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Associations of N-terminal pro–B-type natriuretic peptide with kidney function decline in persons without clinical heart failure in the Heart and Soul Study

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Abstract

Background—Subclinical volume overload in the absence of diagnosed heart failure (HF) may be an underrecognized contributor to kidney function decline in coronary artery disease (CAD) patients. We evaluated associations of circulating N-terminal pro–B-type natriuretic peptide (NT-proBNP), a marker of ventricular stretch, with change in estimated glomerular filtration rate (eGFR).

Methods—We evaluated 535 patients with stable CAD and no history of HF, who were enrolled in the Heart and Soul Study and followed up for 5 years. N-terminal pro–B-type natriuretic peptide was measured at baseline. We evaluated the associations of NT-proBNP with change in kidney function over 5 years: (*a*) annual percent change in eGFR, (*b*) rapid kidney function loss (>3% per year for 5 years), and (*c*) incident eGFR <60 mL/min per 1.73 m^2. In multivariable models, we adjusted for demographics, comorbid conditions, echocardiographic parameters, medications, and baseline kidney function.

Results—Among 535 participants, median NT-proBNP was 130.6 (interquartile range 61.8-280.9) pg/mL, and median B-type natriuretic peptide (BNP) was 32.5 (14.4-75.9) pg/mL. Individuals with NT-proBNP levels in the highest quartile (>280.9 pg/mL) had a greater odds of rapid kidney function loss after full adjustment (odds ratio 2.95; 95% CI 1-8.65; $P = .0492$). Associations with incident eGFR <60 mL/min per 1.73 m^2 were also significant (adjusted odds ratio 4.23; 95% CI 1.05-16.98; $P = .0422$). Results were similar when analyzed using BNP as the predictor.

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Conclusions—N-terminal pro–B-type natriuretic peptide and BNP are strongly and independently associated with accelerated kidney function loss, even in the absence of clinical HF. These findings suggest that subclinical cardiovascular dysfunction may contribute to elevated kidney disease risk in persons with CAD.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted from left ventricular myocytes in response to left ventricular stretch[1] from pressure or volume overload.[2] Higher levels of NT-proBNP are associated with increased left ventricular mass[3-5] and may precede development of clinical cardiac disease. Levels of NT-proBNP are also increased in chronic heart failure (HF),[6] acute coronary syndromes,[7] and are correlated with inducible ischemia.[8] Moreover, increased levels of NT-proBNP have been shown to predict incident HF and death in community-dwelling individuals.[9] Thus, NT-proBNP is an established marker for prediction of adverse events in various clinical settings.[10]

Despite the high burden of kidney disease among patients with cardiovascular disease,[11] few studies have examined the association of NT-proBNP with changes in kidney function. Levels of NT-proBNP are commonly elevated in patients with reduced kidney function,[4,5,12-15] resulting from extracellular volume expansion, left ventricular hypertrophy, comorbid heart disease, and reduced renal clearance of NT-proBNP.[4,14,16] Subclinical cardiac remodeling as indicated by elevated NT-proBNP may be a marker of early onset of abnormal cardiac physiology,[17] which may in turn have adverse effects on kidney function. For example, venous congestion is thought to be the main etiology of worsening renal function in acute HF,[18] but whether “subclinical” chronic volume overload contributes to long-term kidney function decline in individuals without clinical HF is not well studied. Understanding these associations at subclinical stages of disease may help elucidate the complex bidirectional relationship between cardiac disease and kidney disease in high-risk individuals.

In a previous study, B-type natriuretic peptide (BNP) was found to predict accelerated progression to end-stage renal disease (ESRD) among 508 individuals with stages 3 to 5 CKD not yet on dialysis.[19] In another study, NT-proBNP and BNP were both found to associate with progression in 227 individuals with mild-to-moderate CKD from primary kidney diseases such as glomerulonephritis, polycystic kidney disease, and interstitial nephritis.[20] However, these studies were limited by small size and heterogeneous causes of kidney disease. Therefore, we designed this study to determine associations of circulating NT-proBNP with longitudinal kidney function decline in individuals with coronary artery disease but without clinical HF at baseline and with a broad range of kidney function.

