Cardiac Biomarkers and Risk of Mortality in CKD (the CRIC Study)

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Introduction: Cardiovascular disease (CVD) is the leading cause of mortality among individuals with chronic kidney disease (CKD). Cardiac biomarkers of myocardial distention, injury, and inflammation may signal unique pathways underlying CVD in CKD. In this analysis, we studied the association of baseline levels and changes in 4 traditional and novel cardiac biomarkers with risk of all-cause, CV, and non-CV mortality in a large cohort of patients with CKD.

Methods: Among 3664 adults with CKD enrolled in the Chronic Renal Insufficiency Cohort Study, we conducted a cohort study to examine the associations of baseline levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac high-sensitivity troponin T (hsTnT), growth differentiation factor−15 (GDF-15), and soluble ST-2 (sST-2) with risks of all-cause and cardiovascular (CV) mortality. Among a subcohort of 842 participants, we further examined the associations between change in biomarker levels over 2 years with risk of all-cause mortality. We used Cox proportional hazards regression models and adjusted for demographics, kidney function measures, cardiovascular risk factors, and medication use.

Results: After adjustment, elevated baseline levels of each cardiac biomarker were associated with increased risk of all-cause mortality: NT-proBNP (hazard ratio [HR] = 1.92, 95% confidence interval [CI] = 1.73−2.12); hsTnT (HR = 1.62, 95% CI = 1.48, 1.78]); GDF-15 (HR = 1.61, 95% CI = 1.46−1.78]); and sST-2 (HR = 1.26, CI = 1.16−1.37). Higher baseline levels of all 4 cardiac biomarkers were also associated with increased risk of CV. Declines in NT-proBNP (adjusted HR = 0.55, 95% CI = 0.36−0.86) and sST2 (HR = 0.55, 95% CI = 0.36−0.86]) over 2 years were associated with lower risk of all-cause mortality.

Conclusion: In a large cohort of CKD participants, elevations of NT-proBNP, hsTnT, GDF-15, and sST-2 were independently associated with greater risks of all-cause and CV mortality.

Cardiovascular disease (CVD) is the leading cause of mortality in patients with chronic kidney disease (CKD).[1−3] The increased risk for CVD in CKD is only partially explained by the prevalence of traditional cardiovascular risk factors.[4,5] Therefore, identifying novel pathways that uniquely contribute to CVD risk in CKD is an important step toward identifying underlying disease mechanisms and potentially developing effective therapies.

Cardiac biomarkers of myocardial distention, injury, and inflammation may signal unique pathways underlying CVD in CKD. N-terminal pro–B-type natriuretic peptide (NT-proBNP) is secreted from

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cardiac myocytes in response to ventricular wall stretch,[6] and levels increase with increasing left ventricular mass.[7−9] Concentrations of high-sensitivity cardiac troponin T (hsTnT) rise in response to myocardial injury.[10,11] Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor−β cytokine family and plays a role in cardiomyocyte repair.[12−14] Soluble ST2 (sST2) is a member of the interleukin-1 receptor family and its expression is up-regulated in the setting of myocardial injury.[15] These 4 biomarkers have been extensively investigated in CVD patients and healthy individuals, with higher levels associated with greater risk of mortality.[10,16−33] Although a few studies have examined the association of these biomarkers with clinical outcomes in CKD, these studies are limited by small sample size and short duration of follow-up.[34−38]

We sought to determine the associations of baseline concentrations of NT-proBNP, hsTnT, GDF-15, and sST2 with subsequent all-cause and cardiovascular (CV) mortality in the large, multi-center cohort of CKD individuals from the Chronic Renal Insufficiency Cohort (CRIC) Study. We further examined the change in biomarkers over time in a subcohort of study participants.

METHODS

Study Population

We performed an ancillary study of the Chronic Renal Insufficiency Cohort (CRIC) Study, a multi-center and prospective study of that enrolled 3939 adults with CKD between June 2003 and August 2008 at 7 clinical centers across the United States.[39,40] The CRIC study enrolled participants with Modification of Diet in Renal Disease (MDRD) equation−based estimated glomerular filtration rate (eGFR) between 20 and 70 ml/min per 1.73 m^2 for ages 21 to 44 years; 20 to 60 ml/min per 1.73 m^2 for ages 45 to 64 years; and 20 to 50 ml/min per 1.73 m^2 for ages 65 to 74 years.[41] Inclusion and exclusion criteria have been previously described.[39] Participants on maintenance dialysis or with a kidney transplant were not included at cohort entry. All study participants provided written informed consent, and the study protocol was approved by institutional review boards at each of the participating sites.

For our primary analysis, we excluded participants without baseline blood samples and those who were not able to have all 4 biomarkers measured concurrently, resulting in a final analytical cohort of 3664 participants. We further sampled and measured biomarkers in a random subcohort of 1002

participants at year 2 to assess longitudinal changes in biomarker levels. After excluding those with incomplete biomarkers measured at baseline and year 2, a total of 842 participants remained for this secondary analysis.

Cardiac Biomarkers

Both GDF-15 and sST2 were measured in batch from baseline plasma samples stored at −70°C and year 2 at the University of Pennsylvania Laboratory using an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). For GDF-15, the quantitative range was 23.4 to 1500 pg/ml, with a lower limit of detection of 2.0 pg/ml. At a concentration of 98.8 pg/ml, the intra-assay CV was 7.2%; at a concentration of 624 pg/ml, it was 4.5%. For sST2, the quantitative range was 0.63–40 ng/ml, with a limit of detection of 0.1 ng/ml. At a concentration of 2.6 ng/ml, the intra-assay CV was 11.2%; at 0.94 ng/ml, it was 8.5%.

