NT-ProBNP and Troponin T and Risk of Rapid Kidney Function Decline and Incident CKD in Elderly Adults

Nisha Bansal, Ronit Katz,* Lorien Dalrymple,† Ian de Boer,* Christopher DeFilippi,‡ Bryan Kestenbaum,* Meyeon Park,§ Mark Sarnak,‖ Stephen Seliger,¶ and Michael Shlipak**††‡‡§§*

Abstract

Background and objectives Elevations in N-terminal pro–B-type natriuretic peptide and high-sensitivity troponin T are associated with poor cardiovascular outcomes. Whether elevations in these cardiac biomarkers are associated with decline in kidney function was evaluated.

Design, setting, participants, & measurements N-terminal pro–B-type natriuretic peptide and troponin T were measured at baseline in 3752 participants free of heart failure in the Cardiovascular Health Study. eGFR was determined from the Chronic Kidney Disease Epidemiology Collaboration equation using serum cystatin C. Rapid decline in kidney function was defined as decline in serum cystatin C eGFR≥30%, and incident CKD was defined as the onset of serum cystatin C eGFR<60 among those without CKD at baseline (n=2786). Cox regression models were used to examine the associations of each biomarker with kidney function decline adjusting for demographics, baseline serum cystatin C eGFR, diabetes, and other CKD risk factors.

Results In total, 503 participants had rapid decline in serum cystatin C eGFR over a mean follow-up time of 6.41 (1.81) years, and 685 participants developed incident CKD over a mean follow-up time of 6.41 (1.74) years. Participants in the highest quartile of N-terminal pro–B-type natriuretic peptide (>237 pg/ml) had an 67% higher risk of rapid decline and 38% higher adjusted risk of incident CKD compared with participants in the lowest quartile (adjusted hazard ratio for serum cystatin C eGFR rapid decline, 1.67; 95% confidence interval, 1.25 to 2.23; hazard ratio for incident CKD, 1.38; 95% confidence interval, 1.08 to 1.76). Participants in the highest category of troponin T (>10.58 pg/ml) had 80% greater risk of rapid decline compared with participants in the lowest category (adjusted hazard ratio, 1.80; 95% confidence interval, 1.35 to 2.40). The association of troponin T with incident CKD was not statistically significant (hazard ratio, 1.17; 95% confidence interval, 0.92 to 1.50).

Conclusions Elevated N-terminal pro–B-type natriuretic peptide and troponin T are associated with rapid decline of kidney function and incident CKD. Additional studies are needed to evaluate the mechanisms that may explain this association.

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*Kidney Research Institute, Division of Nephrology, University of Washington, Seattle, Washington; †Division of Nephrology, University of California, Davis, Sacramento, California; Divisions of ‡Cardiology and ¶Nephrology, University of Maryland, Baltimore, Maryland; §Division of Nephrology and Departments of **Medicine, ††Epidemiology, and ‡‡Biostatistics, University of California, San Francisco, California; ‖Division of Nephrology, Tufts Medical Center, Boston, Massachusetts; and §§Division of General Internal Medicine, San Francisco Veterans Affair Medical Center, San Francisco, California

Correspondence: Dr. Nisha Bansal, Kidney Research Institute, University of Washington, 908 Jefferson Street, 3rd Floor, Seattle, WA 98104. Email: nbansal@nephrology.washington.edu

Introduction

Elevated levels of N-terminal pro–B-type natriuretic peptide (NT-proBNP) and troponin T (TnT) are associated with adverse outcomes, including incident heart failure (HF), major cardiovascular events, and mortality (1–12). NT-proBNP is secreted into the circulation from cardiac myocytes in response to stimuli, such as pressure or volume overload (13). Similarly, TnT concentrations may become elevated in response to myocardial injury, myocardial remodeling, or left ventricular hypertrophy (LVH) (14,15). Elevated NT-proBNP and TnT concentrations may serve as early markers of abnormal cardiac physiology, which may also be associated with poor kidney outcomes as well.

Levels of NT-proBNP and TnT are commonly elevated in patients with reduced kidney function (15–21), resulting from multiple physiologic stresses, including extracellular volume expansion, LVH, myocardial ischemia, and possibly, reduced renal clearance (16,20,22–24). Most studies to date have primarily focused on the association between NT-proBNP and TnT and cardiovascular and/or all-cause death. However, kidney outcomes are also important in management of high-risk patients, because decreased kidney function and kidney function decline are well established risk factors for cardiovascular disease (CVD) and mortality (25–27). Subclinical cardiac abnormalities—as indicated by preclinical elevations in NT-proBNP and TnT—may potentially identify physiologic processes that contribute to loss of kidney function.

Previous studies in persons with established CKD have suggested an association between these cardiac biomarkers and adverse kidney outcomes. For example, among participants in the Trial to Reduce Cardiovascular

Events with Aranesp Therapy (TREAT) with CKD and type 2 diabetes, elevated NT-proBNP and TnT levels were independently associated with higher risk of ESRD (28). However, to our knowledge, no studies have examined associations of NT-proBNP and TnT with kidney function decline in a community-based cohort with and without CKD, which may highlight the contribution of subclinical CVD to adverse kidney outcomes and identify opportunities for early interventions. Thus, in our study, we examined the association of NT-proBNP and TnT with decline of kidney function in older adults free of clinical HF with and without CKD at baseline.

Materials and Methods

Study Population

The Cardiovascular Health Study (CHS) is a prospective, longitudinal study of older community-dwelling adults. The study methods have been previously described (29). Participants were recruited from Health Care Financing Administration Medicare eligibility lists at four locations: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. To be eligible, participants were required to be community-dwelling, age 65 years or older, expected to remain in the area for 3 years after recruitment, not receiving active treatment for cancer, and able to give informed consent without a proxy. An initial 5201 participants were recruited between 1989 and 1990. An additional 687 African-American participants were added to the study in 1992 and 1993. For our study, we excluded participants who were missing measures of NT-proBNP or TnT at baseline because of insufficient serum (n=1472). We also excluded participants with missing baseline cystatin C (n=476) and those who had prevalent HF at baseline (n=188), leaving a final analytic sample of n=3752. Those who were excluded were more likely to be men, were more likely to have prevalent CVD, and had lower eGFR (Supplemental Table 1).