Methods

Participants

This is a prospective cohort study of patients with stable ischemic heart disease enrolled in the Heart and Soul Study. Methods have been described in detail previously.[21] Between September 2000 and December 2002, 1,024 subjects were recruited from outpatient clinics in the San Francisco Bay Area based on ≥1 of the following criteria: (1) history of myocardial infarction, (2) angiographic evidence of 50% stenosis in ≥1 coronary vessels, (3)

evidence of exercise-induced ischemia by treadmill or nuclear testing, or (4) history of coronary revascularization. At the baseline examination, individuals underwent a medical history, physical examination, and comprehensive health status questionnaire. After a 12-hour fast, morning venous blood samples were drawn. After 5 years of follow-up, all surviving participants were invited to return for a repeat examination. Of 1,024 individuals in the original Heart and Soul cohort, 185 were excluded due to HF at baseline or missing assessment of HF and 30 were excluded due to missing NT-proBNP measures. One hundred sixty-three died and 75 were lost to follow-up by year 5 and 36 had missing kidney function measures at year 5, leaving 535 for this analysis (online Appendix Supplementary Figure).

Primary predictors

Our primary predictor was the level of serum NT-proBNP at baseline. N-terminal pro-B-type natriuretic peptide has a longer half-life and may be more stable when measured from stored samples compared with BNP.[15,22] Blood samples were obtained after a 12-hour fast and were collected in EDTA acid tubes, centrifuged, aliquoted, and then stored at −70°C until measurement. We measured NT-proBNP using the Elecsys 2010 proBNP electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN). The assay range is 5 to 35,000 pg/mL. The within-run coefficient of variation ranges from 1.8% to 2.7%, and the between-run coefficient of variation ranges from 2.3% to 3.2%.

A secondary predictor was BNP. Triage B-type natriuretic fluorescence immunoassay (Biosite Diagnostics, San Diego, CA) was used to measure BNP levels with minimal detectable threshold of 5 pg/mL. The interassay coefficient of variation was 10.1% for 28.8 pg/mL, 12.4% for 586 pg/mL, and 16.2% for 1180 pg/mL.

Outcomes

Estimated glomerular filtration rate (eGFR) was determined by the combined creatinine-cystatin C equation ($eGFR_{cr\text{-}cys}$).[23] Our primary outcome was change in kidney function over 5 years. We defined change in kidney function in 3 ways: (1) annualized percent change in eGFR, (2) rapid kidney function loss, and (3) incident eGFR <60 mL/min per 1.73 m^2. Annualized percent change in eGFR was calculated from the difference between baseline and 5-year follow-up $eGFR_{cr\text{-}cys}$ divided by the baseline $eGFR_{cr\text{-}cys}$, annualized over 5 years. Rapid kidney function loss was defined as a change in $eGFR_{cr\text{-}cys}$ of >3% per year over 5 years based on prior work.[24] Incident eGFR <60 mL/min per 1.73 m^2 was defined as an $eGFR_{cr\text{-}cys}$ <60 mL/min per 1.73 m^2 at follow-up with a concomitant $eGFR_{cr\text{-}cys}$ decline of ≥1 mL/min per year over 5 years. We chose this definition to minimize misclassification due to changes close to the eGFR threshold of 60 mL/min per 1.73 m^2. Serum creatinine was measured by the rate Jaffe method (milligrams per deciliter) in baseline serum samples. Cystatin C was measured from frozen samples collected at the baseline study visit with the use of a BNII nephelometer (Dade Behring Inc, Deerfield, IL) with a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring, Inc).[25]

Other patient characteristics

All covariates in this analysis were taken from the baseline study visit and examination. Demographic characteristics, medical history (including HF), and smoking status were ascertained by standardized questionnaire. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Resting systolic blood pressure (SBP) and diastolic blood pressure and heart rate were measured by standard, calibrated sphygmomanometer in the supine position after 5-minute rest by trained study personnel. Participants were asked to bring their medication bottles to all study visits, and research personnel recorded all current medications, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and statins. High-density lipoprotein and total cholesterol were measured from fasting serum samples. The Friedewald equation was used to calculate low-density lipoprotein (LDL) cholesterol concentrations.[26] Individuals with high triglyceride levels had missing LDL values. Complete resting 2-dimensional echocardiography and Doppler ultrasound examinations included standard 2-dimensional parasternal short-axis, apical 2-chamber and 4-chamber, and subcostal views using an Acuson Sequoia Ultrasound System (Siemens Medical Solutions USA, Inc, Mountain View, CA). Left ventricular (LV) end-diastolic and end-systolic volumes were estimated using the modified biplane methods of discs. Left ventricular ejection fraction (LVEF) was calculated as (LV end-diastolic volume – LV end-systolic volume)/LV end-systolic volume. Left ventricular mass was estimated using the truncated ellipsoid method and indexed to body surface area (left ventricular mass index [LVMI]).[27] Diastolic dysfunction was defined as the presence of ≥1 of the following: impaired relaxation defined as a ratio of peak mitral early diastolic to atrial contraction velocity (E/A) of ≤0.75 with systolic dominant pulmonary vein flow, pseudonormal defined as $0.75 < E/A < 1.5$ with diastolic dominant pulmonary vein flow, or restrictive filling defined as an E/A ≥1.5 with diastolic dominant pulmonary vein flow.[28] Echocardiograms were read by a single viewer blinded to clinical information.

