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Association of Cardiac Troponin T With Left Ventricular Structure and Function in CKD

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Abstract

Background—Serum cardiac troponin T (cTnT) is associated with increased risk of heart failure and cardiovascular death in several population settings. We evaluated associations of cTnT with cardiac structural and functional abnormalities in a cohort of chronic kidney disease (CKD) patients without heart failure.

Study Design—Cross-sectional.

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*N SECTION: A list of the the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators appears in the Acknowledgements.

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Setting & Participants—Chronic Renal Insufficiency Cohort (CRIC; N= 3,243)

Predictor—The primary predictor was cTnT. Secondary predictors included demographic and clinical characteristics, hemoglobin level, high-sensitivity C-reactive protein, and estimated glomerular filtration rate using cystatin C.

Outcomes—Echocardiography was used to determine left ventricular (LV) mass and LV systolic and diastolic function.

Measurements—Circulating cTnT was measured in stored sera using the highly sensitive assay. Logistic and linear regression models were used to examine associations of cTnT with each echocardiographic outcome.

Results—cTnT was detectable in 2,735 (84%) persons; the median was 13.3 (IQR, 7.7–23.8) pg/mL. Compared with undetectable cTnT (<3.0 pg/mL), the highest quartile (23.9 – 738.7 pg/mL) was associated with approximately two times as likely to experience LV hypertrophy (OR, 2.43; 95% CI, 1.44–4.09) in the fully adjusted model. cTnT had a more modest association with LV systolic dysfunction; as a log-linear variable, a significant association was present in the fully adjusted model (OR of 1.4 [95% CI, 1.1–1.7] per 1-log unit; p<0.01). There was no significant independent association between cTnT and LV diastolic dysfunction. When evaluated as a screening test, cTnT functioned only modestly for LV hypertrophy and concentric hypertrophy detection (area under the curve, 0.64 for both) with weaker areas under the curve for the other outcomes.

Limitations—The presence of coronary artery disease was not formally assessed using either noninvasive or angiographic techniques in this study.

Conclusions—In this large CKD cohort without heart failure, detectable cTnT had a strong association with LV hypertrophy, a more modest association with LV systolic dysfunction, and no association with diastolic dysfunction. These findings indicate that circulating cTnT levels in CKD are predominantly an indicator of pathological LV hypertrophy.

Keywords

Troponin T; left ventricular structure; chronic kidney disease

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Chronic kidney disease (CKD) is a common condition in the United States; its estimated prevalence is 13%, and it substantially increases the risk of cardiovascular disease (CVD) and heart failure (HF).(1, 2) In patients with HF, the presence of CKD is associated with a worse prognosis. (3) (4) Pathological changes in cardiac structure that are associated with elevated risk of cardiovascular (CV) morbidity and mortality, such as left ventricular hypertrophy (LVH) (5, 6), have increased prevalence in patients with CKD.(5) Therefore, it may be important to identify biomarkers that can detect patients with CKD who have developed early subclinical pathological changes in cardiac structure and function and, hence, are at increased future risk of CVD.

Cardiac troponin T (cTnT) is an integral part of the contractile apparatus of the cardiomyocyte that is released into the circulation with cellular injury and resultant loss of integrity of the cell membrane. It can be detected by highly sensitive assays and is now the preferred biochemical marker for the detection of myocardial necrosis in acute coronary syndromes.(7) A recent study, using the highly sensitive assay, demonstrated a moderately high prevalence of detectable cTnT in the general population and an association between cTnT and LV structural and functional abnormalities as well as increased mortality risk.(8) In patients with end-stage renal disease (ESRD), circulating cTnT is associated with LVH and with poor prognosis.(9–12) However, data on the LV structural and functional correlates of cTnT in patients with CKD are limited. In a relatively small study of 222 patients with

CKD using a standard assay, there was no independent association between cTnT and LV mass.(13) On the other hand, cTnT has been associated with cardiovascular events and death in CKD. (14, 15)

In order to better understand the correlates of cTnT in CKD, we sought to examine the associations of circulating cTnT, measured with the highly sensitive assay, with LV structure and function in a large, diverse population of ambulatory patients with CKD without heart failure.