The CHS study was approved by the institutional review boards of the University of Washington and each of the participating centers. All CHS participants provided written informed consent.

Biomarkers

NT-proBNP and TnT were measured in serum collected at baseline in the original CHS cohort (1989–1990) and the supplemental cohort (1992–1993) as previously described (30,31). All biomarker measurements were performed on serum samples stored at −70°C to −80°C and thawed just before testing (maximum of three freeze-thaw cycles). NT-proBNP was measured in 2007 on the Elecsys 2010 system (Roche Diagnostics, Indianapolis, IN) (31). The coefficient of variation for the NT-proBNP assay was 2%–5% during the testing period, and the analytical measurement range for NT-proBNP was 5–35,000 pg/ml (31). TnT concentrations were measured in 2010 with highly sensitive reagents on an Elecsys 2010 analyzer (Roche Diagnostics), with an analytical measurement range of 3–10,000 pg/ml (30).

Outcomes

Our primary outcomes were (*1*) absolute annual eGFR decline, (*2*) rapid kidney function decline defined as an eGFR decline ≥30% (a definition used by the Food and Drug Administration as a clinically important decline in kidney function [32]) from baseline, and (*3*) incident CKD defined as an eGFR<60 ml/min per 1.73 m^2. eGFR was measured at baseline, year 3, and year 7 for the initial cohort and year 3 and year 7 for the African-American cohort (for a range of 4–7 years of follow-up).

For the outcome of absolute annual eGFR decline, participants had to have at least one addition measure of eGFR after the baseline measure. For this analysis, 800 participants were missing a subsequent eGFR measure and excluded, leaving an analytic sample of 3062. For the outcome of rapid kidney function decline, all 3752 participants from our study were included. Participants were censored at lost to follow-up (*e.g.*, including missing a subsequent measure of eGFR) or death. To meet criteria for incident CKD, participants had to have met the following criteria: eGFR>60 ml/min per 1.73 m^2 at baseline (n=966 excluded), at least a 1-ml/min per 1.73 m^2 decline in eGFR per year in follow-up, and eGFR<60 ml/min per 1.73 m^2 at a follow-up visit. We chose these criteria to capture participants with clinically significant eGFR decline. With these exclusions, 2786 participants were available for this analysis.

We elected to use cystatin C to estimate eGFR in our primary analysis, because prior work has shown that cystatin C estimates larger declines in kidney function compared with creatinine-based eGFR (33) and that these declines predict adverse events (26,27). eGFR was determined from cystatin C using the 2012 CKD Epidemiology Collaboration equation, which includes age and sex (34). eGFR was expressed as milliliters per minute per 1.73 m^2 body surface area, and cystatin C was expressed in milligrams per liter. All renal function assays were performed at the University of Vermont in May and June of 2008 on serum stored at −70°C. Cystatin C was measured using a BN II nephelometer (N Latex Cystatin C; Dade Behring, Munich, Germany) using a particle-enhanced immunonepholometric assay, and the intra-assay coefficient of variation for cystatin C ranged from 2.0% to 2.8% (35).

Covariates

Clinical characteristics were obtained from the baseline CHS study visit and included demographic characteristics (age, sex, and race) and comorbid diseases (coronary heart disease [CHD], stroke, hypertension, and diabetes). CVD was defined as history of CHD or stroke. CHD was defined as a history of angina, myocardial infarction (MI), coronary angioplasty, or coronary artery bypass surgery. Information on tobacco use was collected from self-report (never, former, or current). Diabetes was defined as fasting glucose >126 mg/dl or use of oral hypoglycemic medications or insulin. Physical examination measures (systolic and diastolic BP and body mass index in kilograms per meter^2) and laboratory values (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) were considered in the analysis. Medication use (antihypertensive [including angiotensin converting enzyme inhibitors/angiotensin receptor blocker and diuretics] and lipid-lowering medications) was determined by participants' pill bottles and recorded by study personnel. An electrocardiogram was performed at baseline, and left ventricular mass (LVM) was estimated from the electrocardiogram (36). LVH was defined by the Cornell criteria (37). Serum creatinine, measured using a colorimetric

Table 1. Characteristics of the study population by baseline N-terminal pro–B-type natriuretic peptide concentration (*n*=3752)