Urine albumin and creatinine were measured in a 24-hour urine collection at baseline. At the intake appointment, participants were provided with a 3-L collection jug for urine and were asked to save all urine between the end of their intake appointment and the time when a research technician recovered the urine at the participant's home 24 hours later. Participants were instructed to keep the urine collections refrigerated at all times. The research technician arrived at the patient's home 24 hours after the timed collection was initiated to avoid overcollection or undercollection. If participants reported missing any urine or if the collections were <1 or >3 L, then collections were repeated. If participants were unable to collect all urine for any reason or had urinary incontinence, then no data were recorded. A urine albumin-to-creatinine ratio (ACR) was calculated in milligrams per gram from the 24-hour sample.[29] Albuminuria was defined as ACR >30 mg/g.[30] The assay detection limit for urine ACR was 0 mg/g.

Statistical analyses

Because of the skewed distribution of NT-proBNP, we categorized NT-proBNP into quartiles. We first described the baseline characteristics of all participants by quartiles of NT-proBNP status. In analyses assessing the outcomes at year 5, we used sequential linear

regression models to evaluate the associations of NT-proBNP levels with annualized percent eGFR loss. We first adjusted for demographics (age, sex, and race) plus baseline eGFR, then for comorbid conditions (hypertension assessed by SBP and diabetes assessed by hemoglobin A1c) and relevant laboratory values (uric acid and hemoglobin level), medications (ACEI/ARB and diuretic use), and echocardiographic parameters (LVEF, LVMI, and diastolic function), and finally, for log-transformed urine ACR, to account for the known effect of ACR on kidney function progression.[31] To further evaluate associations with rapid kidney function loss and incident eGFR <60 mL/min per 1.73 m^2, we also examined the unadjusted proportions of these outcomes by level of NT-proBNP. We used a series of sequential logistic regression models (sequence described above) to determine associations between quartiles of NT-proBNP and the outcomes of rapid kidney function loss and incident eGFR <60 mL/min per 1.73 m^2. Analyses were performed using STATA/SE version 13.

Additional analyses

We performed 2 sensitivity analyses. First, to account for possible effects of kidney filtration on levels of both NT-proBNP and BNP and on rate of kidney function decline,[32] we conducted additional analyses restricted to individuals with eGFR >60 mL/min per 1.73 m^2 to evaluate the associations independent of any degree of renal dysfunction. Second, to evaluate associations of BNP with our outcomes, we conducted separate analyses for all outcomes using BNP as our predictor (n = 534). The rationale for these analyses was the difference in availability of NT-proBNP versus BNP in some clinical settings as well as to address the concern that NT-proBNP may be more influenced by renal excretion than BNP.[15]

We also performed a mediation analysis to assess the effect of incident (new) HF events before follow-up year 5 (n = 67) to determine whether the associations of NT-proBNP were mediated by development of clinical HF.

Results

Participant characteristics

Among 535 individuals with serum measurements of NT-proBNP and without HF at baseline, mean age was 67 (±11) years, 81.6% were men, 60% were white, 69% had hypertension, and 24% had diabetes. Mean LVEF was 62.9% (±8.6%), and mean LVMI was 95 (±24) g/m^2. Median NT-proBNP was 130.6 (interquartile range 61.8-280.9) pg/mL, and median BNP was 32.5 (14.4-75.9) pg/mL. Mean $eGFR_{cr\text{-}cys}$ at baseline was 75.6 (±20) mL/min per 1.73 m^2, and the prevalence of $eGFR_{cr\text{-}cys}$ <60 mL/min per 1.73 m^2 at baseline was 22.5%. Compared with individuals in the lowest quartile of NT-proBNP, those with the highest levels of NT-proBNP were more likely to be older; white; and have higher SBP, LVMI, and prevalence of abnormal diastolic function as well as lower LDL and LVEF (Table I). Participants with the highest NT-proBNP were also more likely to have lower eGFR, higher cystatin C, and higher ACR and were more likely to have eGFR <60 mL/min per 1.73 m^2 at baseline (Table I).