Methods

Participants

The National Institute of Diabetes and Digestive and Kidney Diseases established the Chronic Renal Insufficiency Cohort (CRIC) Study in 2001 as an observational study to assess the determinants of progression to ESRD and CVD among persons with CKD.(16, 17) Participants were recruited from 7 clinical centers between July 2003 and March 2007. Inclusion criteria were an estimated glomerular filtration rate (eGFR) between 20–70 ml/min/1.73m^2 for persons aged 21–44, 20–60 ml/min/1.73m^2 for persons aged 45–64, and 20–50 ml/min/1.73m^2 for those aged 65–74. Exclusion criteria included prior transplantation, polycystic kidney disease, multiple myeloma, use of immunosuppression, and severe comorbid illnesses such as cirrhosis, HIV disease, and severe heart failure, defined as New York Heart Association class III or IV heart failure at baseline. For this analysis, we further excluded participants with self-reported heart failure (n=443) or with more than mild mitral regurgitation or significant aortic valve disease based on transthoracic echocardiography (TTE; n=263). TTE was performed in all CRIC participants at year 1 of follow-up according to American Society of Echocardiography guidelines (18) and the data were sent to a core echocardiography laboratory for measurement and analysis (University of Pennsylvania). This core laboratory was also responsible for standardization of the performance of TTEs across sites and for quality control. Of 3,939 participants, 3,243 were included in this analysis.

Predictors

The primary predictor for this paper was cardiac troponin T (cTnT), measured using the highly sensitive assay on the Elecsys 2010 analyzer (Roche Diagnostics) at the University of Maryland, with an analytical measurement range of 3 to 10,000 pg/mL(19). Secondary predictors included demographic characteristics (age, sex, and race); clinical characteristics (cause of kidney disease, body mass index, systolic and diastolic blood pressure, hypertension, diabetes, hypercholesterolemia, current smoking, alcohol and illicit drug use, coronary artery disease [prior myocardial infarction or revascularization], and peripheral vascular disease); hemoglobin level, high-sensitivity C-reactive protein (hsCRP) and eGFR using serum concentration of cystatin C (CKD Epidemiolology Collaboration equation for nonstandardized cystatin C (20), ie, eGFR = 76.7 × [cystatin C]$^{-1.19}$).

Outcomes

Left ventricular (LV) volumes, geometry, mass and systolic and diastolic function were evaluated using M-mode, two-dimensional and Doppler echocardiography. Multiple reproducibility, inter-reader reliability, intra-reader reliability and reader drift analyses were performed throughout the course of this large-scale, prospective cohort study. These were performed on a 2% random sample of the entire cohort each year. The intra-class correlation coefficients for the echocardiographic measures are as follows: LVH, 0.759 (kappa statistic, 0.61); diastolic dysfunction, 0.848 (kappa statistic, 0.75); and LV ejection fraction, 0.854 (not applicable).

Left Ventricular Hypertrophy and Geometry—LV mass was calculated using the area-length method and indexed to height$^{2.7}$.(18) LVH was defined as LV mass/height$^{2.7}$ ≥ 47 g/m$^{2.7}$ in women and ≥ 50 g/m$^{2.7}$ in men.(21) Relative wall thickness (RWT) was calculated as 2 × posterior wall thickness/LV internal linear dimension in diastole. RWT was considered to be increased if ≥ 0.45. LV mass and RWT were used to categorize LV geometry: normal (normal LV mass, normal RWT), concentric remodeling (normal LV mass, increased RWT), eccentric hypertrophy (increased LV mass, normal RWT) and concentric hypertrophy (increased LV mass, increased RWT).

Left Ventricular Systolic Function—LV end-diastolic and end-systolic volumes (EDV and ESV, respectively) were calculated using the modified biplane method and ejection fraction (EF) was calculated as: (EDV – ESV)/EDV LV systolic dysfunction was defined as an EF < 0.45.(22–25)

Left Ventricular Diastolic Function—Mitral inflow E- and A-wave velocities, E-wave deceleration time and pulmonary venous reverse A-wave duration were used to categorize LV diastolic function into: normal, mildly, moderately or severely abnormal.(26) Since one center was unable to evaluate diastolic function, these measures were unavailable in 564 participants.

Statistical Analysis

We first depicted the distribution of cTnT in this unique clinical setting of participants with CKD. We then categorized cTnT as undetectable (< 3.0 pg/mL) and quartiles of detectable levels to allow the unbiased portrayal of levels. In addition, cTnT was modeled as a continuous variable after log-transformation because of its skewed distribution (508 participants with undetectable cTnT were assigned random values between 0 and <3.0 pg/mL for analysis). Demographic, laboratory and echocardiographic values were compared across categories of cTnT using the ANOVA for continuous variables and chi-square test for categorical variables. Demographic and laboratory covariates were entered into the multivariable-adjusted models based on the strength of their bivariate association with the outcome (P<0.05).