Characteristic	N-Terminal Pro–B-Type Natriuretic Peptide Quartiles (pg/ml)				
	All	≤58	59–115	116–237	>237
Number of participants	3752	961	985	959	847
Demographics					
Age (yr) (SD)	72 (5)	70 (4)	71 (5)	73 (5)	75 (6)
Women, *n* (%)	2351 (63)	540 (56)	662 (67)	637 (66)	512 (60)
Black race, *n* (%)	657 (18)	217 (23)	174 (18)	145 (15)	121 (14)
Prevalent cardiovascular disease, *n* (%)					
History of coronary heart disease	679 (18)	103 (11)	123 (13)	183 (19)	270 (32)
History of stroke	134 (4)	18 (2)	28 (3)	35 (4)	53 (6)
History of cardiovascular disease	777 (21)	117 (12)	144 (15)	210 (22)	306 (36)
Left ventricular hypertrophy (electrocardiogram Cornell volt)	199 (5)	27 (3)	34 (4)	39 (4)	99 (12)
Cardiovascular disease risk factors					
Hypertension, *n* (%)	2254 (60)	504 (52)	531 (54)	592 (62)	627 (74)
Systolic BP (mmHg) (SD)	137 (22)	132 (19)	134 (20)	137 (21)	145 (24)
Diastolic BP (mmHg) (SD)	71 (11)	71 (11)	71 (10)	70 (12)	72 (12)
Hypertension medications, *n* (%)	1779 (48)	396 (41)	413 (42)	466 (49)	504 (60)
ACE inhibitors, *n* (%)	251 (7)	71 (7)	56 (6)	59 (6)	65 (8)
Diuretics, *n* (%)	1048 (28)	245 (26)	242 (25)	270 (28)	291 (34)
Diabetes, *n* (%)	654 (17)	203 (21)	150 (15)	152 (16)	149 (18)
Smoking, *n* (%)					
Never	1784 (48)	416 (43)	478 (49)	475 (50)	415 (49)
Former	1533 (41)	419 (44)	398 (40)	383 (40)	333 (39)
Current	431 (12)	125 (13)	108 (11)	100 (10)	98 (12)
Body mass index (kg/m^2) (SD)	26.8 (4.8)	27.7 (4.7)	26.9 (4.7)	26.5 (4.8)	26.0 (4.7)
Total cholesterol (mg/dl) (SD)	213 (39)	217 (39)	216 (37)	211 (38)	207 (42)
LDL cholesterol (mg/dl) (SD)	131 (35)	134 (35)	133 (34)	128 (34)	127 (37)
HDL cholesterol (mg/dl) (SD)	55 (16)	54 (15)	56 (16)	56 (17)	54 (16)
Triglycerides (mg/dl), median [interquartile range]	120 [92–164]	128 [94–175]	122 [95–165]	118 [91–160]	116 [87–155]
Troponin (pg/ml), median [interquartile range]	5.01 [2.99–9.64]	3.12 [2.99–6.95]	3.53 [2.99–7.67]	5.43 [2.99–9.41]	9.45 [5.01–16.08]
Kidney function					
eGFR[a] (ml/min per 1.73 m^2) (SD)	72 (19)	79 (17)	75 (17)	71 (18)	62 (19)
Cystatin C (mg/L) (SD)	1.05 (0.33)	0.95 (0.20)	0.99 (0.21)	1.05 (0.29)	1.21 (0.51)

[a]eGFR cystatin C (Chronic Kidney Disease Epidemiology Collaboration). ACE, angiotensin converting enzyme.

Table 2. Characteristics of study population by baseline troponin T concentration (*n*=3752)

Characteristic	Troponin T Quartiles			
	≤2.99 (Below Limit of Detection)	3.00–5.57	5.58–10.58	>10.58
Number of participants	1336	671	926	819
Demographics				
Age (yr) (SD)	70 (4)	72 (5)	73 (5)	75 (6)
Women, *n* (%)	1050 (79)	463 (69)	515 (56)	323 (39)
Black race, *n* (%)	248 (19)	94 (14)	143 (15)	172 (21)
Prevalent cardiovascular disease, *n* (%)				
History of coronary heart disease	161 (12)	103 (15)	192 (21)	223 (27)
History of stroke	20 (2)	17 (3)	34 (4)	63 (8)
History of cardiovascular disease	177 (13)	116 (17)	220 (24)	264 (32)
Left ventricular hypertrophy (electrocardiogram Cornell volt)	40 (3)	30 (5)	54 (6)	75 (9)
Cardiovascular disease risk factors				
Hypertension, *n* (%)	689 (52)	368 (55)	623 (67)	574 (70)
Systolic BP (mmHg) (SD)	133 (20)	135 (20)	140 (22)	142 (23)
Diastolic BP (mmHg) (SD)	70 (11)	70 (11)	72 (12)	72 (12)
Hypertension medications, *n* (%)	531 (40)	286 (43)	485 (52)	474 (58)
ACE inhibitors, *n* (%)	67 (5)	42 (6)	73 (8)	69 (8)
Diuretics, *n* (%)	310 (23)	161 (24)	274 (30)	303 (37)
Diabetes, *n* (%)	151 (11)	100 (15)	172 (19)	231 (28)
Smoking, *n* (%)				
Never	634 (48)	331 (50)	450 (49)	369 (45)
Former	512 (38)	273 (41)	386 (42)	362 (44)
Current	189 (14)	65 (10)	89 (10)	88 (11)
Body mass index (kg/m^2) (SD)	26.7 (4.7)	26.5 (4.9)	27.0 (4.9)	26.8 (4.6)
Total cholesterol (mg/dl) (SD)	219 (38)	215 (37)	211 (38)	204 (41)
LDL cholesterol (mg/dl) (SD)	134 (36)	132 (34)	130 (35)	125 (35)
HDL cholesterol (mg/dl) (SD)	58 (16)	55 (16)	54 (16)	51 (16)
Triglycerides (mg/dl), median [interquartile range]	120 [93–164]	120 [91–163]	120 [91–164]	121 [93–166]
Troponin (pg/ml), median [interquartile range]	80 [44–142]	94 [51–182]	127 [66–247]	207 [98–469]
Kidney function				
eGFR[a] (ml/min per 1.73 m^2) (SD)	78 (16)	75 (17)	71 (17)	60 (20)
Cystatin C (mg/L) (SD)	0.95 (0.18)	0.99 (0.22)	1.04 (0.22)	1.26 (0.55)

[a]eGFR cystatin C (Chronic Kidney Disease Epidemiology Collaboration). ACE, angiotensin converting enzyme.

method (Ektachem700; Eastman Kodak, Rochester, NY), was calibrated to isotope dilution mass spectrometry, and the intra-assay coefficient of variation was 1.9%.

Statistical Methods

Characteristics of the study population were compared across quartiles of NT-proBNP and across categories of TnT (undetectable and tertiles of the detectable range). We used linear mixed models to test the association of NT-proBNP and TnT with absolute annual eGFR decline. We then performed Cox regression models to examine the association of NT-proBNP and TnT with risk of rapid kidney function decline and incident CKD. We used the Fine and Gray model to account for the competing risk of death. We chose covariates to adjust for *a priori* that may be important confounders. We first adjusted for demographic characteristics (age, sex, and race), baseline eGFR, and other important covariates (systolic and diastolic BP, body mass index, diabetes mellitus, antihypertensive medications, and prevalent CVD), and in a final model, we adjusted for the alternative cardiac biomarker. We tested for interactions by sex, age, baseline eGFR, and CKD (defined as eGFR<60 ml/min per 1.73 m^2) at baseline.