Association of NT-proBNP with annual percent change in eGFR (n = 533)

Overall, the median change in eGFR per year was 1.3 mL/min per 1.73 m^2 (IQR −6.2 to 8.7). For every SD increase in NT-proBNP, the annual percent change in eGFR was 0.04% (95% CI −0.29 to 0.37; *P* = .8045). Among the 535 participants, those in the highest quartile of NT-proBNP (compared with the lowest quartile) had a significantly greater annual percent loss in $eGFR_{cr\text{-}cys}$ over 5 years in demographic-adjusted models only (1.09%; 95% CI 0.06-2.12; *P* = .0377) (Table II). The strength of this association was somewhat stronger when the analyses was restricted to individuals with eGFR >60 at baseline (n = 413) (1.56%; 95% CI 0.59-2.54; *P* = .0017) (Table III). These associations were attenuated by adjustment for covariates including ACR. Our findings did not change in a mediation analysis including incident HF events (online Appendix Supplementary Table III).

Association of NT-proBNP with rapid kidney function loss (n = 533)

Overall, 87 individuals experienced rapid kidney function loss (>3% loss in $eGFR_{cr\text{-}cys}$ per year for 5 years) (online Appendix Supplementary Table I). In unadjusted models, the proportion of individuals with rapid kidney function loss steadily increased across quartiles of NT-proBNP (Figure). For every SD change in NT-proBNP, the odds ratio (OR) for rapid kidney function loss increased by 1.21 (95% CI 0.99-1.48; *P* = .0566). Proportions were similar when stratified between subgroups of eGFR <60 and eGFR >60. Compared with the lowest quartile, participants in the highest quartile of NT-proBNP had 4 times the odds of rapid kidney function loss over 5 years in multivariable models adjusted for demographics, comorbid conditions, medications, and echo parameters (Table V). These associations were partially attributable to the effects of ACR on kidney disease progression. Associations were similar among individuals with eGFR >60 at baseline; those with the highest levels of NT-proBNP also had 4 times the OR (4.2; 95% CI 1.32-13.3; *P* = .0148) of rapid decline over 5 years after multivariable adjustment, including adjustment for ACR. Again, our findings did not change in a mediation analysis including incident HF events (online Appendix Supplementary Table IV).

Association of NT-proBNP with incident eGFR <60 mL/min per 1.73 m^2 (n = 415)

Overall, 43 individuals experienced incident eGFR <60 mL/min per 1.73 m^2 (online Appendix Supplementary Table II). For every SD change in NT-proBNP, the odds of incident CKD increased 2-fold (OR 2.04; 95% CI 1.23-3.39; *P* = .006). Compared with those in the lowest quartile, participants in the highest quartile of NT-proBNP had greater odds of incident CKD after full adjustment (OR 4.23; 95% CI 1.05-16.98; *P* = .04) (Table VIII). Our findings did not change in a mediation analysis including incident HF events (online Appendix Supplementary Table V). (See Table VI.)

Sensitivity analysis: associations of BNP with changes in kidney function

We performed a sensitivity analysis using BNP rather than NT-proBNP as our primary exposure (n = 529). In longitudinal analyses, the multivariable association (adjusted for patient characteristics, comorbidities, echo parameters, and ACR) of elevated BNP with longitudinal percent eGFR loss was similar to associations observed with NT-proBNP (quarterly 4 [Q4] vs Q1 annual change 1.59% per year over 5 years [95% CI 0.4-2.77], *P* = .

01) (Tables IV and V). Similarly, those with the highest quartile of BNP compared with the lowest quartile had 4-fold odds of rapid kidney function loss in multivariable models (fully adjusted OR 3.79; 95% CI 1.44-10; $P = .01$) (Table VII). Associations with incident eGFR <60 mL/min per 1.73 m^2 were significant in unadjusted (OR 6; 95% CI 2.08-17.29; $P = .0009$) but not adjusted models (OR 2.41; 95% CI 0.67-8.67; $P = .1773$) (Table IX).

Discussion

Among individuals with stable ischemic heart disease and without HF, elevated levels of NT-proBNP were strongly associated with subsequent rapid kidney function loss and incident CKD, after accounting for a broad range of risk factors including comorbid diseases, laboratory values, echocardiographic parameters, medication use, and urine ACR. These associations were robust even when restricting our analysis to individuals without reduced eGFR at baseline. We were unable to detect an association with annualized eGFR percent loss. Our findings suggest that NT-proBNP may capture subclinical cardiovascular changes, such as elevated central venous congestion, which may be a risk factor for kidney function decline.