Cardiac hs-TnT and NT-proBNP were measured at baseline in 2008 from ethylenediamine tetraacetic acid (EDTA) plasma stored at −70 °C, both by chemiluminescent microparticle immunoassay (Roche Diagnostics, Basel, Switzerland) on the Elecsys 2010. Cardiac hs-TnT was measured with a high-sensitivity assay with a range of values from 3 to 10,000 ng/l.[42] The limit of blank was 3 ng/l, and limit of detection was <5 ng/l. For hsTnT, the intraassay CV was 3% at a concentration of 30 ng/l and 5.8% at 2213 ng/l. The value at the 99th percentile cutoff from a healthy reference population was 13.5 ng/l for hsTnT, with a 10% intraassay CV.[42] The range of values for NT-proBNP was from 114 to 5900 ng/l, and the intra-assay CV was 4.25% at a concentration of 132 ng/l and 5.3% at 4640 ng/l. For biomarkers with values that were below the limit of detection, we set the value to half of the lower limit of detection (n = 202 for NT-proBNP, n = 39 for hsTnT). Values that were below the limit of detection were set to half of the lower limit of detection. There were 202 of these for NT-proBNP and 39 of these for hsTnT (none for the other biomarkers).

In 2017, we added year 2 measures of NT-proBNP and hsTnT and remeasured a subset of baseline samples to calibrate the measures. The new measurements in 2017 were performed on the Roche E601. We remeasured NT-proBNP in 100 random samples from baseline and all the year 2 samples (n = 947). We developed and applied a Deming regression[43] to calibrate the 2008 baseline NT-proBNP measures with the 2017 NT-proBNP measures.

Similarly, for hsTnT, we remeasured any baseline measure with a value <5 ng/l using the newer Roche E601 instrument, which had a limit of blank of 2.5 ng/l

and limit of detection of <3 ng/l. At a concentration of 13.5 ng/l, the intraassay CV was 1.9%; at 4831 ng/l, the CV was 0.8% with the newer instrument. We also measured a random subset of 100 samples at baseline and all samples at the year 2 visit (n = 947). We developed and applied a Deming regression to calibrate the 2008 baseline hsTnT measures with the 2017 hsTnT measures.

Mortality

The primary outcome was all-cause mortality. Deaths in CRIC were ascertained by reports from next of kin, retrieval of death certificates, and state death files, if available. As secondary analyses, we assessed the association between biomarker concentrations with cardiovascular (CV) mortality. When a death occurred during a hospitalization that was adjudicated, concordant reviews by 2 physicians determined whether the death was CV related. For nonadjudicated deaths, a super learning algorithm that used adjudicated death events as the gold standard was used to predict the probability of CV-related events based on cause of death codes from the National Death Index data.[44] Of the 918 deaths in our analytic population of 3664, 353 were classified as CV death, 411 classified as non-CV death, and 154 were unable to be classified as either CV or non-CV death.

Measurement of Covariates

At the baseline visit, participants provided information on their demographic characteristics, medical history, medication use, and social habits. Anthropometric measurements and blood pressure (BP) were assessed using standard protocols.[45] Body mass index (BMI) 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 (Ortho Clinical Diagnostics, Raritan, NJ) at the CRIC Central Laboratory and standardized to isotope dilution mass spectrometry—traceable values,[46,47] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate the glomerular filtration rate (GFR).[48] Additional assays measured included serum phosphorus, 24-hour urine total protein, glucose, low-density lipoprotein (LDL) cholesterol (mathematically derived), high-density lipoprotein (HDL) cholesterol, total parathyroid hormone level (PTH), and fibroblast growth factor (FGF) 23. All assays were performed at the central laboratory with the exception of plasma PTH (CV <5%; Scantibodies, Santee, CA).[49]

Statistical Analysis

We log-transformed biomarker concentrations due to skewed distributions. We modeled biomarker concentrations both continuously and in categories. To generate categories of roughly the same size, we examined hsTnT across quartiles and the other biomarkers across quintiles. We calculated mortality rates and created cumulative incidence curves for mortality across biomarker categories. We used Cox regression to estimate associations of baseline biomarker concentrations (exposure) with all-cause mortality and tested the proportional hazards assumption using Schoenfeld residuals.[50] We also separately assessed associations with CV mortality. We constructed nested models to evaluate confounding characteristics. Model 1 adjusted for demographic factors including age, sex, race, clinical site, and traditional cardiovascular risk factors including diabetes, CVD, smoking, protein excretion, estimated glomerular filtration rate (GFR), systolic blood pressure, BMI, LDL, and HDL levels. Model 2 added additional adjustments for pertinent medication use and markers of mineral metabolism. These covariables for chosen *a priori* based on biological plausibility. We further adjusted for the other 3 biomarkers of interest under model 3 to assess independent associations of each biomarker. A small number (<5%) of participants were missing covariates used in modeling; these were multiply imputed using chained equations.[51] The multiple analyses over the imputations were combined using the Rubin rules to account for the variability in the imputation procedure.[52]

We further assessed whether changes in biomarker levels were associated with all-cause mortality. We defined change by subtracting year 2 from baseline measurements. We then examined the distribution of absolute change of each biomarker and created 3 categories: the lowest quartile of absolute change; the middle 2 quartiles of absolute change; and the top quartile of absolute change. Participants were considered at risk from the date of the year 2 visit until death, or until they were censored because of dropout or loss of follow-up. For this analysis, adjustment models were the same as in the primary analysis.

