia and/or injury. In the general population, hsTnT has been shown to be independently associated with AF risk.[8] Myocardial cell damage causing elevations in hsTnT concentrations is a

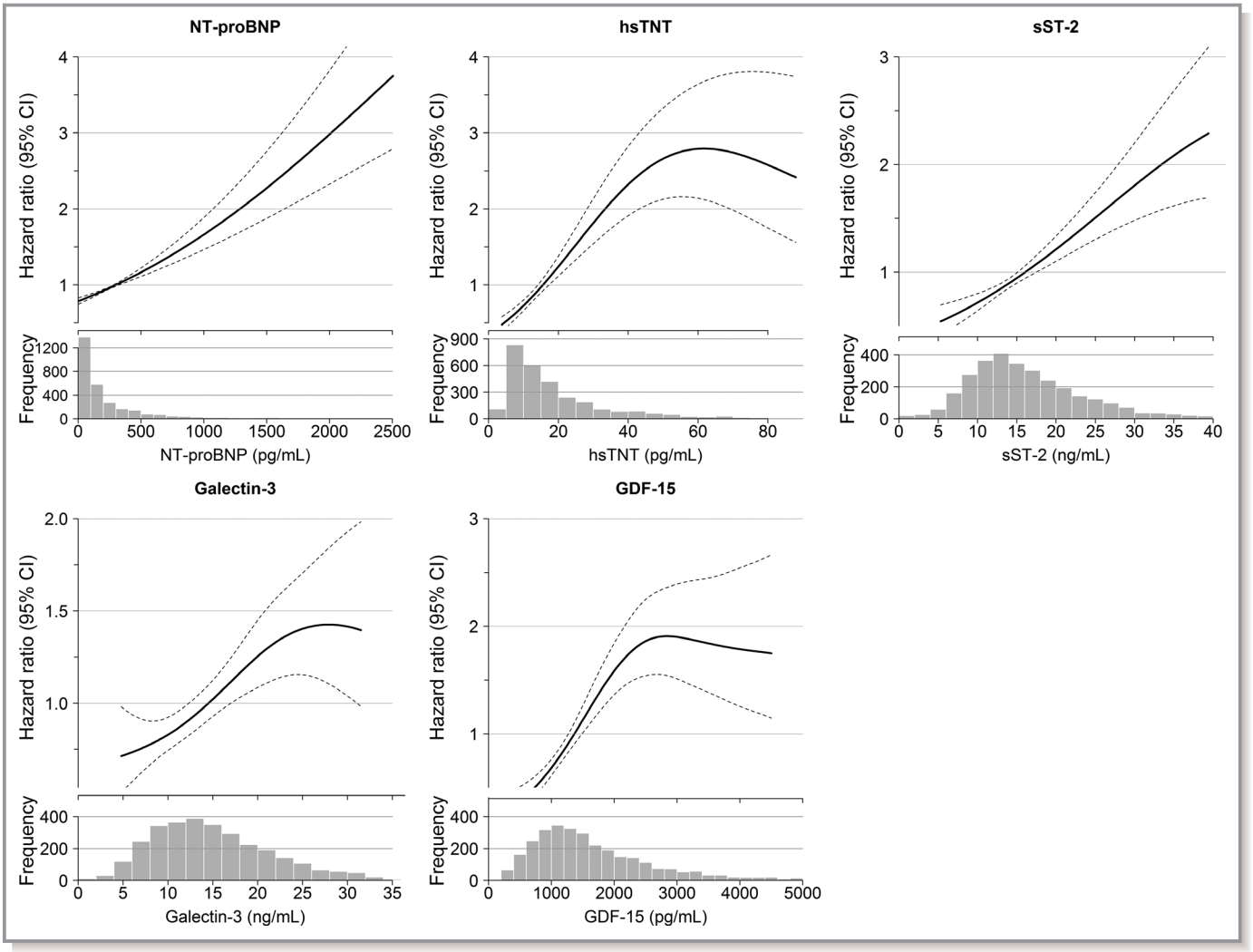

Figure. Distribution and unadjusted associations of cardiac biomarkers and incident atrial fibrillation. GDF-15 indicates growth differentiation factor-15; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST-2, soluble ST-2.

common finding in patients with HF with elevated cardiac filling pressures, myocardial inflammatory states, and acute myocardial pressure-overload, even in the absence of obstructive epicardial coronary artery disease.[33,34] Taken together, the strong observed associations of NT-proBNP and hsTnT with AF suggest that elevated filling pressures with secondary myocardial injury, and possibly microvascular ischemic disease, which are highly prevalent in patients with CKD,[35–38] may be important mechanisms for the onset of AF.

In contrast to our observations for the associations between NT-proBNP and hsTnT and AF risk, observations for the association between galectin-3, GDF-15 and SST2, and incident AF, were modest and inconsistent. These results differ from studies conducted in the general population that have found significant and consistent associations between these markers and AF risk.[17,18] Although these observations do not serve as evidence for atrial inflammation, fibrosis, and remodeling as pathways leading to AF in the setting of CKD, our findings must be interpreted cautiously. We evaluated factors associated with the first occurrence of AF, at which time atrial remodeling may not have yet occurred. This is an important consideration since atrial remodeling and fibrosis may be the consequence of the cumulative exposure to AF triggers.[39] In addition, results from analyses of surrogate biomarkers may not translate into predictable physiologic processes.