N-terminal pro–B-type natriuretic peptide is a known predictor of incident HF, other cardiovascular events, and death;[33] but fewer studies have studied associations of NT-proBNP or BNP with kidney function decline. Evaluating decline in kidney function as an outcome is important because reduced eGFR is associated with higher risk of CVD and mortality, particularly in patients with other CVD risk factors.[34] N-terminal pro–B-type natriuretic peptide was found to predict progression to ESRD among individuals with CKD in the TREAT Study; however, individuals with HF were not excluded in this study.[35] In another population with overt HF, NT-proBNP was also found to predict worsening renal function.[36] In a smaller study of individuals with ejection fraction >40%, levels of BNP were found to be associated with a composite end point of progression to ESRD and doubling of creatinine.[19] Similarly, in the Mild to Moderate Kidney Disease Study, levels of both BNP and NT-proBNP were associated with the combined renal end point of ESRD and doubling of creatinine, although only NT-proBNP predicted doubling of creatinine.[20] These studies were primarily limited by the absence of echocardiography corresponding to levels of NT-proBNP. Our study builds on these previous studies by demonstrating that, among individuals with and without CKD at high risk for HF, higher levels of NT-proBNP were significantly associated with rapid kidney function loss and incident CKD in a high-risk cardiac population free of clinical HF. Our study highlights the importance of NT-proBNP as a prognostic biomarker for early kidney function decline.

The mechanism of kidney function decline in individuals with cardiovascular disease, specifically ischemic heart disease, is not well understood. Left ventricular hypertrophy and increased left ventricular mass occur in the absence of clinical HF in individuals with CKD,[37,38] and these subclinical cardiac abnormalities are associated with kidney function decline even in the absence of CKD.[39] These effects may be attributable, at least, partly to hypertension as a mediator, although these studies are adjusted for hypertension. The cardiorenal syndrome describes the intertwined physiology of heart and kidney dysfunction in both acute and chronic clinical HF,[17] but this phenomenon is less well described at

subclinical stages of HF. In acute HF, studies have found that worsening renal function can be attributed to venous congestion.[18] Chronic HF is also associated with longitudinal kidney function decline,[36,40] and venous congestion may be a mechanism underlying worsening kidney function in the chronic state as well.[41] Activation of the renin-angiotensin-aldosterone system may also contribute to CKD.[20] Overall, our study supports a role for subclinical cardiovascular dysfunction as indicated by elevated concentrations of NT-proBNP as a contributor to kidney function decline.

The use of BNP and NT-proBNP for clinical prognostic purposes in cardiac patients is well established,[33] yet the use of these cardiac biomarkers for renal prognosis remains underrecognized. Focusing on the early detection of kidney disease in this setting may be of benefit,[42] as methods to reverse established kidney disease are currently unavailable. Use of NT-proBNP in the absence of both HF and kidney disease may help risk stratify individuals at risk for developing both conditions. This may be of particular interest for guiding treatment, such as diuresis because targeting a BNP level has been suggested to be of benefit for HF.[43,44] Future studies should focus on measurement of these peptides in subclinical heart disease and changes in outcomes based on therapy and renal function.

Our study has several strengths. The Heart and Soul cohort is a well-characterized cohort of patients with coronary artery disease who are at high risk for adverse renal outcomes. This cohort has robust measurements of NT-proBNP, BNP, and repeated measures of eGFR in 535 individuals. We also have standardized baseline echocar-diographic data and were able to adjust for LVMI, diastolic dysfunction, and ejection fraction, which are important confounders. Albumin-to-creatinine ratio was determined by timed 24-hour urine collections. We had serial measures of both cystatin C and creatinine and were able to examine kidney function by the combined eGFR equation, which may correlate better with outcomes, particularly in participants with eGFR >60 mL/min per 1.73 m^2.[45]

Our study also has several limitations. First, we were unable to account for changes in NT-proBNP and BNP over time. Although we have robust measurements of kidney function at baseline and at 5 years of follow-up, this cohort has a relatively low prevalence and incidence of kidney disease. We were unable to detect significant associations with annualized eGFR percent loss or with changes in eGFR using NT-proBNP as a continuous predictor. However, we believe that rapid kidney function loss and incident CKD are more meaningful outcomes, as the annual rate of change in eGFR may be more accelerated at worse levels of eGFR, and the outcomes of rapid kidney function loss and incident CKD are more useful clinically. Intermediate study visits to capture kidney function measures of individuals who died before year 5 would have been of interest. Furthermore, our ability to account for changes in medication use is limited, although we do not believe that this limitation challenges the generalizabil-ity of our findings. We had inadequate power to stratify by race, and there were relatively few women in this cohort, limiting generalizability. Finally, we were underpowered to detect associations with more severe changes in kidney function, such as decline in eGFR of >50% or incident ESRD. Furthermore, we cannot determine the exact cause of elevated NT-proBNP in each patient. As with any observational study, our ability to make conclusions regarding causality is limited.