The association of cTnT with LV mass/height$^{2.7}$ was assessed by multivariable linear regression. Different methods of multivariable logistic regression were used depending on the number of outcome categories and their hierarchical nature. Because LVH and systolic dysfunction were dichotomized, we used multivariable logistic regression for these analyses. As the four categories of LV geometry were not clearly ranked in severity, we used multivariable nominal logistic regression. We dichotomized the four levels of diastolic dysfunction into normal and mildly abnormal vs. moderate and severely abnormal and modeled these using logistic regression. Analyses of diastolic dysfunction were repeated with normal function as the referent category in the subset of participants with LV ejection fraction ≥ 0.45 in order to evaluate the association with cTnT independent of systolic dysfunction.

For the above unadjusted analyses, we evaluated the C-statistic, which is equivalent to the area under the ROC curve, for cTnT as a predictor of each outcome. We then created the ROC curves to examine the sensitivity and specificity trade-off across cTnT levels, and we calculated the positive and negative likelihood-ratios of different cut-points of cTnT as predictors of LVH, abnormal LV geometry, and LV systolic and diastolic dysfunction. STATA version 11 (StataCorp LP) was used for the analysis.

Results

Participant Characteristics by Troponin T Level

The mean age of the participants was 59 ± 11 (standard deviation) years. 45% were women and 43% were white. By the high-sensitivity assay, 2,735 participants (84%) had detectable cTnT. Participants with the highest level of cTnT were older and were more likely to be male and black or Hispanic (Table 1). Higher levels of cTnT were also associated with higher prevalences of diabetes, hypertension, hyperlipidemia, and cardiovascular and peripheral vascular disease; with higher BMI, systolic blood pressure (SBP), and urine albumin-creatinine ratio; and with lower hemoglobin level and eGFR using cystatin C.

Troponin T and Left Ventricular Structure

Across cTnT levels, from undetectable to the four quartiles of detectable levels, LV mass appeared to rise incrementally (medians were 42.5 [interquartile range (IQR), 37.3 – 48.9] pg/mL for undetecatable; 45.6 [IQR, 39.3 – 52.9] pg/mL for quartile 1; 47.1 [IQR, 41.1 – 56.0] pg/mL for quartile 2; 51.1 [IQR, 44.0 – 59.9] pg/mL for quartile 3; and 56.1 [IQR, 47.9 – 66.1] pg/mL for quartile 4; $p<0.001$). After demographic adjustment, participants with detectable cTnT had significantly higher mass compared with undetectable cTnT. In the multivariable-adjusted linear regression model, the highest three quartiles of cTnT had significantly higher LV mass/height$^{2.7}$ (quartile 1: β, 0.2 g/m$^{2.7}$ [95% confidence interval (CI), −1.5 to − 1.8; p=0.9]; quartile 2: β, 1.7 g/m$^{2.7}$ [95% CI, 0.0–3.5; p=0.05]; quartile 3: β, 2.6 g/m$^{2.7}$ [95% CI, 0.8–4.5; p<0.01]; quartile 4: β, 5.8 g/m$^{2.7}$ [95% CI, 3.7–7.8; p<0.001]).

Overall, there was a high prevalence of LVH in this cohort, ranging from 23% in the group with undetectable cTnT to 52% in those with the highest level of cTnT (Table 2). In a multivariable adjusted logistic regression model, detectable cTnT level as a log transformed continuous variable was significantly associated with prevalent LVH (odds ratio [OR], 1.3 per log pg/mL; 95% CI, 1.0–1.5; p=0.03). The highest two quartiles of cTnT were associated with more than four-fold odds of LVH after demographic adjustment; these odds were partially attenuated in an intermediate model that also adjusted for variables associated with occlusive arterial disease and further attenuated to approximately two-fold after full multivariable adjustment (Table 2). Median cTnT also increased in a stepwise fashion from normal LV geometry (5.9 [IQR, 2.4–11.5] pg/mL) to concentric remodeling (9.1 [IQR, 4.8–16.5] pg/mL) to eccentric hypertrophy (12.0 [IQR, 5.7–25.7] pg/mL) to concentric hypertrophy (15.0 [IQR, 7.5–28.6] pg/mL; p<0.001). In the multivariable-adjusted nominal logistic regression model, detectable cTnT levels were significantly associated with concentric hypertrophy (OR, 1.4 per 1-log unit; 95% C.I., 1.1–2.0; p<0.01) but not with concentric remodeling (OR, 1.2 per 1-log unit; 95% C.I., 0.9–1.6; p=0.2) or eccentric hypertrophy (OR, 1.3 per 1-log unit; 95% C.I., 0.9–1.8; p=0.1).