We believe that these observations advance the knowledge of the mechanisms leading to the disproportionate high burden of AF in people with CKD and may inform future therapeutic trials aimed at decreasing the high cardiovascular risk experienced by these patients. For instance, our observations suggest that AF may be part of the same spectrum of disorders as HF and the cardiorenal syndrome.[40] It is therefore possible that more judicious use of diuretics may reduce the burden of AF in CKD. In addition, our study leads

Table 2. Associations of Cardiac Biomarkers and Incident AF in Participants With Chronic Kidney Disease

Cardiac Biomarker	N at Risk (N events)	Model 1*		Model 2†	
		HR (95% CI)	*P* Value‡	HR (95% CI)	*P* Value
Continuous predictors (per SD higher concentration)					
Log-NT-proBNP		2.12 (1.77, 2.55)	<0.0001	2.11 (1.75, 2.55)	<0.0001
Log-hsTnT		1.51 (1.29, 1.77)	<0.0001	1.42 (1.20, 1.68)	<0.0001
Log-sST-2		1.4 (1.19, 1.64)	<0.0001	1.35 (1.16, 1.58)	0.0001
Log-galectin-3		1.09 (0.94, 1.27)	0.26	1.05 (0.91, 1.22)	0.49
Log-GDF-15		1.28 (1.06, 1.53)	0.009	1.16 (0.96, 1.4)	0.14
Categorical predictors					
NT-proBNP, pg/mL					
(Reference: ≤2.7)	611 (17)				
32.8–81	610 (36)	1.92 (1.08, 3.4)	<0.0001	1.94 (1.09, 3.44)	<0.0001
81.1–176	611 (44)	2.22 (1.26, 3.91)		2.27 (1.28, 4.03)	
176.1–423	610 (74)	3.85 (2.22, 6.65)		4.02 (2.3, 7.02)	
>423	611 (108)	7.12 (4.01, 12.63)		7.31 (4.05, 13.17)	
hsTnT, pg/mL					
(Reference: <10)	1019 (44)				
10.1–15.6	669 (61)	1.58 (1.05, 2.37)	0.0001	1.54 (1.02, 2.33)	0.002
15.7–26.9	684 (81)	2.04 (1.35, 3.09)		1.97 (1.3, 2.96)	
>26.9	681 (93)	2.8 (1.78, 4.4)		2.47 (1.55, 3.96)	
sST-2, ng/mL					
(Reference: ≤10.4)	611 (37)				
10.5–13.5	611 (48)	1.07 (0.69, 1.65)	0.05	1.05 (0.67, 1.62)	0.13
13.6–17.1	611 (46)	1.05 (0.68, 1.63)		1.02 (0.65, 1.59)	
17.2–22.7	609 (68)	1.39 (0.92, 2.11)		1.34 (0.88, 2.03)	
>22.7	611 (80)	1.68 (1.09, 2.58)		1.55 (1, 2.4)	
Galectin-3, ng/mL					
(Reference: ≤9.27)	612 (46)				
9.28–12.6	609 (55)	1.08 (0.73, 1.6)	0.39	1.05 (0.71, 1.56)	0.59
12.7–15.8	612 (48)	0.97 (0.64, 1.47)		0.91 (0.6, 1.38)	
15.9–20.8	609 (59)	1.14 (0.76, 1.73)		1.07 (0.71, 1.61)	
>20.8	611 (71)	1.4 (0.92, 2.12)		1.25 (0.82, 1.92)	
GDF-15, pg/mL					
(Reference: ≤880)	611 (24)				
881–1250	610 (48)	1.52 (0.89, 2.6)	0.04	1.47 (0.86, 2.52)	0.27
1251–1670	612 (57)	1.43 (0.83, 2.46)		1.31 (0.76, 2.26)	
1671–2370	609 (71)	1.89 (1.06, 3.39)		1.65 (0.93, 2.94)	
>2370	611 (79)	2.36 (1.29, 4.3)		1.88 (1.02, 3.46)	

SD for each predictor: NT-proBNP (1.68), hsTnT (0.82), sST-2 (0.57), galectin-3 (0.50), GDF-15 (0.59). AF indicates atrial fibrillation; FGF-23, fibroblast growth factor-23; GDF-15, growth differentiation factor-15; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST-2, soluble ST-2.

*Model 1: Adjusted for age, age^2, sex, race, site, diabetes mellitus, cardiovascular disease, smoking, 24-h urinary protein, estimated glomerular filtration rate, systolic blood pressure, body mass index, low-density lipoprotein, high-density lipoprotein.

†Model 2: Adjusted for variables in model 1 plus angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, diuretics, β-blockers, phosphate, parathyroid hormone, FGF-23.

‡*P* values in categorical models are for differences between categories.

to additional questions about whether novel therapies that directly affect cardiorenal outcomes may be effective in decreasing the risk of AF in patients with CKD.[41,42] Specifically, sodium-glucose-cotransporter-2 inhibitors have direct hemodynamic effects because of significant reductions in plasma volume reducing intracardiac filling pressures and myocardial injury.[43,44] Furthermore, our observation may help identify patients at highest risk for cardiovascular disease who would potentially derive most benefit from these interventions. Finally, our study may inform future research aimed at improving predictive models for the onset of AF in people with CKD.

Important strengths of this study include the large and well-characterized cohort of CKD participants. Incident AF was systematically ascertained and rigorously adjudicated using standardized criteria. All biomarkers were measured concurrently. We controlled for a large set of possible confounders, which included markers of mineral metabolism and echocardiographic measures of heart structure and function.

Limitations of our study include that we did not have available rhythm monitoring measurements that would enable us to identify the type of AF (eg, paroxysmal versus persistent AF) or assess the arrhythmic AF burden (if paroxysmal) present in patients newly diagnosed with AF. In addition, we defined incident AF solely based on hospitalized cases. Therefore, we did not capture cases occurring in outpatient settings. It is likely that this resulted in an underestimation of the true incidence of AF. Although in our analyses we accounted for a large set of clinical characteristics, it is possible that unmeasured confounding may in part account for the observed results. Finally, the study sample consisted of research volunteers followed in nephrology clinics, potentially limiting the generalizability of these findings to all CKD populations.

In conclusion, among patients with CKD, elevated NT-proBNP and hsTnT were strongly and independently associated with the risk of incident AF. There was a modest association of SST2 with incident AF, which was not observed for galectin-3 or GDF-15. These results provide further mechanistic insights into the strong association between CKD and AF and may inform future trials of therapeutic interventions aimed at reducing the risk of AF in patients with CKD.