In conclusion, elevated NT-proBNP and BNP are associated with increased risk of kidney function loss in individuals with known coronary heart disease and without HF. The accelerated kidney function loss is independent of baseline-reduced eGFR, albuminuria, hypertension, diabetes, and echocardiographic measures. This study indicates a possible role for subclinical cardiac dysfunction in the development and progression of CKD among individuals with preexisting cardiovascular disease. Future investigations should focus on the pathophysiology of venous congestion and poor forward flow as a determinant of kidney function decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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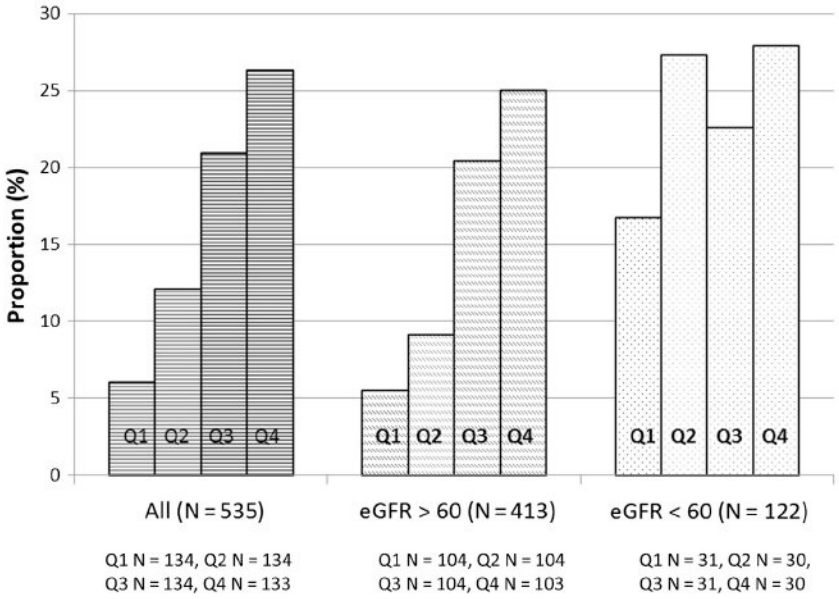

Figure.

Proportion of participants with rapid kidney function loss by quartile of NT-proBNP.

Proportion of participants with rapid kidney function loss (defined as >3% per year over 5 years) by quartile of NT-proBNP among all participants (left) and in stratified analyses restricted to individuals with eGFR >60 mL/min per 1.73 m^2 (middle) and eGFR <60 mL/min per 1.73 m^2 (right) at baseline.

Table I

Baseline characteristics by quartile of NT-proBNP

	Q1 (<61.8 pg/mL), n = 134	Q2 (61.9-130.5 pg/mL), n = 134	Q3 (130.6-280.8 pg/mL), n = 134	Q4 (>280.9 pg/mL), n = 133	*P*
Age (mean, SD)	60.8 (9.7)	66.1 (10.5)	67.8 (8.6)	69.6 (9.7)	.0001
Male	80.6%	84.3%	85.8%	75.9%	.158
Race					.036
Hispanic/Latino	6.7%	9.7%	9.7%	12%	
Asian/Pacific Isl	12.7%	11.2%	17.2%	6.8%	
Black/Af. Amer.	18.7%	22.4%	9%	12%	
Caucasian	58.2%	53%	61.9%	67.7%	
Other	3.7%	3.73%	67.7%	1.5%	
BMI	28.7 (4.7)	28.8 (5.6)	27.9 (5.2)	28.7 (5.2)	.2743
$eGFR_{cr\text{-}cys}$ (milliliters per minute per 1.73 m^2)	86.4 (16.6)	76.6 (17.7)	72.1 (17.7)	62.7 (20)	.0001
eGFR <60 at baseline	4.5%	16.7%	23.1%	45.9%	<.0001
ACR (milligrams per gram)	7.1 (4.2-10.4)	6 (3.9-9.2)	8.2 (5.2-17.5)	10.9 (6.3-19.5)	.0001
Cystatin C (milligrams per liter)	0.93 (0.16)	1 (0.21)	1.1 (0.33)	1.3 (0.49)	.0001
SBP (millimeters of mercury)	130.3 (17.5)	131.7 (19.9)	132.5 (19.8)	138.4 (24.1)	.0178
LDL (milligrams per deciliter)	111.2 (31.8)	106.2 (36.9)	103.3 (30.3)	98.1 (30.5)	.0088
Hypertension	60.5%	61.9%	72.4%	73.7%	.035
Diabetes mellitus	22.4%	14.9%	27.6%	21.8%	0.17
ACEI/ARB	39.6%	34.3%	50.8%	63.2%	<.0001
Diuretics	19.4%	22.4%	18.7%	30.8%	.07
LVEF (%)	64.6 (6.2)	64.5 (6.7)	63.9 (8.3)	60.1 (10.3)	.0005
LVMI (grams per square meter)	85 (16.6)	91.5 (20)	95.5 (24)	101.2 (27.8)	.0001
Abnormal diastolic function	20.9%	30.7%	36.3%	49.5%	<.0001