In a secondary analysis, we examined the ability of each cardiac biomarker to predict all-cause and CV mortality, and evaluated the discriminatory ability via the 10-fold cross-validated Harrell C-index with accompanying 95% confidence intervals.[53,54] We compared a baseline clinical model (age, sex, race/ethnicity, site, diabetes, CVD, BMI, smoking, systolic blood pressure (SBP), LDL, HDL, eGFR, log-transformed 24-hour urinary protein) to a baseline clinical model plus each cardiac biomarker.

A nominal *P* value of < 0.05 was taken as evidence of statistical significance in all analyses. All analyses were conducted using the R 3.6.0 computing environment (R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Baseline characteristics by quintile of baseline NT-proBNP level (N = 3664)

Characteristic	Overall	≤37.1	37.14–92.5	92.71–199.2	199.21–497	>497
Patients, n	3664	733	733	732	733	733
Age, yr	57.8 (11.0)	53.4 (11.6)	56.6 (10.8)	58.9 (10.7)	59.6 (10.5)	60.4 (9.9)
Women, n	1673 (46)	269 (37)	350 (48)	349 (48)	390 (53)	315 (43)
Race/ethnicity						
Non-Hispanic white	1544 (42)	317 (43)	311 (42)	347 (47)	318 (43)	251 (34)
Non-Hispanic black	1505 (41)	332 (45)	312 (43)	268 (37)	284 (39)	309 (42)
Hispanic	467 (13)	50 (7)	71 (10)	92 (13)	109 (15)	145 (20)
Other	148 (4)	34 (5)	39 (5)	25 (3)	22 (3)	28 (4)
Estimated glomerular filtration rate, ml/min per 1.73 m²	44.3 (14.8)	53.6 (14.2)	48.0 (14.5)	43.3 (13.8)	40.0 (12.4)	36.3 (12.3)
Urinary protein to creatinine ratio from 24-h urine test	0.2 (0.1–0.8)	0.1 (0.0–0.2)	0.1 (0.0–0.5)	0.1 (0.1–0.5)	0.2 (0.1–1.1)	0.6 (0.1–2.6)
Diabetes mellitus	1785 (49)	244 (33)	312 (43)	353 (48)	402 (55)	474 (65)
History of CVD	1207 (33)	100 (14)	151 (21)	210 (29)	303 (41)	443 (60)
History of atrial fibrillation	609 (17)	60 (8)	82 (11)	99 (14)	147 (20)	221 (30)
History of CHF	348 (9)	17 (2)	22 (3)	34 (5)	90 (12)	185 (25)
Current smoker	464 (13)	68 (9)	74 (10)	92 (13)	113 (15)	117 (16)
Alcohol use	2312 (63)	540 (74)	510 (70)	455 (62)	419 (57)	388 (53)
Body mass index, kg/m²	32.1 (7.9)	31.9 (6.8)	32.1 (7.7)	32.4 (8.5)	32.3 (8.3)	31.9 (7.9)
Systolic blood pressure, mm Hg	128.6 (22.1)	119.3 (15.9)	123.9 (18.6)	126.0 (19.2)	132.9 (22.4)	141.1 (26.3)
Diastolic blood pressure, mm Hg	71.5 (12.8)	72.5 (11.2)	71.9 (11.6)	70.3 (12.1)	71.0 (13.5)	71.8 (15.3)
Hemoglobin, g/dl	12.6 (1.8)	13.5 (1.6)	12.8 (1.6)	12.6 (1.6)	12.2 (1.7)	11.8 (1.9)
LDL cholesterol, mg/dl	103.0 (35.3)	107.2 (33.5)	104.7 (35.2)	102.5 (35.0)	101.5 (34.1)	99.1 (38.2)
HDL cholesterol, mg/dl	47.7 (15.5)	47.3 (14.3)	48.5 (15.7)	48.0 (15.3)	48.1 (16.4)	46.5 (15.8)
ACEi/ARBs	2509 (68)	486 (66)	509 (69)	508 (69)	514 (70)	492 (67)
Diuretics	2164 (59)	327 (45)	387 (53)	441 (60)	449 (61)	560 (76)
β-Blockers	1795 (49)	181 (25)	269 (37)	360 (49)	450 (61)	535 (73)
Fibroblast growth factor–23 (RU/ml), median (IQR)	145.0 (96.5–235.7)	102.5 (75.7–149.7)	124.3 (87.1–188.1)	142.6 (97.4–218.1)	169.8 (115.9–258.8)	221.8 (142.1–361.6)
Serum phosphorus, mg/dl	3.7 (0.7)	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 (IQR)	54.0 (35.0–89.0)	41.2 (30.0–58.0)	47.8 (32.6–78.0)	53.7 (33.0–84.0)	62.0 (39.0–101.2)	80.0 (49.5–128.1)

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CHF, congestive heart failure; CVD, cardiovascular disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Entries are mean (SD) or n (%), except as noted. All plasma concentrations are in nanograms per liter (ng/l).

RESULTS

Baseline Participant Characteristics

Among the 3664 participants, mean age was 58 ± 11 years, 46% were women, 42% were white, 41% were black, and 13% were Hispanic. Mean eGFR was 44.3 ± 14.8 ml/min per 1.73 m² with a median protein excretion of 0.2 g/24 h. In all, 49% of the participants reported a history of diabetes, and 33% reported a history of CVD (Table 1). Compared to participants in the lowest quintile of NT-proBNP, those in the highest quintile tended to be older and to have more CV-related comorbidities and lower baseline eGFR (Table 1). Participants with higher levels of hsTnT and sST-2 were more likely to be male; otherwise, similar patterns were seen across levels of hsTnT, GDF-15, and sST-2 (Supplementary Tables S1–S3).