Appendix

CRIC Study Investigators

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Supplemental Material

Table S1. Demographic and clinical characteristics by quantile of baseline Galectin-3.

	Overall	**≤ 9.27**	**9.28 – 12.6**	**12.7 – 15.8**	**15.9 – 20.8**	**> 20.8**
N	3053	612	609	612	609	611
Age (years)	57.1 (11.2)	55.2 (11.3)	57.0 (11.8)	57.0 (10.9)	57.8 (11.2)	58.7 (10.5)
Women	1381 (45)	205 (33)	249 (41)	283 (46)	298 (49)	346 (57)
Race/ethnicity						
Non-Hispanic white	1295 (42)	336 (55)	309 (51)	262 (43)	203 (33)	185 (30)
Non-Hispanic black	1208 (40)	208 (34)	217 (36)	245 (40)	266 (44)	272 (45)
Hispanic	421 (14)	41 (7)	61 (10)	77 (13)	109 (18)	133 (22)
Other	129 (4)	27 (4)	22 (4)	28 (5)	31 (5)	21 (3)
eGFR (CKD-EPI), mL/min/1.73m^2	44.6 (14.8)	53.1 (14.2)	48.8 (14.5)	44.9 (13.4)	40.5 (12.4)	35.7 (12.8)
24-hour urine protein (g/d), median	0.2 (0.1-0.8)	0.1 (0.0-0.3)	0.1 (0.0-0.6)	0.1 (0.1-0.7)	0.2 (0.1-1.1)	0.4 (0.1-2.0)
Diabetes	1470 (48)	205 (33)	233 (38)	293 (48)	340 (56)	399 (65)
History of CVD	855 (28)	125 (20)	152 (25)	168 (27)	182 (30)	228 (37)
History of HF	182 (6)	18 (3)	29 (5)	31 (5)	39 (6)	65 (11)
Current smoker	389 (13)	57 (9)	68 (11)	94 (15)	80 (13)	90 (15)
Alcohol use	1966 (64)	460 (75)	428 (70)	388 (63)	347 (57)	343 (56)
BMI (kg/m^2)	32.0 (7.8)	30.4 (6.9)	31.5 (7.4)	32.0 (7.6)	32.8 (8.2)	33.1 (8.5)
SBP (mmHg)	128.7 (22.1)	123.1 (19.3)	127.3 (21.5)	127.4 (22.0)	131.6 (22.8)	134.0 (23.0)
DBP (mmHg)	72.0 (12.8)	73.0 (12.3)	72.0 (12.5)	72.2 (12.6)	72.2 (13.6)	70.8 (13.0)
Hemoglobin (g/dL)	12.6 (1.8)	13.4 (1.7)	13.0 (1.6)	12.7 (1.7)	12.3 (1.7)	11.7 (1.7)
LDL cholesterol (mg/dL)	103.7 (35.1)	105.0 (33.8)	105.5 (33.5)	104.2 (33.8)	102.8 (36.1)	101.1 (38.1)
HDL cholesterol (mg/dL)	47.9 (15.8)	48.6 (15.5)	47.6 (15.8)	48.4 (16.3)	47.6 (15.0)	47.1 (16.3)
ACEi/ARBs	2071 (68)	380 (62)	408 (67)	424 (69)	423 (69)	436 (71)
Diuretics	1725 (57)	260 (42)	318 (52)	348 (57)	374 (61)	425 (70)
Beta blockers	1397 (46)	227 (37)	263 (43)	270 (44)	314 (52)	323 (53)
FGF-23 (RU/mL), median	138.6 (94.3-225.3)	100.4 (72.3-147.4)	123.6 (84.9-186.2)	138.7 (95.9-205.9)	156.8 (107.3-250.7)	207.1 (129.6-349.3)
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 PTH (pg/mL), median	52.7 (34.0-88.0)	39.5 (29.0-61.3)	45.0 (31.2-74.8)	51.8 (34.9-83.9)	60.5 (38.9-99.7)	76.0 (46.0-131.2)
EF from echocardiogram	54.9 (7.6)	55.0 (7.4)	55.5 (7.3)	55.4 (7.4)	54.4 (8.1)	54.4 (7.6)
LVMI	63.2 (22.7)	57.3 (20.2)	62.2 (22.2)	62.9 (22.2)	66.3 (23.9)	68.8 (23.7)

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

Table S2. Demographic and clinical characteristics by quantile of baseline hsTnT.

	< 10	**10.1 – 15.6**	**15.7 – 26.9**	**> 26.9**
N	1019	669	684	681
Age (years)	57.1 (11.2)	53.4 (11.8)	58.7 (10.8)	59.8 (9.9)
Women	1381 (45)	657 (64)	301 (45)	250 (37)
Race/ethnicity				
Non-Hispanic white	1295 (42)	513 (50)	323 (48)	268 (39)
Non-Hispanic black	1208 (40)	356 (35)	243 (36)	286 (42)
Hispanic	421 (14)	96 (9)	75 (11)	105 (15)
Other	129 (4)	54 (5)	28 (4)	25 (4)
eGFR (CKD-EPI), mL/min/1.73m^2	44.6 (14.8)	51.8 (15.3)	45.0 (12.6)	41.8 (12.8)
24-hour urine protein (g/d), median	0.2 (0.1-0.8)	0.1 (0.0-0.3)	0.1 (0.1-0.4)	0.2 (0.1-1.0)
Diabetes	1470 (48)	250 (25)	290 (43)	380 (56)
History of CVD	855 (28)	153 (15)	163 (24)	247 (36)
History of HF	182 (6)	17 (2)	29 (4)	49 (7)
Current smoker	389 (13)	131 (13)	89 (13)	85 (12)
Alcohol use	1966 (64)	722 (71)	443 (66)	433 (63)
BMI (kg/m^2)	32.0 (7.8)	30.8 (7.6)	31.7 (7.7)	33.0 (8.1)
SBP (mmHg)	128.7 (22.1)	120.9 (18.1)	126.9 (20.6)	131.9 (22.4)
DBP (mmHg)	72.0 (12.8)	72.3 (11.6)	71.5 (12.3)	71.6 (13.7)
Hemoglobin (g/dL)	12.6 (1.8)	13.0 (1.6)	12.8 (1.8)	12.6 (1.8)
LDL cholesterol (mg/dL)	103.7 (35.1)	108.2 (33.4)	103.4 (33.5)	99.6 (34.2)
HDL cholesterol (mg/dL)	47.9 (15.8)	51.5 (16.1)	48.0 (16.0)	45.5 (15.3)
ACEi/ARBs	2071 (68)	583 (57)	467 (70)	521 (76)
Diuretics	1725 (57)	401 (39)	375 (56)	450 (66)
Beta blockers	1397 (46)	332 (33)	316 (47)	368 (54)
FGF-23 (RU/mL), median	138.6 (94.3-225.3)	111.9 (78.2-171.0)	133.1 (93.8-211.0)	148.5 (100.7-229.7)
Serum phosphorus, mg/dL	3.7 (0.7)	3.6 (0.6)	3.6 (0.6)	3.7 (0.7)
Total PTH (pg/mL), median	52.7 (34.0-88.0)	43.0 (31.0-65.9)	46.8 (32.0-78.0)	60.0 (37.8-91.0)
EF from echocardiogram	54.9 (7.6)	56.0 (6.3)	55.7 (7.6)	54.5 (8.0)