Interim CVD is a possible competing risk as well as a potential mediator in the association of cardiac biomarkers with kidney function decline. Therefore, we also adjusted for interim HF hospitalizations as well as interim MI hospitalizations.

In a final analysis, we examined potential additive associations of elevated NT-proBNP and TnT with decline in kidney function. For this analysis, we defined participants as having one or both biomarkers in the highest quartile or category of NT-proBNP (>237 pg/ml) and TnT (>10/58 pg/ml; high/high NT-proBNP/TnT, high/low NT-proBNP/TnT, low/high NT-proBNP/TnT) relative to the referent group of participants in the lowest category of both biomarkers (low/low NT-proBNP/TnT). We calculated the additive interaction of including both biomarkers in the models.

We performed several sensitivity analyses. In the first sensitivity analysis, we excluded participants with prevalent

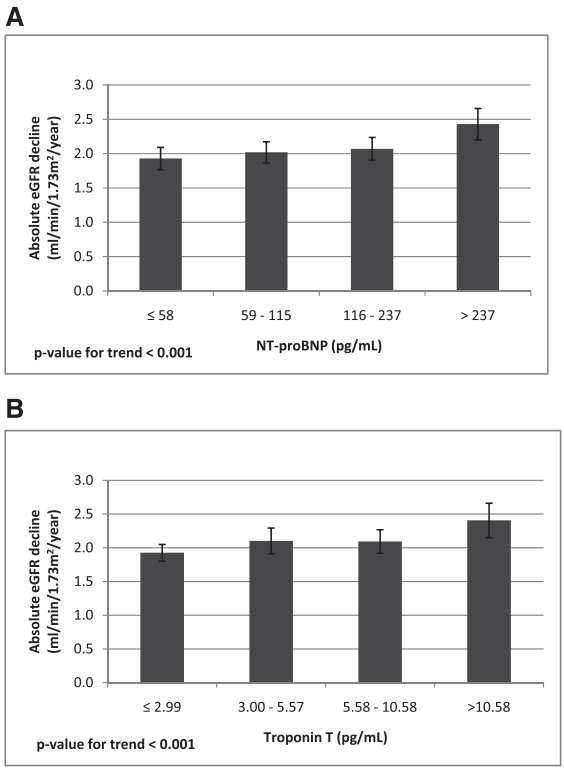

Figure 1. | The absolute decline of eGFR significantly increased across quartiles of NT-proBNP and troponin T. Mean serum cystatin C eGFR (milliliters per minute per 1.73 m^2) decline by quartile of (A) N-terminal pro–B-type natriuretic peptide (NT-proBNP) and (B) troponin T.

CHD at baseline and repeated our Cox regression models, examining the association of each cardiac biomarker with rapid kidney function decline. The rationale for this sensitivity analysis was to exclude clinical heart disease as a possible confounder in our analysis. In a second sensitivity analysis, we explored using a dichotomous NT-proBNP cutoff of >190 pg/ml and sex-stratified TnT cutpoints of >17 pg/ml for women and >31 pg/ml for men to define high risk. These cutoffs were chosen on the basis of prior work in the CHS that defined risk thresholds for cardiovascular events in the elderly (31,38). In a third sensitivity analysis, we adjusted for baseline measures of left ventricular ejection fraction (LVEF) and LVM as determine by echocardiography in the subset of participants who had these available measures. In a final sensitivity analysis, we repeated our main analyses using the 2012 combined creatinine–cystatin C equation to calculate eGFR (34).

All analyses were conducted using SPSS 21.0.0.1 (released 2012, IBM SPSS Statistics for Windows, Version 21.0; IBM Corp., Armonk, NY) and Stata (Version 13.1; College Station, TX), and P values <0.05 were considered statistically significant for all analyses.

Results

Baseline Characteristics

Among 3752 participants included in our study, mean age was 72 (±5) years, 63% were women, and 18% were African American. Mean serum cystatin C eGFR (eGFRcys) was 72 (±19) ml/min per 1.73 m^2 at baseline. Median (interquartile range) NT-proBNP was 80 (44–142) pg/ml, and median TnT was 5.01 (2.99–9.64) pg/ml. Participants with the highest levels of NT-proBNP and detectable TnT levels were more likely to be older, have a history of CVD or LVH, and have hypertension and diabetes, and they had lower eGFRcys (Tables 1 and 2).

NT-proBNP and Decline of Kidney Function

The absolute rate of decline of eGFRcys was higher among participants with higher NT-proBNP (Figure 1A, Table 3) over a mean follow-up time of 5.58 (1.80) years.

Table 3. Association of baseline N-terminal pro–B-type natriuretic peptide and troponin T with absolute decline of kidney function (*n*=3062)

	Annual Change (95% Confidence Interval) in eGFR (*n*=3062)		
	Mean (SD) Unadjusted Rate (ml/min per year)	Model 1[a]	Model 2[b]
NT-proBNP quartiles (pg/ml)			
≤58	−1.93 (2.40)	0 (reference)	0 (reference)
59–115	−2.02 (2.30)	−0.14 (−0.34 to 0.06)	−0.17 (−0.37 to 0.03)
116–237	−2.07 (2.37)	−0.28 (−0.49 to −0.07)[c]	−0.30 (−0.51 to −0.09)[c]
>237	−2.43 (2.85)	−0.49 (−0.76 to −0.22)[c]	−0.48 (−0.75 to −0.20)[c]
Troponin T categories (pg/ml)			
≤2.99	−1.93 (2.19)	0 (reference)	0 (reference)
3.00–5.57	−2.10 (2.34)	−0.14 (−0.36 to 0.07)	−0.11 (−0.32 to 0.10)
5.58 10.58	−2.09 (2.23)	−0.12 (−0.33 to 0.08)	−0.01 (−0.20 to 0.20)
>10.58	−2.41 (3.08)	−0.48 (−0.75 to −0.20)[c]	−0.33 (−0.59 to −0.06)[c]

NT-proBNP, N-terminal pro–B-type natriuretic peptide.
[a]Adjusted for demographics and baseline eGFR.
[b]Additionally adjusted for body mass index, diastolic BP, systolic BP, hypertension medications, diabetes mellitus, and prevalent cardiovascular disease.
[c]P<0.05.