Table II

Associations of NT-proBNP with annualized percent change in eGFR over 5 years (n = 533)

	Q1 (<61.8 pg/mL)	Q2 (61.9-130.5 pg/mL)	Q3 (130.6-260.8 pg/mL)	Q4 (>280.9 pg/mL)
Unadjusted % change	Ref	−0.19 (−1.12 to 0.74), *P* = .6888	0.19 (−0.74 to 1.11), *P* = .6926	0.69 (−0.24 to 1.61), *P* = .1467
Demographic + baseline eGFR-adjusted % change	Ref	−0.16 (−1.11 to 0.79), *P* = .7388	0.38 (−0.59 to 1.35), *P* = .4392	1.09 (0.06-2.12), *P* = .0377
Multivariable*-adjusted % change	Ref	−0.01 (−0.98 to 0.95), *P* = .9774	0.36 (−0.65 to 1.37), *P* = .4879	1.01 (−0.15 to 2.17), *P* = .0886
Multivariable + urine ACR-adjusted % change	Ref	0 (−1 to 1), *P* = .9984	0.2 (−0.85 to 1.25), *P* = .7082	0.77 (−0.45 to 1.99), *P* = .2152

Table III

Associations of NT-proBNP with annualized percent change in eGFR over 5 years, baseline eGFR >60 only (n = 413)

	Q1 (<61.8 pg/mL)	Q2 (61.9-130.5 pg/mL)	Q3 (130.6-260.8 pg/mL)	Q4 (>280.9 pg/mL)
Unadjusted % change	Ref	−0.49 (−1.33 to 0.35), *P* = .2519	0.13 (−0.72 to 0.98), *P* = .7703	1.18 (0.23-2.13, *P* = .0145
Demographic + baseline eGFR adjusted % change	Ref	−0.42 (−1.26 to 0.42, *P* = .3306	0.31 (−0.57 to 1.18, *P* = .4927	1.56 (0.59-2.54, *P* = .0017
Multivariable*-adjusted % change	Ref	−0.13 (−1 to 0.73, *P* = .76	0.07 (−0.87 to 1.01, *P* = .8837	1.06 (−0.06 to 2.17, *P* = .0641
Multivariable + urine ACR-adjusted % change	Ref	−0.16 (−1.05 to 0.73, *P* = .7201	−0.09 (−1.07 to 0.89, *P* = .8532	0.81 (−0.36 to 1.98, *P* = .1753

* Adjusted for age, race, sex, BMI, SBP, hemoglobin A1c, hemoglobin, uric acid, ACEI/ARB and diuretic use, LVEF, LVMI, diastolic dysfunction, and baseline eGFR.

Table IV

Associations of BNP with annualized percent change in eGFR over 5 years (n = 529)

	Q1 (<14.4 pg/mL)	Q2 (14.5-32.5 pg/mL)	Q3 (32.6-75.8 pg/mL)	Q4 (>75.9 pg/mL)
Unadjusted % change	Ref	0.73 (−0.21 to 1.66), *P* = .1263	0.39 (−0.53 to 1.32), *P* = .4059	0.92 (−0.01 to 1.84), *P* = .0523
Demographic + baseline eGFR adjusted % change	Ref	0.81 (−0.13 to 1.74), *P* = .0923	0.58 (−0.39 to 1.53), *P* = .2469	1.28 (0.28-2.28), *P* = .012
Multivariable*-adjusted % change	Ref	0.86 (−0.1 to 1.82), *P* = .0779	0.46 (−0.55 to 1.46), *P* = .3747	1.1 (−0.02 to 2.22), *P* = .0549
Multivariable + urine ACR-adjusted % change	Ref	0.87 (−0.11 to 1.86), *P* = .0823	0.38 (−0.66 to 1.43), *P* = .4754	0.97 (−0.19 to 2.13), *P* = .1022

Table V

Associations of BNP with annualized percent change in eGFR over 5 years, baseline eGFR >60 only (n = 410)