LVMI	63.2 (22.7)	53.3 (16.8)	61.5 (18.9)	67.7 (23.6)

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

Table S3. Demographic and clinical characteristics by quantile of baseline GDF-15.

	≤ 880	**881 – 1250**	**1251 – 1670**	**1671 – 2370**	**> 2370**
N	611	610	612	609	611
Age (years)	57.1 (11.2)	50.9 (11.7)	56.3 (11.1)	58.5 (10.7)	59.9 (9.9)
Women	1381 (45)	301 (49)	285 (47)	269 (44)	276 (45)
Race/ethnicity					
Non-Hispanic white	1295 (42)	343 (56)	276 (45)	258 (42)	239 (39)
Non-Hispanic black	1208 (40)	206 (34)	236 (39)	253 (41)	250 (41)
Hispanic	421 (14)	37 (6)	66 (11)	84 (14)	92 (15)
Other	129 (4)	25 (4)	32 (5)	17 (3)	28 (5)
eGFR (CKD-EPI), mL/min/1.73m^2	44.6 (14.8)	58.9 (12.8)	48.6 (12.0)	42.9 (11.3)	38.7 (12.2)
24-hour urine protein (g/d), median	0.2 (0.1-0.8)	0.1 (0.0-0.2)	0.1 (0.0-0.4)	0.1 (0.1-0.6)	0.3 (0.1-1.4)
Diabetes	1470 (48)	101 (17)	227 (37)	312 (51)	388 (64)
History of CVD	855 (28)	59 (10)	130 (21)	184 (30)	229 (38)
History of HF	182 (6)	13 (2)	23 (4)	32 (5)	48 (8)
Current smoker	389 (13)	38 (6)	46 (8)	81 (13)	108 (18)
Alcohol use	1966 (64)	484 (79)	430 (70)	374 (61)	345 (57)
BMI (kg/m^2)	32.0 (7.8)	30.9 (7.3)	32.0 (7.9)	32.9 (7.9)	32.4 (7.9)
SBP (mmHg)	128.7 (22.1)	119.9 (17.9)	124.6 (19.2)	128.2 (20.9)	133.4 (23.0)
DBP (mmHg)	72.0 (12.8)	74.0 (11.7)	73.1 (12.6)	71.1 (12.7)	71.4 (13.4)
Hemoglobin (g/dL)	12.6 (1.8)	13.6 (1.5)	13.1 (1.6)	12.6 (1.6)	12.1 (1.6)
LDL cholesterol (mg/dL)	103.7 (35.1)	111.4 (33.3)	105.7 (34.0)	103.1 (34.9)	101.2 (36.1)
HDL cholesterol (mg/dL)	47.9 (15.8)	50.4 (16.3)	48.8 (15.6)	47.0 (15.0)	47.0 (16.0)
ACEi/ARBs	2071 (68)	329 (54)	429 (70)	442 (72)	457 (75)
Diuretics	1725 (57)	211 (35)	306 (50)	377 (62)	396 (65)
Beta blockers	1397 (46)	176 (29)	259 (42)	285 (47)	329 (54)
FGF-23 (RU/mL), median	138.6 (94.3-225.3)	90.6 (66.8-123.3)	116.8 (84.4-166.1)	142.7 (103.3-207.0)	173.1 (121.8-268.4)
Serum phosphorus, mg/dL	3.7 (0.7)	3.4 (0.5)	3.6 (0.6)	3.7 (0.6)	3.8 (0.7)
Total PTH (pg/mL), median	52.7 (34.0-88.0)	38.0 (28.9-53.0)	44.8 (31.8-67.9)	54.7 (35.2-83.2)	67.0 (40.8-105.2)
EF from echocardiogram	54.9 (7.6)	55.2 (6.8)	55.2 (7.4)	55.4 (7.5)	54.7 (8.1)

LVMI	63.2 (22.7)	53.2 (18.0)	60.5 (21.8)	65.0 (21.9)	67.6 (23.5)

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

Table S4. Demographic and clinical characteristics by quantile of SST-2.