Troponin T and Left Ventricular Function

There were only 229 participants with LV systolic dysfunction (EF < 0.45). Compared with those with normal systolic function, participants with systolic dysfunction had higher levels of cTnT (Table 2; median of 14.4 [IQR, 7.1 – 27.8] vs. 10.3 [IQR 4.9 – 19.6] pg/mL; p<0.001). As a log transformed continuous variable, detectable cTnT levels were significantly associated with systolic dysfunction after multivariable adjustment (OR, 1.4 per 1-log unit; 95% C.I., 1.1–1.7; p<0.01). However, this association was no longer apparent when comparing those with the highest levels of cTnT to those with undetectable cTnT, perhaps due to the low prevalence of reduced EF (Table 2). There was also a high prevalence of LV diastolic dysfunction (71%), with the majority of participants having mild diastolic dysfunction (62%). Participants with diastolic dysfunction had higher cTnT than those with normal diastolic function (median of 11.7 [IQR, 6.0 – 21.5] vs. 8.7 [IQR, 3.8 –

17.6] pg/mL; p<0.001). Moreover, there was a higher prevalence of moderate or severe diastolic dysfunction in those with the highest level of cTnT compared with those without detectable cTnT (Table 2). However, in the intermediate and multivariable-adjusted models, there was no significant association between level of cTnT and moderate or severe diastolic dysfunction (Table 2). In the subgroup of participants with EF≥0.45, multivariable-adjusted analysis demonstrated a significant association between cTnT and mildly abnormal diastolic dysfunction (OR, 1.2 per 1-log unit; 95% CI, 1.0–1.5; p=0.05) but not with moderately or severely abnormal diastolic dysfunction.

Detection of LV Structural and Functional Abnormalities by cTnT

When evaluated as a screening test, cTnT functioned only modestly for the detection of LVH (AUC, 0.64) or concentric hypertrophy (AUC, 0.64) (Table 3). Performance was worse for the detection of LV systolic (AUC, 0.59) and diastolic dysfunction (AUC, 0.52). For each of these structural and functional abnormalities, we identified no optimal threshold value of cTnT; the 90th percentile of cTnT for the detection of concentric LVH had the highest positive likelihood ratio (2.88) and measurable cTnT for the detection of LVH had the lowest negative likelihood ratio (0.41).

Discussion

In ESRD and in the general population, circulating cTnT is associated with pathological cardiac structural and functional changes and predicts poor outcome, including HF and death.(8, 9, 27, 28) Moreover, in CKD, cardiac biomarkers such as cTnT and N-terminal pro–brain natriuretic peptide might enhance the identification of patients in whom renal replacement therapy will likely be required.(29) While pathological cardiac structural changes, such as LVH, are associated with adverse outcome in patients with CKD, there are limited data on the cardiac structural and functional correlates of circulating cTnT.(30) Since cTnT is more easily obtainable in the outpatient setting than an echocardiogram, it is important to better define the cardiac structural and functional correlates of circulating cTnT. Our principal findings were: a) there was a high prevalence of detectable cTnT as measured by the highly sensitive assay; b) detectable cTnT is strongly associated with LVH and, in particular, concentric hypertrophy; and c) detectable cTnT has modest adjusted associations with LV systolic dysfunction but not with diastolic dysfunction. These findings indicate that circulating cTnT levels in CKD are predominantly an indicator of pathological LVH.

cTnT is detectable with the highly sensitive assay in nearly two-thirds of ambulatory older adults and in a quarter of community-dwelling adults aged 30 to 65.(8, 27) In both of these groups, decreased kidney function was associated with higher levels of cTnT. Previous studies of patients with ESRD have reported a prevalence of 41%–45% of detectable cTnT, measured with the standard assay.(28, 31) In CKD, the prevalence of detectable cTnT, using the standard assay, has ranged from 16% to 43% in prior smaller studies.(13–15) We report a much higher prevalence of detectable cTnT. The likely explanation for this is the detection limit of 0.003 ng/mL for the highly sensitive assay compared with the detection limit of 0.01 ng/mL for the standard assay. A similar difference in the prevalence of circulating cTnT in the general population was observed in the study by de Lemos *et al.*, in which the prevalence of cTnT using the highly sensitive assay (25%) was much greater than that obtained using the standard assay (0.7%).(8)