	Q1 (<14.4 pg/mL)	Q2 (14.5-32.5 pg/mL)	Q3 (32.6-75.8 pg/mL)	Q4 (>75.9 pg/mL)
Unadjusted % change	Ref	0.74 (−0.11 to 1.6), *P* = .0867	0.25 (−0.61 to 1.11), *P* = .5669	1.4 (0.46-2.34), *P* = .0036
Demographic + baseline eGFR adjusted % change	Ref	0.78 (−0.07 to 1.63), *P* = .0706	0.45 (−0.43 to 1.32), *P* = .3212	1.71 (0.75-2.68), *P* = .0005
Multivariable* -adjusted % change	Ref	0.63 (−0.24 to 1.49), *P* = .1556	0.11 (−0.82 to 1.03), *P* = .8207	1.11 (0.03-2.2), *P* = .0449
Multivariable + urine ACR-adjusted % change	Ref	0.67 (−0.22 to 1.55), *P* = .1407	−0.09 (−1.05 to 0.87), *P* = .8518	1.02 (−0.01 to 2.15), P= .0751

*Adjusted for age, race, sex, BMI, SBP, hemoglobin A1c, hemoglobin, uric acid, ACEI/ARB and diuretic use, LVEF, LVMI, diastolic dysfunction, and baseline eGFR.

Table VI

Associations of NT-proBNP with rapid kidney function loss (defined as >3% per year over 5 years) (n = 533)

	Q1 (<61.8 pg/mL)	Q2 (61.9-130.5 pg/mL)	Q3 (130.6-260.8 pg/mL)	Q4 (>280.9 pg/mL)
Unadjusted OR	Ref	2.17 (0.9-5.27), *P* = .0859	4.16 (1.82-9.51), *P* = .0007	5.62 (2.5-12.65), *P* <. 0001
Multivariable*-adjusted OR	Ref	2.02 (0.75-5.41), *P* = .1629	3.59 (1.4-9.21), *P* = .008	4.18 (1.5-11.66), *P* = . 0064
Multivariable* + urine ACR-adjusted OR	Ref	1.97 (0.71-5.42), *P* = .1918	3.39 (1.29-8.89), *P* = .0132	2.95 (1-8.65), *P* = .0492

Table VII

Associations of BNP with rapid kidney function loss (defined as 3% per year over 5 years) (n = 529)

	Q1 (<14.4 pg/mL)	Q2 (14.5-32.5 pg/mL)	Q3 (32.6-75.8 pg/mL)	Q4 (>75.9 pg/mL)
Unadjusted OR	Ref	3.14 (1.34-7.38), *P* = .0086	3.7 (1.6-8.55), *P* = .0022	4.91 (2.16-11.15), *P* = .0001
Multivariable*-adjusted OR	Ref	3.34 (1.24-8.96), *P* = .0167	3.46 (1.28-9.4), *P* = .0147	3.69 (1.′3-10.51), *P* = .0144
Multivariable* + urine ACR-adjusted OR	Ref	3.62 (1.31-10.05), *P* = .0133	3.37 (1.2-9.49), *P* = .0214	3.24 (1.1-9.58), *P* = .0334

*Adjusted for age, race, sex, BMI, SBP, hemoglobin A1c, hemoglobin, uric acid, ACEI/ARB and diuretic use, LVEF, LVMI, diastolic dysfunction, and baseline eGFR.

Table VIII

Associations of NT-proBNP with incident CKD (eGFR b60 mL/min per 1.73 m^2) (n = 415)

	Q1 (<61.8 pg/mL)	Q2 (61.9-130.5 pg/mL)	Q3 (130.6-260.8 pg/mL)	Q4 (>280.9 pg/mL)
Unadjusted OR	Ref	2.15 (0.07-6.62), *P* = .1821	3.55 (1.22-10.32), *P* = .0198	5.94 (2.04-17.27), *P* = .0011
Multivariable*-adjusted OR	Ref	1.67 (0.44-6.33), *P* = .45234	1.37 (0.38-4.85), *P* = .6299	4.23 (1.05-16.98), *P* = .0422

Table IX

Associations of BNP with incident CKD (eGFR <60 mL/min per 1.73 m^2) (n = 412)

	Q1 (<14.4 pg/mL)	Q2 (14.5-32.5 pg/mL)	Q3 (32.6-75.8 pg/mL)	Q4 (>75.9 pg/mL)
Unadjusted OR	Ref	2.72 (0.91-8.1), *P* = .0719	2.27 (0.74-7.01), *P* = .1527	6 (2.08-17.29), *P* = .0009
Multivariable*-adjusted OR	Ref	1.54 (0.43-5.49), *P* = .5044	0.83 (0.23-3), *P* = .7818	2.41 (0.67-8.67), *P* = .1773

*Adjusted for age, race, sex, BMI, SBP, hemoglobin A1c, hemoglobin, uric acid, ACEI/ARB and diuretic use, LVEF, LVMI, diastolic dysfunction, and baseline eGFR.