	≤ 10.4	**10.5 – 13.5**	**13.6 – 17.1**	**17.2 – 22.7**	**> 22.7**
N	611	611	611	609	611
Age (years)	57.1 (11.2)	55.3 (12.0)	57.5 (10.4)	57.9 (10.8)	58.3 (10.8)
Women	1381 (45)	382 (63)	324 (53)	274 (45)	222 (36)
Race/ethnicity					
Non-Hispanic white	1295 (42)	234 (38)	274 (45)	258 (42)	267 (44)
Non-Hispanic black	1208 (40)	280 (46)	259 (42)	244 (40)	221 (36)
Hispanic	421 (14)	64 (10)	56 (9)	80 (13)	98 (16)
Other	129 (4)	33 (5)	22 (4)	29 (5)	23 (4)
eGFR (CKD-EPI), mL/min/1.73m^2	44.6 (14.8)	47.7 (15.2)	45.1 (14.9)	45.4 (14.7)	43.4 (14.4)
24-hour urine protein (g/d), median	0.2 (0.1-0.8)	0.1 (0.0-0.3)	0.1 (0.1-0.4)	0.1 (0.1-0.7)	0.2 (0.1-1.3)
Diabetes	1470 (48)	202 (33)	244 (40)	281 (46)	359 (59)
History of CVD	855 (28)	117 (19)	160 (26)	162 (27)	200 (33)
History of HF	182 (6)	35 (6)	32 (5)	30 (5)	38 (6)
Current smoker	389 (13)	88 (14)	79 (13)	81 (13)	71 (12)
Alcohol use	1966 (64)	419 (69)	392 (64)	391 (64)	375 (62)
BMI (kg/m^2)	32.0 (7.8)	31.5 (7.9)	32.7 (7.7)	32.3 (7.5)	32.0 (8.1)
SBP (mmHg)	128.7 (22.1)	123.5 (20.5)	126.4 (20.8)	128.5 (21.6)	132.1 (23.4)
DBP (mmHg)	72.0 (12.8)	72.5 (12.7)	72.1 (12.6)	71.8 (12.7)	71.9 (13.2)
Hemoglobin (g/dL)	12.6 (1.8)	12.8 (1.6)	12.7 (1.7)	12.6 (1.7)	12.6 (1.8)
LDL cholesterol (mg/dL)	103.7 (35.1)	106.6 (34.4)	104.7 (32.9)	103.2 (34.0)	103.4 (35.6)
HDL cholesterol (mg/dL)	47.9 (15.8)	48.7 (15.1)	47.9 (15.1)	48.0 (15.4)	46.4 (14.8)
ACEi/ARBs	2071 (68)	370 (61)	411 (67)	420 (69)	436 (72)
Diuretics	1725 (57)	299 (49)	331 (54)	336 (55)	373 (61)
Beta blockers	1397 (46)	244 (40)	250 (41)	274 (45)	314 (52)
FGF-23 (RU/mL), median	138.6 (94.3-225.3)	123.1 (83.7-201.3)	137.8 (95.6-210.2)	131.4 (91.1-201.3)	146.4 (97.0-236.6)
Serum phosphorus, mg/dL	3.7 (0.7)	3.7 (0.6)	3.7 (0.6)	3.7 (0.6)	3.7 (0.7)
Total PTH (pg/mL), median	52.7 (34.0-88.0)	50.0 (32.5-78.2)	49.9 (33.8-82.8)	48.4 (33.0-81.5)	56.0 (36.0-91.0)
EF from echocardiogram	54.9 (7.6)	55.6 (7.9)	55.4 (7.2)	54.9 (7.5)	54.6 (7.6)

LVMI	63.2 (22.7)	59.0 (22.0)	62.3 (22.3)	63.5 (22.7)	65.6 (22.4)

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

Table S5. Demographic and clinical characteristics by kidney function.

	Overall N = 3053	eGFR < 30 N = 543	eGFR 30- <45 N = 1091	eGFR 45- <60 N = 954	eGFR ≥60 N = 465
Demographics					
Age (years)	57.1 (11.2)	57.9 (11.4)	59.0 (11.1)	57.6 (10.4)	50.9 (10.8)
Women	1381 (45)	265 (49)	516 (47)	387 (41)	213 (46)
Race/ethnicity					
Non-Hispanic white	1295 (42)	179 (33)	436 (40)	439 (46)	241 (52)
Non-Hispanic black	1208 (40)	221 (41)	446 (41)	374 (39)	167 (36)
Hispanic	421 (14)	119 (22)	171 (16)	95 (10)	36 (8)
Other	129 (4)	24 (4)	38 (3)	46 (5)	21 (5)
Medical history					
Diabetes	1470 (48)	305 (56)	590 (54)	423 (44)	152 (33)
History of CVD	855 (28)	183 (34)	353 (32)	248 (26)	71 (15)
History of heart failure	182 (6)	54 (10)	77 (7)	38 (4)	13 (3)
Current smoker	389 (13)	73 (13)	154 (14)	102 (11)	60 (13)
Alcohol use	1966 (64)	311 (57)	646 (59)	661 (69)	348 (75)
Markers of Kidney function					
eGFR (CKD-EPI); mL/min/1.73m^2	44.6 (14.8)	24.6 (3.7)	37.9 (4.3)	51.8 (4.3)	69.0 (8.4)
24-hour urine protein (g/d), median (IQR)	0.2 (0.1-0.8)	0.7 (0.2-2.4)	0.2 (0.1-1.1)	0.1 (0.0-0.4)	0.1 (0.0-0.2)
Clinical characteristics and laboratory measurements					
BMI (kg/m^2)	32.0 (7.8)	32.1 (8.1)	32.3 (7.7)	31.8 (7.9)	31.3 (7.4)
SBP (mmHg)	128.7 (22.1)	133.5 (24.5)	130.4 (22.5)	127.1 (20.5)	122.2 (19.4)
DBP (mmHg)	72.0 (12.8)	71.2 (13.6)	71.2 (12.7)	72.5 (12.4)	74.0 (12.8)
Hemoglobin (g/dL)	12.6 (1.8)	11.7 (1.6)	12.4 (1.7)	13.0 (1.7)	13.4 (1.6)
LDL cholesterol (mg/dL)	103.7 (35.1)	101.8 (37.5)	102.1 (35.1)	104.3 (34.4)	108.6 (33.1)
HDL cholesterol (mg/dL)	47.9 (15.8)	46.3 (15.2)	47.0 (15.1)	48.8 (16.2)	49.7 (16.7)