Table 4. Association between baseline N-terminal pro–B-type natriuretic peptide and decline of kidney function in community-dwelling older adults

NT-proBNP Quartiles (pg/ml)	Hazard Ratio (95% Confidence Interval) for ≥30% Decline (n=3752)					Hazard Ratio (95% Confidence Interval) for Incident CKD (n=2786)[a]				
	N (%)	Adjusted for Demographics and Baseline eGFR	Adjusted for Demographics, Baseline eGFR, and Confounders[b]	Adjusted for Demographics, Baseline eGFR, Confounders,[b] and Troponin T	Adjusted for Demographics, Baseline eGFR, Confounders,[b] and Interim HF or MI	*N* (%)	Adjusted for Demographics and Baseline eGFR	Adjusted for Demographics, Baseline eGFR, and Confounders[b]	Adjusted for Demographics, Baseline eGFR, Confounders,[b] and Troponin T	Adjusted for Demographics, Baseline eGFR, Confounders,[b] and Interim HF or MI
≤58	101 (12)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	157 (21)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
59–115	108 (12)	1.01 (0.77 to 1.33)	1.06 (0.80 to 1.40)	1.03 (0.78 to 1.35)	1.05 (0.79 to 1.38)	195 (28)	1.15 (0.93 to 1.42)	1.20 (0.97 to 1.49)	1.21 (0.97 to 1.50)	1.18 (0.96 to 1.47)
116–237	115 (15)	1.08 (0.82 to 1.42)	1.12 (0.85 to 1.48)	1.07 (0.81 to 1.41)	1.10 (0.83 to 1.45)	191 (33)	1.27 (1.03 to 1.47)[c]	1.29 (1.04 to 1.61)[c]	1.30 (1.04 to 1.61)[c]	1.29 (1.04 to 1.60)[c]
>237	150 (25)	1.73 (1.32 to 2.28)[c]	1.67 (1.25 to 2.23)[c]	1.51 (1.12 to 2.03)[c]	1.56 (1.17 to 2.08)[c]	142 (41)	1.34 (1.05 to 1.69)[c]	1.38 (1.08 to 1.76)[c]	1.39 (1.08 to 1.79)[c]	1.33 (1.04 to 1.70)[c]

NT-proBNP, N-terminal pro–B-type natriuretic peptide; HF, heart failure; MI, myocardial infarction.
[a]Incident CKD defined as at least a 1-ml/min per 1.73 m^2 decline in eGFR per year in follow-up and eGFR<60 ml/min per 1.73 m^2 at a follow-up visit.
[b]Additionally adjusted for body mass index, diastolic BP, systolic BP, hypertension medications, diabetes mellitus, and prevalent cardiovascular disease.
[c]P<0.05.

In multivariable models, participants in the highest quartile of NT-proBNP had a statistically greater difference in annual eGFR decline of 0.48 ml/min per 1.73 m^2 (95% confidence interval [95% CI], 0.75 to 0.20 ml/min per 1.73 m^2 decline) compared with those in the lowest quartile of NT-proBNP.

Over a mean follow-up time of 6.41 (1.81) years, 744 participants died, and 503 participants had rapid kidney function decline defined as ≥30% decline in eGFRcys. After adjustment for demographics, baseline eGFRcys, comorbid diseases, and pertinent medications, participants in the highest quartile of NT-proBNP had 67% (95% CI, 25% to 223%) higher risk of rapid kidney function decline compared with those in the lowest quartile. This association was attenuated but remained statistically significant after adjustment for TnT (Table 4). Prevalent CKD at baseline, baseline eGFR, sex, or age did not modify the association between NT-proBNP and rapid kidney function decline (P value for interaction >0.05 for all).

Of 2786 CHS participants at risk for incident CKD, a total of 685 participants developed incident CKD over a mean time of 6.41 (1.74) years. After multivariable adjustment, those in the highest quartile of NT-proBNP had a 38% (95% CI, 8% to 76%) greater risk of incident CKD compared with those in the lowest quartile (Table 4). These associations were largely unchanged with additional adjustment for TnT. Sex or age did not modify this association (P value for interaction >0.05).

There were 115 interim HF hospitalizations and 51 interim MI hospitalizations. Adjustment for these events did not change the association of NT-proBNP with either rapid kidney function decline or incident CKD (Table 4).

TnT and Decline of Kidney Function

The mean decline of eGFRcys was higher among participants with higher TnT (Figure 1B, Table 3). Those with the highest level of detectable TnT had a significantly greater difference in annual eGFR decline of 0.33 (95% CI, 0.06 to 0.59) ml/min per 1.73 m^2 compared with those with undetectable TnT (Table 3).

Participants in the highest category of TnT had 80% (95% CI, 35% to 240%) higher risk of rapid kidney function decline compared with participants with undetectable TnT (Table 5). These associations were slightly attenuated but remained strong and statistically significant after adjustment for NT-proBNP (Table 5). Prevalent CKD at baseline, baseline eGFR, sex, or age did not modify the association between TnT and rapid kidney function decline (P value for interaction >0.05 for all).

Participants in the highest quartile of TnT had higher unadjusted rates of incident CKD. This association was no longer statistically significant after adjustment for confounders (Table 5). Sex or age did not modify this association (P value for interaction >0.05).