Associations of Baseline NT-proBNP, hsTNT, GDF-15, and sST-2 With All-Cause Mortality

Over a median (IQR) follow-up period of 8.5 (6.8–9.6) years, there were 918 deaths (3.2 deaths per 100 person-years). Unadjusted rates of all-cause mortality increased in a graded fashion with higher levels of each biomarker (Figure 1a). After adjustment for potential confounders, cumulative incidence of all-cause mortality also varied across levels of each biomarker (Supplementary Figure S1A).

All 4 biomarkers were significantly associated with all-cause mortality, with the strongest association observed for NT-proBNP (Table 2). After adjustments for demographics, comorbidities, clinical characteristics, and kidney function measures (model 1), every 1-SD higher log-transformed NT-proBNP level was associated with almost 2-fold higher risk of all-cause mortality, and this association remained robust after further adjustments for mineral metabolism markers and medication use (model 2). hsTnT and GDF-15 demonstrated comparable associations with all-cause mortality. The association of sST-2 with all-cause mortality was the weakest among the 4 biomarkers, although it remained robust after covariate adjustment. Additional adjustments for alternative biomarkers in our combined analysis (model 3) slightly attenuated the observed associations, but they remained strong and statistically significant for all biomarkers.
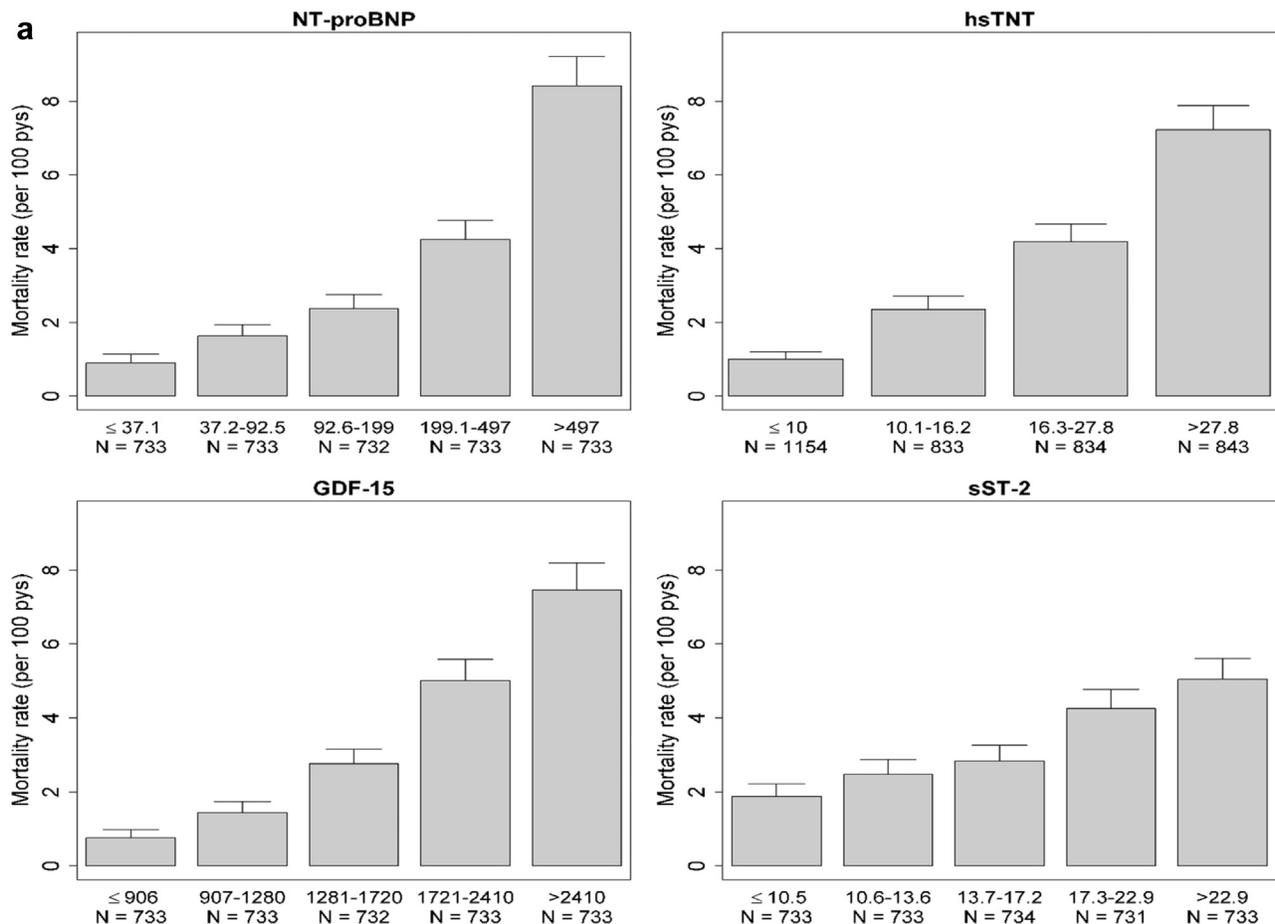
Figure 1. (a) Rates of all-cause mortality, by biomarker category. (b) Rates of cardiovascular (CV) mortality, by biomarker category. GDF-15, growth differentiation factor−15; hsTNT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pys, person-years; sST-2, soluble ST-2. (Continued)

Associations of Baseline NT-proBNP, hsTNT, GDF-15, and sST-2 With CV Mortality

Over a median (IQR) follow-up period of 8.5 (6.8−9.6) years, there were 353 deaths (1.2 deaths per 100 person-years) from CV mortality. Rates of CV mortality increased incrementally across levels of each biomarker (Figure 1b). Adjusted cumulative incidence of CV mortality rates varied across categories of the 4 biomarkers, although the observed differences were less for sST-2 (Supplementary Figure S1B).