FGF-23 (RU/mL), median (IQR)	138.6 (94.3-225.3)	241.9 (169.7-377.8)	156.3 (109.4-238.5)	115.7 (82.3-164.6)	91.7 (67.6-120.3)
Serum phosphorus, mg/dL	3.7 (0.7)	4.1 (0.8)	3.8 (0.6)	3.5 (0.6)	3.5 (0.5)
Total PTH (pg/mL), median (IQR)	52.7 (34.0-88.0)	104.0 (64.4-174.9)	60.0 (39.0-93.0)	44.0 (31.0-65.0)	35.5 (27.3-48.6)
Medications					
ACEi/ARBs	2071 (68)	364 (67)	797 (73)	670 (70)	240 (52)
Diuretics	1725 (57)	378 (70)	699 (64)	478 (50)	170 (37)
Beta blockers	1397 (46)	297 (55)	554 (51)	407 (43)	139 (30)
Echocardiographic measurements					
LVEF from echocardiogram	54.9 (7.6)	54.5 (7.9)	54.8 (7.7)	55.2 (7.4)	55.1 (7.2)
LVMI (g/m^2)	63.2 (22.7)	71.4 (23.6)	65.4 (23.4)	60.8 (21.1)	55.4 (20.3)

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

NT-proBNP (N-terminal pro-B-type natriuretic peptide); CVD (cardiovascular disease); eGFR (estimated glomerular filtration rate); BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); LDL (low-density lipoprotein); HDL (high-density lipoprotein); PTH (parathyroid hormone); ACEi/ARBs (angiotensin converting enzyme inhibitor/angiotensin receptor blocker); LVEF (left ventricular ejection fraction); LVMI (left ventricular mass index).

Table S6. Associations of cardiac biomarkers and incident atrial fibrillation in the CRIC Study, adjusting for alternative cardiac biomarkers and echocardiographic measures.

Cardiac Biomarker		Final model*		Final model + adjustment for alternative cardiac biomarkers †		Final model + adjustment for echocardiographic measurements ‡	
	N at risk (N events)	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		1.05 (0.91, 1.22)	0.49	1.06 (0.91, 1.23)	0.44	1.06 (0.91, 1.23)	0.49
Log(NT-proBNP) per 1 SD (1.68) increase		2.11 (1.75, 2.55)	< 0.0001	2.08 (1.72, 2.52)	< 0.0001	1.86 (1.52, 2.26)	< 0.0001
Log(hsTnT) per 1 SD (0.82) increase		1.42 (1.20, 1.68)	< 0.0001	1.35 (1.14, 1.61)	0.0007	1.31 (1.09, 1.56)	0.003
Log(GDF-15) per 1 SD (0.59) increase		1.16 (0.96, 1.40)	0.14	1.09 (0.89, 1.33)	0.42	1.14 (0.94, 1.39)	0.18
Log(SST-2) per 1 SD (0.57) increase		1.35 (1.16, 1.58)	0.0001	1.29 (1.11, 1.51)	0.001	1.35 (1.16, 1.59)	0.0001
Categorical predictors							
Galectin-3							
(Reference: ≤ 9.27)	612 (46)						
9.28 – 12.6	609 (55)	1.05 (0.71, 1.56)	0.59	1.08 (0.72, 1.62)	0.56	1.03 (0.68, 1.54)	0.67
12.7 – 15.8	612 (48)	0.91 (0.60, 1.38)		0.92 (0.60, 1.41)		0.93 (0.61, 1.41)	
15.9 – 20.8	609 (59)	1.07 (0.71, 1.61)		1.08 (0.71, 1.63)		1.07 (0.71, 1.62)	
> 20.8	611 (71)	1.25 (0.82, 1.92)		1.29 (0.84, 1.98)		1.25 (0.81, 1.94)	
NT-proBNP, pg/mL							
(Reference: ≤ 32.7)	611 (17)						
32.8 – 81	610 (36)	1.94 (1.09, 3.44)	< 0.0001	1.94 (1.09, 3.46)	< 0.0001	1.87 (1.05, 3.32)	< 0.0001
81.1 – 176	611 (45)	2.27 (1.28, 4.03)		2.27 (1.28, 4.04)		2.03 (1.14, 3.62)	
176.1 – 423	610 (74)	4.02 (2.30, 7.02)		4.00 (2.29, 7.01)		3.59 (2.05, 6.28)	
> 423	611 (108)	7.31 (4.05, 13.17)		7.27 (4.02, 13.15)		5.43 (2.94, 10.03)	
hsTnT, pg/mL							
(Reference: < 10)	1019 (44)						
10.1 – 15.6	669 (61)	1.54 (1.02, 2.33)	0.002	1.54 (1.02, 2.33)	0.005	1.45 (0.96, 2.19)	0.05
15.7 – 26.9	684 (81)	1.97 (1.30, 2.96)		1.93 (1.27, 2.91)		1.69 (1.11, 2.57)	
> 26.9	681 (93)	2.47 (1.55, 3.96)		2.33 (1.44, 3.76)		1.94 (1.19, 3.15)	

GDF-15							
(Reference: ≤ 880)	611 (24)						
881 – 1250	610 (48)	1.47 (0.86, 2.52)	0.27	1.49 (0.87, 2.55)	0.45	1.43 (0.84, 2.45)	0.31
1251 – 1670	612 (57)	1.31 (0.76, 2.26)		1.33 (0.77, 2.30)		1.30 (0.75, 2.25)	
1671 – 2370	609 (71)	1.65 (0.93, 2.94)		1.64 (0.91, 2.95)		1.62 (0.90, 2.93)	
> 2370	611 (79)	1.88 (1.02, 3.46)		1.71 (0.91, 3.24)		1.85 (0.99, 3.44)	
sST-2							
(Reference: ≤ 10.4)	611 (37)						
10.5 – 13.5	611 (48)	1.05 (0.67, 1.62)	0.13	1.06 (0.68, 1.65)	0.21	1.08 (0.69, 1.69)	0.11
13.6 – 17.1	611 (46)	1.02 (0.65, 1.59)		1.01 (0.65, 1.58)		1.10 (0.70, 1.71)	
17.2 – 22.7	609 (68)	1.34 (0.88, 2.03)		1.33 (0.88, 2.02)		1.40 (0.92, 2.14)	
> 22.7	611 (80)	1.55 (1.00, 2.40)		1.49 (0.96, 2.33)		1.64 (1.06, 2.55)	