An increased prevalence of LVH in CKD, with estimates ranging from 36% to 50%, has previously been reported.(32, 33) While cTnT is associated with LVH in the general population, there have been contradictory findings in CKD and in ESRD.(8, 9, 13, 14) In the study of 224 patients with ESRD on hemodialysis by deFilippi *et al.*, no association between

cTnT and LVH was found.(9) In the study of 176 outpatients with CKD by Goicoechea *et al.*, an independent association between cTnT, measured with the standard assay, and LVH, defined electrocardiographically, was reported.(14) In another study of 222 participants with CKD, there was no independent association between cTnT, measured with the standard assay, and LVH, detected by echocardiography. (13) We found a high prevalence of LVH in our population and confirmed the independent association of cTnT with LV mass index and prevalence of LVH, increasing incrementally from undetectable across categories of detectable cTnT. Differences between our findings and those previously reported may be related to the increased precision of our assay for cTnT and the 10-fold larger sample size in our study compared with those of prior studies.

cTnT is associated with LV systolic dysfunction in the general population and in patients with ESRD.(8, 9, 27, 28) To date, there have been no reports on this association in patients with CKD. In our population, we found an increasing prevalence of LV systolic dysfunction across categories of cTnT levels. In addition, there was an independent association between levels of cTnT and LV systolic dysfunction. This association, however, was not apparent when comparing the group with the highest levels of cTnT with the one with the lowest, likely due to the overall low prevalence of systolic dysfunction in our study population.

In CKD, diastolic dysfunction is common and its severity is correlated with the degree of decreased kidney function.(34–36) Moreover, in patients with HF, CKD-associated mortality may be worse in those with diastolic HF than in those with systolic HF.(4) In a study of 44 patients with acute HF with preserved LV ejection fraction, cTnT was significantly associated with reduced early diastolic mitral annular velocity, E_a, an index of LV diastolic dysfunction.(37) However, there are no reports to date of the association between cTnT levels and diastolic dysfunction in CKD. There was a high prevalence of diastolic dysfunction in our study population, with the majority of participants having only mildly abnormal diastolic function. We observed an increasing prevalence of diastolic dysfunction across categories of cTnT levels but did not find an independent association between cTnT levels and diastolic dysfunction.

Despite its strong association with LVH and more modest association with LV systolic dysfunction, cTnT functions weakly as a diagnostic test in this population with CKD. At the different cut points of cTnT, none of the positive likelihood ratios exceed 3.0 for the detection of LVH, systolic and diastolic dysfunction, and concentric LVH, and measurable cTnT had negative likelihood ratios less than 0.50 only for the detection of LVH and concentric LVH. This suggests that the utility of cTnT for screening patients with CKD for cardiac structural and functional abnormalities is limited. In order for cTnT to be an effective diagnostic test, there would need to be a clearer separation in cTnT levels between those with and without cardiac structural and functional abnormalities. In contrast, in our study there was substantial overlap in cTnT levels between participants with and without cardiac abnormalities. Our findings do not necessarily generalize to other clinical settings.

This paper is a cross-sectional analysis of the cardiac structural and functional correlates of circulating cTnT. As such, this analysis does not establish a causal or mechanistic link between elevated cTnT and LV structural and functional abnormalities and cannot exclude the possibility that a third factor could cause both circulating cTnT and cardiac abnormalities. To explore further a possible causal or mechanistic link, future studies should evaluate and compare the prognostic significance of cTnT and the cardiac structural and functional abnormalities in CKD. Patients with severe heart failure were not enrolled in the CRIC Study and we excluded participants with self-reported heart failure for this analysis. Furthermore, the CKD patients who volunteered for this longitudinal clinical study were likely healthier than the typical population of CKD patients. We excluded patients with heart