All 4 biomarkers were significantly associated with death from CV mortality. Again, we observed the strongest association for NT-proBNP (Table 3 and Supplementary Table S4). Per SD higher log-transformed baseline concentration of NT-proBNP was associated with increased risk of CV mortality (adjusted hazard ratio [HR] = 2.04, 95% confidence interval [CI] = 1.74−2.39) (Table 3). Analogously, hsTnT and GDF-15 were also associated with CV mortality. Again, sST-2 demonstrated the weakest, albeit statistically robust, associations with CV mortality. Adjustment for alternative biomarkers in our combined analysis (model 3) attenuated the observed associations with CV mortality for all four biomarkers.

Associations of 2-Year Change in Cardiac Biomarkers With All-Cause Mortality

There were 842 participants in the subcohort who had repeated measures of each cardiac biomarker 2 years apart. Characteristics of the 842 participants from the random subcohort who had a repeat cardiac biomarker measurement at year 2 were comparable to those in the overall study population (Supplementary Table S5). Compared with participants in the middle 2 quartiles of absolute change (referent group), declines in NT-proBNP and sST2 were associated with lower risk of all-cause mortality (adjusted HR = 0.55, 95% CI = 0.36−0.86, and HR = 0.60, 95% CI = 0.40−0.92], respectively. Declines in hsTnT and GDF-15 did not have significant associations with mortality risk (Table 4). For all 4 biomarkers, the quartile with the greatest increase over 2 years was not significantly

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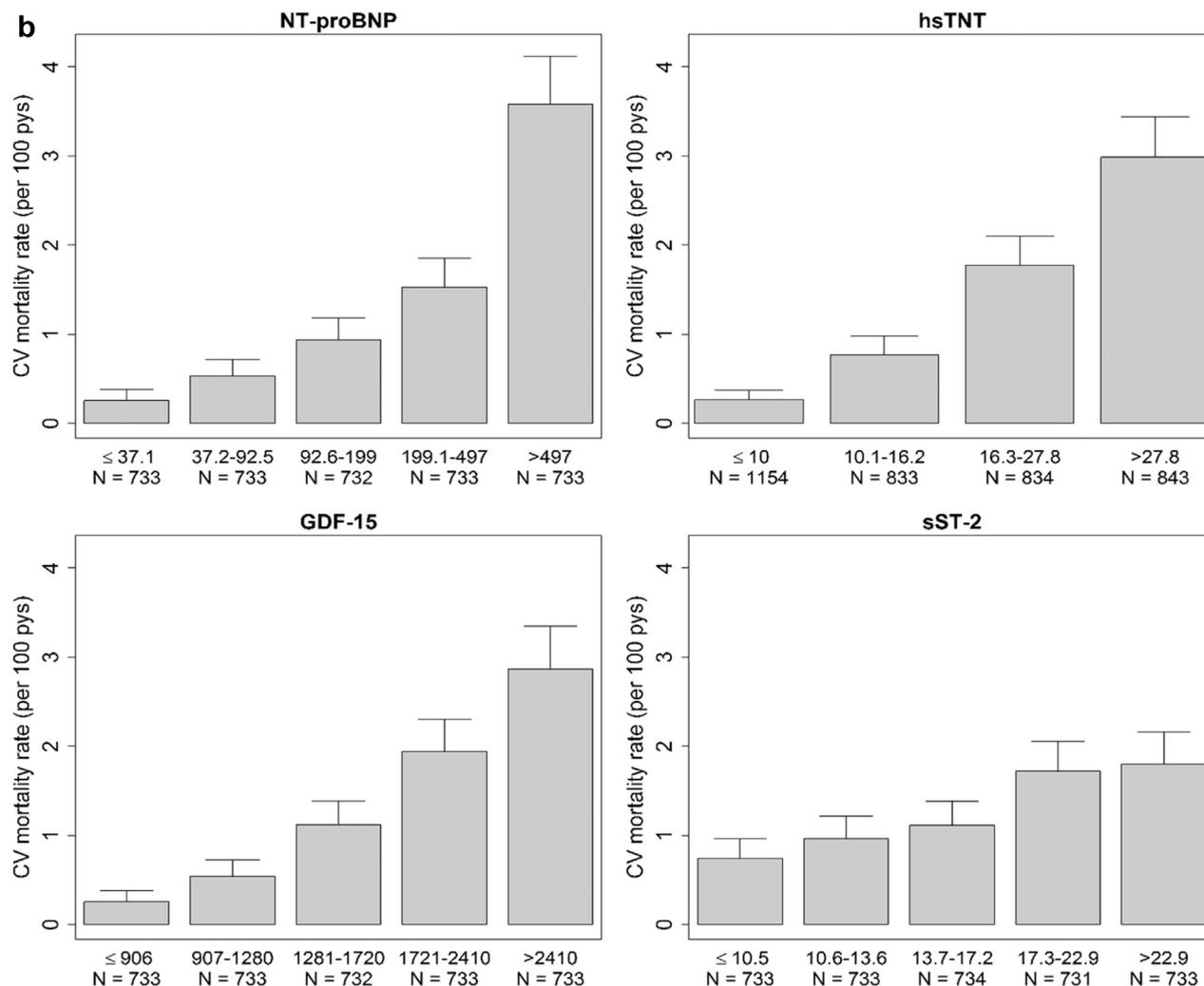
Figure 1. (Continued)

associated with mortality risk compared with participants in the middle 2 quartiles.