Adjustment for interim HF or MI hospitalizations did not change the association of TnT with either rapid kidney function decline or incident CKD (Table 5).

NT-proBNP, TnT, and Risk of Decline of Kidney Function

The 367 participants in the highest category of both NT-proBNP and TnT had significantly higher risk of rapid kidney function decline compared with the participants in

Table 5. Association between baseline troponin T and decline of kidney function in community-dwelling older adults

Troponin T Categories (pg/ml)	Hazard Ratio (95% Confidence Interval) for ≥30% Decline (n=3752)				Hazard Ratio (95% Confidence Interval) for Incident CKD (n=2786)[a]			
	N (%)	Adjusted for Demographics and Baseline eGFR	Adjusted for Demographics, Baseline eGFR, and Confounders[b]	Adjusted for Demographics, Baseline eGFR, Confounders,[b] and NT-proBNP	Adjusted for Demographics, Baseline eGFR, Confounders,[b] and Interim HF or MI	N (%)	Adjusted for Demographics and Baseline eGFR	Adjusted for Demographics, Baseline eGFR, and Confounders[b]	Adjusted for Demographics, Baseline eGFR, Confounders,[b] and NT-proBNP	Adjusted for Demographics, Baseline eGFR, Confounders,[b] and Interim HF or MI
≤2.99	115 (10)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	233 (23)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3.00–5.57	86 (15)	1.36 (1.02 to 1.81)[c]	1.32 (0.99 to 1.75)	1.27 (0.96 to 1.69)	1.31 (0.99 to 1.75)	137 (29)	0.93 (0.75 to 1.16)	0.95 (0.76 to 1.18)	0.91 (0.73 to 1.14)	0.93 (0.75 to 1.16)
5.58–10.58	135 (18)	1.56 (1.21 to 2.03)[c]	1.35 (1.04 to 1.76)[c]	1.26 (0.97 to 1.65)	1.35 (1.04 to 1.75)[c]	190 (33)	0.97 (0.79 to 1.19)	0.92 (0.75 to 1.12)	0.88 (0.71 to 1.08)	0.92 (0.75 to 1.13)
>10.58	138 (25)	2.17 (1.63 to 2.88)[c]	1.80 (1.35 to 2.40)[c]	1.62 (1.21 to 2.18)[c]	1.68 (1.25 to 2.25)[c]	125 (41)	1.30 (1.02 to 1.65)[c]	1.17 (0.92 to 1.50)	1.10 (0.85 to 1.41)	1.14 (0.89 to 1.46)

[a]Incident CKD defined as at least a 1-ml/min per 1.73 m^2 decline in eGFR per year in follow-up and eGFR<60 ml/min per 1.73 m^2 at a follow-up visit.
[b]Additionally adjusted for body mass index, diastolic BP, systolic BP, hypertension medications, diabetes mellitus, and prevalent cardiovascular disease.
[c]P<0.05.

the three lower quartiles of each biomarker (Table 6). However, the additive interaction term was not statistically significant (synergy index=1.87; 95% CI, 0.75 to 3.00). Elevations in both biomarkers were not associated with incident CKD (Table 6).

Sensitivity Analyses

In the first sensitivity analysis, we repeated our analyses examining the association of elevated cardiac biomarkers and rapid kidney function decline after excluding 679 participants with baseline history of CHD, resulting in a study population of 3073 participants. The associations of both NT-proBNP and TnT were largely unchanged (Supplemental Table 2).

In the second sensitivity analysis, we used predefined alternative cutpoints to categorize high NT-proBNP and TnT. In this analysis, only the association of elevated NT-proBNP with rapid decline of kidney function was statistically significant. (Supplemental Table 3). There was no association of high NT-proBNP or TnT with incident CKD or TnT with rapid decline of kidney function (Supplemental Table 3).

In the third sensitivity analysis, we repeated our models, adjusting for baseline measures of LVEF and LVM in the subset of participants who had echocardiograms performed at baseline. Adjustment for LVEF and LVM mildly attenuated our result. Elevated NT-proBNP was only statistically significant for higher risk of incident CKD in multivariable models, and elevated TnT was only statistically significant for higher risk of rapid decline of kidney function (Supplemental Table 4).

In a final sensitivity analysis, we repeated our models using combined creatinine-cystatin C eGFR equation. In these analyses, the results were similar to the primary models using eGFRcys (Supplemental Table 5).

Discussion

In a community-based, multicenter cohort of older adults free of clinical HF, we found that elevations in NT-proBNP (particularly ≥116 pg/ml) were associated with subsequent rapid kidney function decline and incident CKD and that elevations of TnT (≥5.58 pg/ml) were associated with subsequent rapid kidney function decline. These associations were consistent even with exclusion of patients with prevalent CHD. Furthermore, the associations between these cardiac biomarkers and rapid kidney function decline were independent of baseline level of eGFR, other CKD risk factors, and the alternative cardiac biomarker.

Elevated NT-proBNP levels reflect a wide range of cardiac pathophysiology, including changes in myocardial pressure or volume and structural heart disease, such as LVH or asymptomatic systolic dysfunction. Literature has suggested that, even in the absence of clinically overt CVD, there is a strong association between subclinical CVD and kidney function decline (39,40). Similar to our study, others have reported strong associations between higher NT-proBNP and decline in kidney function. One study evaluated the association of NT-proBNP and acute changes in kidney function among 1000 patients undergoing cardiac surgery and found that elevated preoperative NT-proBNP was associated with up to a 3-fold relative risk for postoperative AKI (41). Another study of 500 patients with CKD from a single center found that elevated B-type natriuretic peptide was

Table 6. Combined association of N-terminal pro–B-type natriuretic peptide and troponin T with rapid kidney function decline and incident CKD