failure since they are likely to be evaluated with echocardiography, and we were more interested in the utility of cTnT for the detection of subclinical cardiac structural abnormalities in CKD. However, these factors do limit the generalizability of our findings to a general CKD population that may include patients with heart failure. CAD and myocardial ischemia may be important mechanisms leading to LVH and myocardial damage.(38) Alhough there is considerable overlap between risk factors predisposing patients to coronary atherosclerosis and to CKD, the association between detectable cTnT and angiographic CAD is uncertain. In a retrospective analysis, Obialo *et al.* found no association between detectable cTnT and angiographically evident CAD.(39) However, in the larger prospective study of ESRD patients by deFilippi *et al.*, there was a strong association between cTnT and diffuse CAD.(9) Subclinical CAD, therefore, may also contribute to myocardial damage and circulating cTnT in CKD. The presence of CAD was not formally assessed using either noninvasive or angiographic techniques in this study. Evaluation of LV diastolic function was accomplished using standard Doppler echocardiography. Newer techniques such as tissue Doppler or myocardial strain imaging that may better separate categories of diastolic dysfunction were not widely available when echocardiography was initially performed in this cohort.

In a large CKD cohort without HF, there was a high prevalence of circulating cTnT. Moreover, cTnT was strongly associated with increased LV mass and concentric LVH, but had a more modest association with LV systolic dysfunction and no significant association with diastolic dysfunction. Despite these associations, the utility of cTnT for screening patients with CKD for cardiac structural and functional abnormalities is limited.

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Table 1

Participant characteristics and echocardiographic measures by cTnT category

	Total Cohort (N=3,243)	cTnT category					P
		Undetectable (n=508)	Quartile 1 (n=684)	Quartile 2 (n=684)	Quartile 3 (n=684)	Quartile 4 (n=683)	
Cut Points of cTnT (pg/mL)	1.5–738.7	<3.0	3–7.7	7.8–13.3	13.4–23.8	23.9–738.7	
Participant Characteristics							
Age (y)	59 (11)	52 (12)	57 (12)	60 (11)	62 (10)	60 (10)	<0.001
Female	1466 (45)	378 (74)	368 (54)	306 (45)	236 (34)	178 (26)	<0.001
Race							<0.001
Non-Hispanic White	1406 (43)	260 (51)	343 (50)	338 (49)	271 (40)	194 (28)	
Non-Hispanic Black	1228 (40)	181 (36)	237 (35)	248 (36)	291 (42)	331 (48)	
Hispanic	418 (13)	44 (9)	61 (9)	79 (12)	95 (14)	139 (20)	
Other	131 (4)	23 (4)	43 (6)	19 (3)	27 (4)	19 (3)	
Body Mass Index (kg/m^2)	32 (8)	31 (8)	31 (7)	32 (8)	33 (8)	33 (7)	<0.001
Systolic BP (mmHg)	134 (21)	124 (17)	128 (17)	133 (20)	137 (22.0)	142 (21)	<0.001
Diastolic BP (mmHg)	75 (12)	75 (12)	74 (12)	74 (12)	75 (12.5)	76 (13)	0.08
hsCRP (mg/L)	5.4 (9.7)	4.9 (8.2)	5.0 (8.7)	5.1 (7.4)	5.7 (9.7)	6.3 (13.2)	0.1
Hemoglobin (g/dL)	12.8 (1.8)	13.1 (1.6)	13.3 (1.8)	13.0 (1.8)	12.7 (1.8)	12.0 (1.7)	<0.001
eGFRcys †(mL/min/1.73m^2)	50.3 (19.7)	66 (23)	56 (19)	50 (16)	46 (16)	38 (14)	<0.001
eGFRcr $^{\delta}$(mL/min/1.73m^2)	42 (14.9)	51 (15)	46 (14)	42 (13)	39 (14)	33 (14)	<0.001
Urine ACR (mg/g)	46 (8–424)	11 (5–72)	20 (5–174)	32 (7–245)	80 (14–572)	349 (55–1674)	<0.001
Diabetes	1490 (46)	78 (15)	215 (31)	300 (44)	374 (55)	523 (77)	<0.001
Hypertension	2857 (88)	358 (70)	572 (84)	622 (91)	648 (95)	657 (96)	<0.001
High Cholesterol	2772 (85)	347 (68)	574 (84)	605 (89)	619 (91)	627 (92)	<0.001
Current Smoker	421 (13)	70 (14)	76 (11)	95 (14)	87 (13)	93 (14)	0.7
Alcohol (DHQ, g)	6.4 (22.7)	5.7 (11.7)	6.5 (15.0)	6.4 (25.7)	6.9 (24.7)	6.6 (31.1)	<0.001
Cardiovascular Disease	891 (27)	48 (10)	142 (21)	178 (26)	246 (36)	277 (41)	<0.001
Peripheral Vascular Disease	204 (6)	13 (3)	24 (4)	31 (4)	50 (7)	86 (13)	<0.001
Echocardiographic Measures							