Discriminatory Ability of Cardiac Biomarkers to Predict All-Cause and CV Mortality

The C-statistic for a baseline clinical model for all-cause mortality was 0.74 (95% CI = 0.72−0.76) and for CV mortality was 0.77 (95% CI = 0.75−0.80). Addition of NT-proBNP, hsTnT, GDF-15, and sST2, but not galectin-3, improved the C-statistic for both all-cause and CV mortality (with the greatest improvement seen with NT-proBNP; Table 5).

DISCUSSION

In a well-characterized cohort of more than 3000 adults with CKD, we observed robust associations of higher baseline concentrations of NT-proBNP, hsTnT, GDF-15, and sST-2 with increased risks of all-cause and CV mortality. Among individuals of a randomly sampled subcohort, declines in NT-proBNP and sST-2 over 2 years were associated with lower risk of all-cause

mortality. These results suggest that circulating cardiac biomarkers of myocardial injury and inflammation are associated with adverse clinical outcomes in CKD individuals independent of traditional CVD risk factors.

Numerous large-scale, community-based studies have demonstrated associations between elevations of NT-proBNP and hsTnT with increased risk of CV and all-cause deaths among CVD patients and healthy individuals independent of CVD risk factors.[10,16−21] Cross-sectional studies of CKD patients have shown that elevations of NT-proBNP and hsTnT are associated with increased incidence of left ventricular hypertrophy and left ventricular dysfunction.[9,11,55] However, longitudinal data in CKD are more limited. Among 994 participants with moderate CKD in the African-American Study of Kidney Disease and Hypertension Study, each 2-fold higher concentration of NT-proBNP was associated with an 80% increased risk of CV-related death.[34] Of the 940 CKD individuals from the Atherosclerosis Risk in Communities Study, each 1-SD

Table 2. Association of cardiac biomarker with all-cause mortality

Cardiac biomarker	Number at risk (n events)	Model 0		Model 1		Model 2		Model 3 (combined analysis)	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Continuous predictors									
Log(NT-proBNP) per 1 SD (1.71) increase		2.48 (2.29–2.69)	<0.0001	1.95 (1.77–2.15)	<0.0001	1.92 (1.73–2.12)	<0.0001	1.76 (1.59–1.95)	<0.0001
Log(hsTnT) per 1 SD (0.82) increase		1.96 (1.83–2.09)	<0.0001	1.66 (1.52–1.81)	<0.0001	1.62 (1.48–1.78)	<0.0001	1.49 (1.36–1.63)	<0.0001
Log(GDF-15) per 1 SD (0.59) increase		2.24 (2.09–2.40)	<0.0001	1.69 (1.53–1.86)	<0.0001	1.61 (1.46–1.78)	<0.0001	1.49 (1.34–1.65)	<0.0001
Log(sST-2) per 1 SD (0.56) increase		1.50 (1.39–1.62)	<0.0001	1.31 (1.20–1.42)	<0.0001	1.26 (1.16–1.37)	<0.0001	1.16 (1.07–1.25)	0.0003
Categorical predictors									
NT-proBNP, pg/ml									
(Reference: ≤37.1)	733 (56)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
37.2–92.5	733 (98)	1.83 (1.32–2.55)	<0.0001	1.48 (1.06–2.06)	<0.0001	1.47 (1.05–2.06)	<0.0001	1.49 (1.06–2.08)	<0.0001
92.6–199	732 (142)	2.71 (1.99–3.69)		1.76 (1.28–2.43)		1.75 (1.26–2.42)		1.69 (1.22–2.33)	
199.1–497	733 (236)	4.97 (3.71–6.65)		2.80 (2.04–3.84)		2.81 (2.04–3.87)		2.54 (1.83–3.51)	
>497	733 (386)	10.36 (7.80–13.76)		4.71 (3.41–6.49)		4.51 (3.24–6.27)		3.88 (2.78–5.43)	
hsTnT, pg/ml									
(Reference: ≤10)	1154 (99)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
10.1–16.2	833 (159)	2.39 (1.86–3.06)	<0.0001	1.61 (1.24–2.09)	<0.0001	1.58 (1.22–2.04)	<0.0001	1.56 (1.21–2.02)	<0.0001
16.3–27.8	834 (260)	4.34 (3.44–5.46)		2.41 (1.86–3.12)		2.33 (1.80–3.02)		2.21 (1.70–2.86)	
>27.8	843 (400)	7.82 (6.27–9.75)		3.67 (2.79–4.82)		3.43 (2.60–4.52)		2.90 (2.19–3.84)	
GDF-15									
(Reference: ≤906)	733 (48)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
907–1280	733 (88)	1.92 (1.35–2.73)	<0.0001	1.23 (0.85–1.77)	<0.0001	1.19 (0.83–1.71)	<0.0001	1.20 (0.83–1.73)	<0.0001
1281–1720	732 (163)	3.76 (2.73–5.19)		1.90 (1.35–2.67)		1.80 (1.28–2.54)		1.80 (1.28–2.54)	
1721–2410	733 (267)	7.03 (5.17–9.57)		2.82 (1.99–3.99)		2.64 (1.86–3.73)		2.58 (1.81–3.67)	
>2410	733 (352)	10.77 (7.95–14.6)		3.86 (2.69–5.55)		3.49 (2.42–5.01)		3.11 (2.15–4.51)	
sST-2									
(Reference: ≤10.5)	733 (114)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
10.6–13.6	733 (146)	1.33 (1.04–1.69)	<0.0001	1.05 (0.82–1.35)	<0.0001	1.06 (0.83–1.35)	<0.0001	1.07 (0.84–1.37)	0.02
13.7–17.2	734 (163)	1.54 (1.21–1.96)		1.16 (0.91–1.47)		1.14 (0.90–1.45)		1.12 (0.88–1.43)	
17.3–22.9	731 (231)	2.33 (1.86–2.91)		1.51 (1.20–1.90)		1.48 (1.18–1.87)		1.38 (1.10–1.74)	
>22.9	733 (264)	2.79 (2.24–3.47)		1.67 (1.32–2.11)		1.56 (1.23–1.97)		1.32 (1.04–1.68)	