TnT/NT-proBNP	≥30% Decline in eGFR		Incident CKD	
	Mean (SD) Rate (%/yr)	HR (95% CI)	Mean (SD) Rate (%/yr)	HR (95% CI)
NT-proBNP≤237; TnT≤10.58 (*n*=2453)	1.70 (0.13)	1.00 (reference)	3.38 (0.18)	1.00 (reference)
NT-proBNP≤237; TnT>10.58 (*n*=452)	2.56 (0.45)	1.30 (0.98 to 1.72)	5.35 (0.67)	1.18 (0.92 to 1.50)
NT-proBNP>237; TnT≤10.58 (*n*=480)	2.69 (0.42)	1.45 (1.12 to 1.88)[a]	5.13 (0.59)	1.13 (0.90 to 1.42)
NT-proBNP>237; TnT>10.58 (*n*=367)	3.74 (0.73)	2.00 (1.48 to 2.71)[a]	5.31 (1.17)	0.97 (0.69 to 1.36)

Adjusted for age, sex, race, baseline eGFR, body mass index, diastolic BP, systolic BP, hypertension medications, diabetes mellitus, and prevalent cardiovascular disease. TnT, troponin T; HR, hazard ratio; 95% CI, 95% confidence interval.
[a]$P<0.05$.

associated with a 78% higher rate of ESRD (42). In the TREAT, among participants with nondialysis CKD, anemia, and type 2 diabetes, participants with the highest quartile of NT-proBNP had a nearly 4-fold risk of ESRD compared with those in the lowest quartile in unadjusted models (adjusted models were not reported for each biomarker individually) (28). Similarly, in another study, NT-proBNP was associated with the combined renal end point of ESRD and doubling of creatinine among individuals with mild-to-moderate nondiabetic kidney disease (43). Limitations of these prior studies include single center, small study populations, clinical trial participants (which may not be as generalizable), lack of interim measures of kidney function before ESRD, and a focus on patients with CKD or HF at baseline. Our results expand on these prior studies by reporting a strong association between elevated NT-proBNP and clinically relevant changes in kidney function before the onset of clinically diagnosed CKD among a large, multicenter, community-based cohort of elderly adults free of HF at baseline across a range of kidney function.

Concentrations of TnT may become elevated in response to myocardial injury, myocardial remodeling, or LVH (14,15). Very few studies have examined associations of elevations in TnT and decline in kidney function. A recent study of the Framingham offspring cohort found that TnT was not associated with rapid kidney function decline (≥3 ml/min per 1.73 m^2 per year) or incident CKD (44). However, this population was younger and generally healthier compared with the CHS study population. In the TREAT, among participants with CKD and type 2 diabetes, those with detectable TnT using an older conventional assay (with a nearly 10-fold higher limit of detection) had nearly 4-fold higher rate of progression to ESRD in unadjusted analyses, similar to the associations with NT-proBNP (28). In our study, participants with the highest quartile of detectable TnT (using a more sensitive assay) had a >2-fold higher risk of rapid decline of kidney function. This association was unchanged when participants with prevalent CHD were excluded. These results suggest that subclinical CVD, as indicated by elevations in TnT, may be an important contributor to rapid decline of kidney function in the elderly.

Our study has important implications. Cardiorenal syndrome is the complex bidirectional relationship between HF and kidney disease (45). Many mechanisms have been proposed to explain cardiorenal syndrome, including altered hemodynamics (from both poor cardiac output and venous congestion) (46), alterations in the sympathetic nervous system and the renin-angiotensin-aldosterone system, inflammation, oxidative stress, and atherosclerosis (47,48). Although we cannot determine the mechanism leading to elevations in NT-proBNP and/or TnT in our study population, it is plausible that elevations in these biomarkers reflect early changes in volume and cardiac stretch, venous congestion, subclinical atherosclerosis, or myocardial ischemia, which may contribute to decline in kidney function. It remains unclear if these cardiac changes are causal in the decline of kidney function or if parallel processes are affecting both the heart and the kidney. Interestingly, adjustment for interim HF and MI did not attenuate the observed associations; thus, interim CVD cannot entirely explain our findings. Our study suggests that clinically available cardiac biomarkers may help identify patients without clinical HF that are at high risk for adverse kidney outcomes.

Our study has limitations that warrant consideration. NT-proBNP and TnT were not available in all participants because of inadequate samples; however, prior work has shown few differences in participant characteristics among those who did versus did not have measured cardiac biomarkers (30,31). There were also minimal differences between patients who were included versus excluded (Supplemental Table 1). This was a retrospective analysis. Measures of urine albuminuria or proteinuria were not available at baseline (only available at year 9), and therefore, we were not able to adjust for this possible confounder. We could not determine the etiology of these low-level elevations in cardiac biomarkers and if they may be modifiable. To be included in the study for evaluation of incident CKD as an outcome, participants had to have a repeat measure of kidney function; thus, there may be some bias, because participants who died or were lost to follow-up in the interim were not included. Last, the study was conducted among older community-dwelling adults, and the results may not be generalizable to younger or institutionalized older adults.

In conclusion, in a large community-based cohort of older adults free of clinical HF with a wide range of kidney function, we found that NT-proBNP and TnT were associated with rapid kidney function decline and incident CKD. These results suggest that patients with subclinical cardiac disease are at high risk for adverse kidney outcomes. Additional studies are needed to determine whether treating

this early cardiac dysfunction may help reduce the burden and progression of kidney disease.

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A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

Disclosures

None.