	Total Cohort (N=3,243)	cTnT category					P
		Undetectable (n=508)	Quartile 1 (n=684)	Quartile 2 (n=684)	Quartile 3 (n=684)	Quartile 4 (n=683)	
LV Mass 2D/height$^{2.7}$ ($g/m^{2.7}$)	50 (13)	44 (10)	47 (11)	50 (12)	53 (13)	58 (14)	<0.001
LV Mass Indexed to BSA (g/m^2)	101 (23)	89 (18)	94 (18)	99 (20)	106 (23)	116 (26)	<0.001
E Wave Velocity (cm/s)	72 (19)	71 (17)	70 (18)	71 (19)	72 (20)	75 (22)	0.001
A Wave Velocity (cm/s)	75 (21)	66 (18)	72 (20)	71 (20)	78 (21)	81 (20)	<0.001
Mitral E Wave Deceleration Time (ms)	199 (48)	191 (46)	194 (46)	202 (48)	204 (50)	201 (48)	<0.001
Ejection Fraction (%)	55 (7)	56 (6)	56 (6)	56 (7)	55 (8)	54 (8)	<0.001
Ejection Fraction Category **							<0.001
>50%	83	85	86	84	83	74	
46–50%	9	9	8	8	8	13	
36–45%	6	6	5	6	6	9	
≤35%	2	<1	1	2	2	3	
LV Geometry ** Category							<0.001
Normal	16	33	20	15	9	5	
Concentric Remodeling	23	24	31	26	20	16	
Eccentric Hypertrophy	9	6	9	9	9	11	
Concentric Hypertrophy	27	16	22	24	34	38	
Missing	25	22	19	26	28	30	
Diastolic Function ** Category							<0.001
Normal	29	39	33	27	24	23	
Mildly Abnormal	62	47	58	66	70	68	
Moderately Abnormal	8	12	8	7	6	8	
Severely Abnormal	1	2	1	<1	1	1	

Note: Unless otherwise indicated, values for categorical variables are reported as number (percentage); for continuous variables, values are given as as mean +/− standard deviation or median [interquartile range]. P values are obtained using Kruskal-Wallis tests (non-parametric version of analysis of variance) or non-parametric median comparison test for continuous variables and Chi-square tests for categorical variables.

** Values are percentages; categories sum up to 100% vertically.

† $eGFR_{cys}$ was calculated using the equation $eGFR = 76.7 \times SCysC^{-1.19}$ from the CKD Epidemiology Collaboration, where SCysC is nonstandardized serum cystatin C (20).

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§ $eGFR_{cr}$ was calculated using the 4-variable Modification of Diet in Renal Disease Study equation.

Abbreviations and definitions: ACR, albumin-creatinine ratio; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; BP, blood pressure; high- sensitivity C-reactive protein (hsCRP); Cystatin C-based estimated glomerular filtration rate ($eGFR_{cys}$); Serum creatinine-based estimated glomerular filtration rate ($eGFR_{cr}$); Left Ventricular (LV); body surface area (BSA); 2D, _____; DHQ, _____.

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Table 2

Association between cTnT and LVH, systolic dysfunction, and diastolic dysfunction