CI, confidence interval; GDF-15, growth differentiation factor−15; HR, hazard ratio; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST-2, soluble ST-2.
Model 0: unadjusted. Model 1: age, sex, race/ethnicity, site, diabetes, cardiovascular disease, body mass index, smoking, systolic blood pressure, low-density lipoprotein, high-density lipoprotein, estimated glomerular filtration rate, log-transformed 24-hour urinary protein.. Model 2: Model 1 + fibroblast growth factor−23, phosphorus, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics. Model 3: Model 2 + alternative cardiac biomarker.

higher NT-proBNP was associated with 50% increased risk of developing coronary artery disease, stroke, or heart failure.[35]

We also observed a robust and independent association between GDF-15 with mortality. GDF-15 exerts anti-inflammatory properties and plays a vital counterregulatory role in the context of CV injury. Higher GDF-15 level predicts mortality among CVD and heart failure patients.[24,27−30] Large-scale studies of healthy individuals without CVD have also demonstrated elevated GDF-15 levels to be associated with higher risk of CV and all-cause mortality.[56,57]

Table 3. Association of cardiac biomarkers with CV mortality

Cardiac biomarker	Model 0		Model 1		Model 2		Model 3 (combined analysis)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
CV mortality								
Log(NT-proBNP) per 1 SD (1.71) increase	2.66 (2.35, 3.00)	<0.0001	2.10 (1.80, 2.45)	<0.0001	2.04 (1.74, 2.39)	<0.0001	1.89 (1.60, 2.22)	<0.0001
Log(hsTnT) per 1 SD (0.82) increase	2.12 (1.94, 2.31)	<0.0001	1.87 (1.65, 2.11)	<0.0001	1.82 (1.60, 2.06)	<0.0001	1.71 (1.50, 1.95)	<0.0001
Log(GDF-15) per 1 SD (0.59) increase	2.22 (2.01, 2.45)	<0.0001	1.63 (1.41, 1.89)	<0.0001	1.55 (1.33, 1.81)	<0.0001	1.44 (1.23, 1.68)	<0.0001
Log(sST-2) per 1 SD (0.56) increase	1.50 (1.34, 1.67)	<0.0001	1.27 (1.11, 1.44)	0.0004	1.22 (1.08, 1.39)	0.002	1.13 (1.00, 1.27)	0.04

CI, confidence interval; CV, cardiovascular; GDF-15, growth differentiation factor−15; HR, hazard ratio; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST-2, soluble ST-2.
Model 0: unadjusted. Model 1: age, sex, race/ethnicity, site, diabetes, cardiovascular disease, body mass index, smoking, systolic blood pressure, low-density lipoprotein, high-density lipoprotein, estimated glomerular filtration rate, log-transformed 24-hour urinary protein.. Model 2: Model 1 + fibroblast growth factor−23, phosphorus, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics. Model 3: Model 2 + alternative cardiac biomarker.

Table 4. Among subcohort only, association of change in cardiac biomarkers with all-cause mortality (n = 842)

Cardiac biomarker	N at risk	N events	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Absolute change					
NT-proBNP (pg/ml)					
≤ −14.3	211	56	0.33 (0.22, 0.49)	0.55 (0.36, 0.86)	0.55 (0.36, 0.86)
−14.2 to 285	420	42	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
> 285	211	64	1.17 (0.82, 1.68)	1.31 (0.89, 1.94)	1.24 (0.84, 1.84)
hsTnT (ng/ml)					
≤ −0.247	211	37	0.83 (0.55, 1.24)	0.95 (0.63, 1.45)	0.99 (0.65, 1.50)
−0.246 to 11.1	420	65	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
>11.1	211	60	1.67 (1.11, 2.52)	1.31 (0.85, 2.02)	1.33 (0.86, 2.06)
GDF-15 (pg/ml)					
≤ −122	211	39	0.76 (0.51, 1.13)	1.25 (0.79, 1.97)	1.28 (0.81, 2.03)
−121 to 585	421	63	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
>585	210	60	1.64 (1.09, 2.45)	1.50 (0.93, 2.42)	1.54 (0.95, 2.48)
sST-2 (ng/ml)					
≤ −3.91	211	56	0.49 (0.34, 0.71)	0.67 (0.44, 1.01)	0.60 (0.40, 0.92)
−3.9 to 3.46	420	60	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
>3.46	211	46	0.78 (0.53, 1.15)	0.88 (0.57, 1.38)	0.88 (0.56, 1.37)

CI, confidence interval; GDF-15, growth differentiation factor−15; HR, hazard ratio; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST-2, soluble ST-2.
Model 1: age, sex, race/ethnicity, site, diabetes, cardiovascular disease, body mass index, smoking, systolic blood pressure, low-density lipoprotein, high-density lipoprotein, estimated glomerular filtration rate, log-transformed urine protein, and baseline level of biomarker. Model 2: Model 1 + fibroblast growth factor−23, phosphorus, beta blockers, ACEi/ARBs, diuretics.