*Final model: age, age^2, sex, race, site, diabetes, CVD, smoking, 24h urinary protein, eGFR, SBP, BMI, LDL, HDL plus ACEi/ARBs, diuretics, beta blockers, phosphate, PTH, FGF-23

†Final model plus other biomarkers (NT pro-BP, Galectin-3, hsTnT, GDF-15, sST-2)

‡Final model plus LVMI, LVEF, and left atrial diameter

Table S7. Time-updated associations of cardiac biomarkers with incident atrial fibrillation.

Cardiac Biomarker	Model 1*		Model 2†		Model 3 ‡	
	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	1.10 (0.94, 1.29)	0.24	1.04 (0.85, 1.26)	0.71	1.03 (0.85, 1.26)	0.73
Log(NT-proBNP) per 1 SD (1.68) increase	2.19 (1.85, 2.60)	< 0.0001	2.52 (2.03, 3.14)	< 0.0001	2.45 (1.96, 3.08)	< 0.0001
Log(hsTnT) per 1 SD (0.82) increase	1.45 (1.26, 1.66)	< 0.0001	1.44 (1.18, 1.77)	0.0005	1.36 (1.10, 1.68)	0.005
Log(GDF-15) per 1 SD (0.59) increase	1.26 (1.05, 1.52)	0.01	1.26 (1.00, 1.59)	0.048	1.19 (0.93, 1.52)	0.16
Log(SST-2) per 1 SD (0.57) increase	1.28 (1.09, 1.50)	0.003	1.43 (1.19, 1.72)	0.0001	1.33 (1.10, 1.60)	0.003
Categorical predictors						
Galectin-3						
(Reference: ≤ 9.27)						
9.28 – 12.6	1.27 (0.81, 1.99)	0.17	1.06 (0.66, 1.73)	0.31	1.09 (0.67, 1.76)	0.32
12.7 – 15.8	1.01 (0.63, 1.62)		0.77 (0.45, 1.32)		0.78 (0.46, 1.33)	
15.9 – 20.8	1.4 (0.88, 2.22)		1.06 (0.64, 1.75)		1.05 (0.63, 1.75)	
> 20.8	1.60 (1.00, 2.57)		1.34 (0.79, 2.27)		1.33 (0.78, 2.27)	
NT-proBNP, pg/mL						
(Reference: ≤ 32.7)						
32.8 – 81	1.57 (0.80, 3.06)	< 0.0001	2.00 (0.90, 4.45)	< 0.0001	2.04 (0.92, 4.53)	< 0.0001
81.1 – 176	2.01 (1.06, 3.81)		2.97 (1.37, 6.45)		3.01 (1.39, 6.55)	
176.1 – 423	3.52 (1.90, 6.53)		5.76 (2.72, 12.19)		5.81 (2.73, 12.38)	
> 423	6.88 (3.68, 12.86)		11.41 (5.18, 25.17)		11.33 (5.12, 25.07)	
hsTnT, pg/mL						
(Reference: < 10)						
10.1 – 15.6	1.60 (1.02, 2.51)	0.0001	1.80 (1.06, 3.03)	0.003	1.81 (1.07, 3.06)	0.008
15.7 – 26.9	2.19 (1.41, 3.42)		2.42 (1.42, 4.13)		2.38 (1.39, 4.08)	
> 26.9	2.79 (1.76, 4.43)		3.02 (1.65, 5.54)		2.81 (1.50, 5.25)	
GDF-15						
(Reference: ≤ 880)						
881 – 1250	1.30 (0.75, 2.27)	0.10	1.80 (0.88, 3.66)	0.24	1.80 (0.88, 3.70)	0.34
1251 – 1670	1.20 (0.69, 2.10)		1.70 (0.83, 3.50)		1.73 (0.83, 3.60)	
1671 – 2370	1.73 (0.96, 3.12)		2.24 (1.05, 4.80)		2.25 (1.03, 4.89)	
> 2370	1.95 (1.05, 3.59)		2.48 (1.10, 5.60)		2.26 (0.96, 5.35)	
SST-2						

(Reference: ≤ 10.4)						
10.5 – 13.5	1.17 (0.74, 1.85)	0.24	1.50 (0.85, 2.62)	0.09	1.53 (0.87, 2.69)	0.16
13.6 – 17.1	1.10 (0.69, 1.74)		1.16 (0.65, 2.07)		1.17 (0.65, 2.09)	
17.2 – 22.7	1.35 (0.87, 2.09)		1.66 (0.96, 2.87)		1.64 (0.95, 2.85)	
> 22.7	1.59 (1.01, 2.50)		1.97 (1.12, 3.49)		1.85 (1.04, 3.31)	

*Model 1: age, age^2, sex, race, site, diabetes, CVD, smoking, 24h urinary protein, eGFR, SBP, BMI, LDL, HDL

†Model 2: Model 1 plus ACEi/ARBs, diuretics, beta blockers, phosphate, PTH, FGF-23

‡Model 3: Model 2 plus other biomarkers (NT pro-BP, Gal3, hsTnT, GDF-15, SST-2)

Table S8. Associations of cardiac biomarkers and incident atrial fibrillation, excluding participants with prevalent HF (N = 2871).