	cTnT category					P[†]
	Undetectable	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Cut Points of cTnT (pg/mL)	<3.0	3–7.7	7.8–13.3	13.4–23.8	23.9–738.7	
Prevalence of LVH	117 (23)	226 (33)	243 (36)	304 (44)	352 (52)	<0.001
Odds of LVH[a]						
Demographic-Adjusted[*]	1.00 (ref)	1.72 (1.29–2.30)	2.13 (1.58–2.87)	3.74 (2.73–5.13)	5.72 (4.08–8.04)	
Intermediate Model[**]	1.00 (ref)	1.37 (1.01–1.84)	1.51 (1.10–2.07)	2.37 (1.69–3.32)	3.02 (2.07–4.40)	
Fully-Adjusted[***]	1.00 (ref)	1.26 (0.82–1.93)	1.35 (0.86–2.12)	1.91 (1.20–3.07)	2.43 (1.44–4.09)	
Prevalence of EF <0.45	27 (6)	36 (6)	46 (8)	50 (8)	70 (12)	<0.001
Odds of EF < 0.45[a]						
Demographic-Adjusted[*]	1.00 (ref)	0.94 (0.55–1.58)	1.25 (0.75–2.10)	1.42 (0.84–2.43)	2.19 (1.28–3.74)	
Intermediate Model[**]	1.00 (ref)	0.87 (0.51–1.49)	1.16 (0.68–1.96)	1.22 (0.71–2.12)	1.90 (1.08–3.32)	
Fully-Adjusted[****]	1.00 (ref)	0.76 (0.40–1.42)	1.03 (0.55–1.90)	1.07 (0.57–2.00)	1.52 (0.81–2.87)	
Prevalence of DD	246 (48)	391 (57)	426 (62)	436 (64)	417 (61)	<0.001
Odds of DD[a]						
Demographic-Adjusted[*]	1.00 (ref)	1.06 (0.79–01.41)	1.18 (0.87–1.60)	1.26 (0.91–1.74)	1.39 (0.99–1.97)	
Intermediate Model[**]	1.00 (ref)	0.96 (0.71–1.30)	1.02 (0.74–1.41)	1.10 (0.77–1.56)	1.20 (0.81–1.76)	
Fully-Adjusted[*****]	1.00 (ref)	0.82 (0.53–1.27)	1.03 (0.63–1.64)	1.24 (0.74–2.10)	1.12 (0.63–2.00)	

Note: Prevalence reported as number (percentage). LVH calculated as $2D/height^{2.7}$

[†] P value is for unadjusted analyses.

[*] Adjusted for age, sex, race, and cause of kidney disease.

[**] Adjusted for age, sex, race, diabetes, hypertension, high cholesterol, prior peripheral vascular disease and cardiovascular disease, high-sensitivity C-reactive protein.

[***] Adjusted for age, sex, race, cause of kidney disease, diabetes, hypertension, high cholesterol, prior peripheral vascular disease, any cardiovascular disease, height, weight, body mass index, systolic and diastolic blood pressure, hemoglobin, cystatin C–based estimated glomerular filtration rate, high-senstivity C-reactive protein.

[****] Adjusted for age, sex, race, cause of kidney disease, height, weight, and diastolic blood pressure, any cardiovascular disease.

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***** Adjusted for age, sex, race, cause of kidney disease, height, diabetes, hypertension, high cholesterol, alcohol use, any cardiovascular disease, systolic blood pressure, diastolic blood pressure, hemoglobin, and cystatin C–based estimated glomerular filtration rate.

[a] values given as OR (95% CI).

Abbreviations: cTnT, cardiac troponin T; Left ventricular hypertrophy (LVH); Ejection fraction (EF); Diastolic dysfunction (DD); ref, reference.

Table 3

cTnT as a diagnostic test for LVH, diastolic dysfunction and systolic dysfunction

	ROC	Sensitivity (%)	Specificity (%)	LR+	LR−
LVH	0.64				
Detectable cTnT *	-	90.6	22.9	1.18	0.41
High-Quartile cTnT **	-	28.3	88.7	2.50	0.81
90th Percentile cTnT ***	-	11.8	95.9	2.88	0.92
Diastolic Dysfunction	0.56				
Detectable Troponin T *	-	87.2	20.8	1.10	0.62
High Quartile Troponin T **	-	21.8	83.7	1.34	0.93
90th Percentile Troponin T ***	-	8.8	94.0	1.47	0.97
Systolic Dysfunction	0.59				
Detectable Troponin T *	-	88.2	16.4	1.06	0.72
High Quartile Troponin T **	-	30.6	81.2	1.63	0.85
90th Percentile Troponin T ***	-	13.5	92.6	1.82	0.93
Concentric Hypertrophy	0.64				
Detectable Troponin T *	-	91.0	20.6	1.15	0.44
High Quartile Troponin T **	-	29.6	85.8	2.08	0.82
90th Percentile Troponin T ***	-	12.9	94.7	2.43	0.92

Note: Diastolic dysfunction: normal vs. mildly, moderately and severely abnormal; systolic dysfunction: ejection fraction<0.45.

* Detectable cTnT cut point is ≥3.0 pg/mL.

** High quartile cTnT cut point is 23.84 pg/mL.

*** 90th percentile cTnT cut point is 43.65 pg/mL.

Abbreviations: Receiver operating characteristic (ROC); Likelihood ratio positive (LR+); Likelihood ratio negative (LR−); cTnT, cardiac troponin T; LVH, left ventricular hypertrophy