Similarly, we observed an association between sST-2 with higher risk of all-cause mortality. As a membrane of the interleukin-1 receptor family, ST2 exists in both membrane-bound and soluble forms. Soluble ST2 (sST2) functions as a "decoy" receptor and prevents the binding of interleukin-33, a fibroblast protein with known antihypertrophic properties, to the membrane-bound version of ST2. Among patients with heart failure, elevated sST2 is associated with depressed systolic function and increased risk of CV mortality.[31−33] In a prior study of 883 individuals with moderate CKD, we showed that every 1-SD higher concentration of sST-2 was associated with 36% higher risk of all-cause mortality.[38]

Among the subcohort of participants who had repeated biomarkers measurements, declines in both NT-proBNP and sST-2 over 2 years were associated with lower risk of all-cause mortality. We did not observe associations between increases in biomarker levels with mortality risk; the reason for this is unclear. Our data both support as well as differ from existing studies in non-CKD populations. Among community-dwelling elderly individuals, increase in NT-proBNP levels over 3 years were associated with higher risk of incident heart failure and CV death, whereas declines were associated with improved clinical outcomes.[58] A few clinical trials in heart failure have used BNP thresholds to guide therapies in heart failure

Table 5. Discriminatory ability of cardiac biomarker to predict all-cause and CV mortality in the CRIC study

Cardiac biomarker	Model 0 10-Fold CV C-index (95% bootstrap CI)	Model 1 10-Fold CV C-index (95% bootstrap CI)	Model 1 Difference in C-index, compared to model 0 (95% bootstrap CI)
Overall mortality			
NT-proBNP	0.74 (0.72, 0.76)	0.77 (0.75, 0.78)	0.03 (0.02, 0.04)
hsTNT	0.74 (0.72, 0.76)	0.76 (0.74, 0.78)	0.02 (0.01, 0.03)
GDF-15	0.74 (0.72, 0.76)	0.76 (0.74, 0.77)	0.02 (0.01, 0.02)
Galectin-3	0.74 (0.72, 0.76)	0.75 (0.73, 0.76)	0.00 (0.00, 0.01)
sST-2	0.74 (0.72, 0.76)	0.75 (0.73, 0.76)	0.01 (0.00, 0.01)
CV mortality			
NT-proBNP	0.77 (0.75, 0.80)	0.80 (0.78, 0.82)	0.03 (0.02, 0.04)
hsTNT	0.77 (0.75, 0.80)	0.79 (0.77, 0.81)	0.02 (0.01, 0.03)
GDF-15	0.77 (0.75, 0.80)	0.79 (0.76, 0.81)	0.01 (0.00, 0.02)
Galectin-3	0.77 (0.75, 0.80)	0.77 (0.75, 0.80)	0.00 (0.00, 0.01)
sST-2	0.77 (0.75, 0.80)	0.78 (0.75, 0.80)	0.01 (0.00, 0.01)

CRIC, Chronic Renal Insufficiency Cohort; CV, cardiovascular; 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 0: age, sex, race/ethnicity, site, diabetes, cardiovascular disease, body mass index, smoking, systolic blood pressure, low-density lipoprotein, high-density lipoprotein, estimated glomerular filtration rate, log-transformed 24-hour urinary protein. Model 1: M0 + log-transformed biomarker.

patients. Compared with routine clinical care or symptom-based therapy, titrating heart failure therapy to BNP thresholds has demonstrated clinical benefit in a few studies,[59–61] suggesting that using serial measurements of biomarkers levels to guide medical therapy may improve clinical outcomes. However, a larger clinical trial of patients with more advanced heart failure did not show any clinical benefit.[62] Our findings may suggest that biomarker-guided medical therapy for heart failure may be extended to individuals with CKD.

Our findings have several important clinical implications. Elevations in these biomarkers may provide new insight into key pathways involved in the pathogenesis of CVD in CKD patients and may be used to guide development of new therapies. Assessment of markers of cardiac stress and inflammation may be used in the clinical setting to help risk-stratify CKD patients who are at heighted risk for poor clinical outcomes, even among those without overt CVD. Targeting biomarker levels may also serve as therapeutic targets for treatment of CVD-related complications in CKD patients. Future large, prospective studies and clinical trials of CKD patients are needed to test these hypotheses.

Our study has several strengths. We used data from a large, racially diverse, well-characterized CKD cohort. We also adjusted for a broad range of potential confounders in our analyses. We recognize several limitations as well. First, the prediction of nonadjudicated CV-related deaths may introduce bias in our results. We were not able to determine the cause of death (CV or non-CV) for 16.8% of the deaths in our analytic population. Finally, we observed relatively fewer events among participants of the subcohort with repeated measurements, therefore limiting our power to detect meaningful associations between longitudinal changes in biomarker levels with clinical outcomes.

In summary, elevated baseline levels of NT-proBNP, hs-TnT, GDF-15, and sST-2 were independently associated with increased risk of all-cause and CV mortality among patients with CKD. Declines in NT-proBNP and sST-2 over 2 years were also associated with lower risk of all-cause mortality. Further studies are needed to elucidate the underlying biological mechanisms and to determine whether targeting these biomarkers with therapy can mitigate CVD burden in patients with CKD.

DISCLOSURE

All the authors declare no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Baseline characteristics by category of baseline hsTnT level (N = 3664).

Table S2. Baseline characteristics by category of baseline GDF-15 level (N = 3664).

Table S3. Baseline characteristics by category of baseline sST-2 level (N = 3664).

Table S4. Association of cardiac biomarkers with CV mortality (categorical predictor).

Table S5. Characteristics of subcohort with longitudinal measurements (N = 842).

Figure S1. (A) Kaplan−Meier curves (adjusted) of each biomarker with all-cause mortality. (B) Kaplan−Meier curves (adjusted) of each biomarker with CV mortality.

STROBE Statement for Cohort Studies.

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