Cardiac Biomarker		Model 1*		Model 2†	
	N at risk (N events)	HR (95% CI)	p-value	HR (95% CI)	p-value
Continuous predictors (per SD higher concentration)					
Log-NT-proBNP		2.10 (1.73, 2.55)	< 0.0001	2.10 (1.72, 2.57)	< 0.0001
Log-hsTnT		1.50 (1.27, 1.76)	< 0.0001	1.41 (1.18, 1.68)	0.0001
Log-SST-2		1.38 (1.18, 1.63)	0.0001	1.34 (1.14, 1.57)	0.0004
Log-Galectin-3		1.10 (0.94, 1.29)	0.25	1.06 (0.90, 1.24)	0.48
Log-GDF-15		1.31 (1.09, 1.58)	0.005	1.19 (0.98, 1.45)	0.09
Categorical predictors					
NT-proBNP, pg/mL					
(Reference: ≤ 32.7)	598 (17)				
32.8 – 81	598 (34)	1.84 (1.03, 3.29)	< 0.0001	1.86 (1.04, 3.32)	< 0.0001
81.1 – 176	595 (44)	2.33 (1.32, 4.11)		2.38 (1.34, 4.25)	
176.1 – 423	571 (65)	3.72 (2.12, 6.51)		3.92 (2.21, 6.93)	
> 423	509 (90)	7.21 (4.00, 13.00)		7.44 (4.05, 13.70)	
hsTnT, pg/mL					
(Reference: < 10)	1002 (44)				
10.1 – 15.6	640 (55)	1.51 (0.99, 2.30)	0.0002	1.50 (0.98, 2.29)	0.002
15.7 – 26.9	635 (75)	2.10 (1.37, 3.21)		2.04 (1.34, 3.12)	
> 26.9	594 (76)	2.76 (1.71, 4.44)		2.46 (1.50, 4.03)	
SST-2, ng/ml					
(Reference: ≤ 10.4)	576 (33)				
10.5 – 13.5	579 (43)	1.11 (0.69, 1.76)	0.07	1.09 (0.68, 1.73)	0.15
13.6 – 17.1	581 (43)	1.13 (0.71, 1.78)		1.09 (0.69, 1.73)	
17.2 – 22.7	571 (63)	1.52 (0.98, 2.36)		1.45 (0.94, 2.25)	
> 22.7	564 (68)	1.74 (1.10, 2.75)		1.61 (1.01, 2.57)	
Galectin-3, ng/ml					
(Reference: ≤ 9.27)	594 (43)				

9.28 – 12.6	580 (51)	1.11 (0.74, 1.67)	0.34	1.09 (0.72, 1.64)	0.57
12.7 – 15.8	581 (42)	0.95 (0.62, 1.47)		0.90 (0.58, 1.40)	
15.9 – 20.8	570 (54)	1.21 (0.79, 1.85)		1.13 (0.73, 1.73)	
> 20.8	546 (60)	1.44 (0.92, 2.24)		1.28 (0.82, 2.00)	
GDF-15, pg/ml					
(Reference: ≤ 880)	598 (23)				
881 – 1250	587 (44)	1.64 (0.95, 2.84)	0.02	1.61 (0.93, 2.80)	0.16
1251 – 1670	580 (54)	1.64 (0.94, 2.84)		1.53 (0.88, 2.66)	
1671 – 2370	561 (61)	2.08 (1.15, 3.77)		1.84 (1.02, 3.33)	
> 2370	545 (68)	2.72 (1.47, 5.02)		2.21 (1.18, 4.14)	

NT-proBNP (N-terminal pro-B-type natriuretic peptide), hsTnT (high sensitivity troponin T), SST-2 (soluble ST-2), GDF-15 (growth differentiation factor-15).
Standard deviation for each predictor: NT-proBNP (1.68), hsTnT (0.82), SST-2 (0.57), galectin-3 (0.50), GDF-15 (0.59)
*Model 1: Adjusted for age, age^2, sex, race, site, diabetes, CVD, smoking, 24h urinary protein, eGFR, SBP, BMI, LDL, HDL.
†Model 2: Adjusted for variables in model 1 plus ACEi/ARBs, diuretics, beta blockers, phosphate, PTH, FGF-23.

Table S9. Associations of cardiac biomarkers and incident atrial fibrillation, by eGFR category.

Cardiac Biomarker	Model 1*		Model 2†	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Continuous predictors (per SD higher concentration)				
eGFR ≥ 45 (N=1634)				
Log-NT-proBNP	2.39 (1.77, 3.22)	< 0.0001	2.35 (1.76, 3.15)	< 0.0001
Log-hsTnT	1.70 (1.33, 2.17)	< 0.0001	1.62 (1.25, 2.09)	0.0002
Log-SST-2	1.43 (1.11, 1.83)	0.005	1.39 (1.09, 1.77)	0.008
Log-Galectin-3	1.19 (0.93, 1.52)	0.17	1.15 (0.91, 1.47)	0.25
Log-GDF-15	1.20 (0.94, 1.53)	0.14	1.11 (0.88, 1.41)	0.38
eGFR < 45 (N=1619)				
Log-NT-proBNP	1.98 (1.59, 2.45)	< 0.0001	1.97 (1.58, 2.46)	< 0.0001
Log-hsTnT	1.44 (1.21, 1.71)	< 0.0001	1.33 (1.10, 1.61)	0.003
Log-SST-2	1.39 (1.15, 1.68)	0.0008	1.34 (1.11, 1.60)	0.002
Log-Galectin-3	1.03 (0.86, 1.24)	0.72	0.99 (0.82, 1.19)	0.92
Log-GDF-15	1.34 (1.07, 1.68)	0.01	1.19 (0.94, 1.51)	0.16

NT-proBNP (N-terminal pro-B-type natriuretic peptide), hsTnT (high sensitivity troponin T), SST-2 (soluble ST-2), GDF-15 (growth differentiation factor-15).
Standard deviation for each predictor: NT-proBNP (1.68), hsTnT (0.82), SST-2 (0.57), galectin-3 (0.50), GDF-15 (0.59)
*Model 1: Adjusted for age, age^2, sex, race, site, diabetes, CVD, smoking, 24h urinary protein, eGFR, SBP, BMI, LDL, HDL.
†Model 2: Adjusted for variables in model 1 plus ACEi/ARBs, diuretics, beta blockers, phosphate, PTH, FGF-23.