References

1. Campbell DJ, Woodward M, Chalmers JP, Colman SA, Jenkins AJ, Kemp BE, Neal BC, Patel A, MacMahon SW: Prediction of heart failure by amino terminal-pro-B-type natriuretic peptide and C-reactive protein in subjects with cerebrovascular disease. *Hypertension* 45: 69–74, 2005
2. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P: N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA* 293: 1609–1616, 2005
3. Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E: Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. *J Am Coll Cardiol* 52: 450–459, 2008
4. Rothenbacher D, Koenig W, Brenner H: Comparison of N-terminal pro-B-natriuretic peptide, C-reactive protein, and creatinine clearance for prognosis in patients with known coronary heart disease. *Arch Intern Med* 166: 2455–2460, 2006
5. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM: Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 123: 1367–1376, 2011
6. Betti I, Castelli G, Barchielli A, Beligni C, Boscherini V, De Luca L, Messeri G, Gheorghiade M, Maisel A, Zuppiroli A: The role of N-terminal PRO-brain natriuretic peptide and echocardiography for screening asymptomatic left ventricular dysfunction in a population at high risk for heart failure. The PROBE-HF study. *J Card Fail* 15: 377–384, 2009
7. Bibbins-Domingo K, Gupta R, Na B, Wu AH, Schiller NB, Whooley MA: N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. *JAMA* 297: 169–176, 2007
8. Blankenberg S, McQueen MJ, Smieja M, Pogue J, Balion C, Lonn E, Rupprecht HJ, Bickel C, Tiret L, Cambien F, Gerstein H, Münzel T, Yusuf S, Investigators HS; HOPE Study Investigators: Comparative impact of multiple biomarkers and N-Terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. *Circulation* 114: 201–208, 2006
9. Cleland JG, McMurray JJ, Kjekshus J, Cornel JH, Dunselman P, Fonseca C, Hjalmarson A, Korewicki J, Lindberg M, Ranjith N, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J, Group CS; CORONA Study Group: Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). *J Am Coll Cardiol* 54: 1850–1859, 2009
10. Sato Y, Yamada T, Taniguchi R, Nagai K, Makiyama T, Okada H, Kataoka K, Ito H, Matsumori A, Sasayama S, Takatsu Y: Persistently increased serum concentrations of cardiac troponin t in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. *Circulation* 103: 369–374, 2001
11. Weber M, Bazzino O, Navarro Estrada JL, Fuselli JJ, Botto F, Perez de Arenaza D, Möllmann H, Nef HN, Elsässer A, Hamm CW: N-terminal B-type natriuretic peptide assessment provides incremental prognostic information in patients with acute coronary syndromes and normal troponin T values upon admission. *J Am Coll Cardiol* 51: 1188–1195, 2008
12. Zethelius B, Berglund L, Sundström J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlöv J: Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med* 358: 2107–2116, 2008
13. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, Ogawa H, Okumura K, Mukoyama M, Nakao K: Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 90: 195–203, 1994
14. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK: Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 304: 2503–2512, 2010
15. Mishra RK, Li Y, DeFilippi C, Fischer MJ, Yang W, Keane M, Chen J, He J, Kallem R, Horwitz EJ, Rafey M, Raj DS, Go AS, Shlipak MG; CRIC Study Investigators: Association of cardiac troponin T with left ventricular structure and function in CKD. *Am J Kidney Dis* 61: 701–709, 2013
16. Mishra RK, Li Y, Ricardo AC, Yang W, Keane M, Cuevas M, Christenson R, deFilippi C, Chen J, He J, Kallem RR, Raj DS, Schelling JR, Wright J, Go AS, Shlipak MG; Chronic Renal Insufficiency Cohort Investigators: Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC]). *Am J Cardiol* 111: 432–438, 2013
17. DeFilippi CR, Fink JC, Nass CM, Chen H, Christenson R: N-terminal pro-B-type natriuretic peptide for predicting coronary disease and left ventricular hypertrophy in asymptomatic CKD not requiring dialysis. *Am J Kidney Dis* 46: 35–44, 2005
18. David S, Kümpers P, Seidler V, Biertz F, Haller H, Fliser D: Diagnostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for left ventricular dysfunction in patients with chronic kidney disease stage 5 on haemodialysis. *Nephrol Dial Transplant* 23: 1370–1377, 2008
19. Khan IA, Fink J, Nass C, Chen H, Christenson R, deFilippi CR: N-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide for identifying coronary artery disease and left ventricular hypertrophy in ambulatory chronic kidney disease patients. *Am J Cardiol* 97: 1530–1534, 2006
20. Zoccali C, Mallamaci F, Benedetto FA, Tripepi G, Parlongo S, Cataliotti A, Cutrupi S, Giacone G, Bellanuova I, Cottini E, Malatino LS; Creed Investigators: Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J Am Soc Nephrol* 12: 1508–1515, 2001
21. deFilippi CR, Seliger SL, Maynard S, Christenson RH: Impact of renal disease on natriuretic peptide testing for diagnosing decompensated heart failure and predicting mortality. *Clin Chem* 53: 1511–1519, 2007
22. van Kimmenade RRJ, Januzzi JL Jr, Bakker JA, Houben AJ, Rennenberg R, Kroon AA, Crijns HJGM, van Dieijen-Visser MP, de Leeuw PW, Pinto YM: Renal clearance of B-type natriuretic peptide and amino terminal pro-B-type natriuretic peptide a mechanistic study in hypertensive subjects. *J Am Coll Cardiol* 53: 884–890, 2009
23. Tsutamoto T, Kawahara C, Yamaji M, Nishiyama K, Fujii M, Yamamoto T, Horie M: Relationship between renal function and

serum cardiac troponin T in patients with chronic heart failure. *Eur J Heart Fail* 11: 653–658, 2009
24. Vickery S, Price CP, John RI, Abbas NA, Webb MC, Kempson ME, Lamb EJ: B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis* 46: 610–620, 2005
25. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
26. Shlipak MG, Katz R, Kestenbaum B, Siscovick D, Fried L, Newman A, Rifkin D, Sarnak MJ: Rapid decline of kidney function increases cardiovascular risk in the elderly. *J Am Soc Nephrol* 20: 2625–2630, 2009
27. Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, Newman AB, Sarnak MJ: Rapid kidney function decline and mortality risk in older adults. *Arch Intern Med* 168: 2212–2218, 2008
28. Desai AS, Toto R, Jarolim P, Uno H, Eckardt KU, Kewalramani R, Levey AS, Lewis EF, McMurray JJ, Parving HH, Solomon SD, Pfeffer MA: Association between cardiac biomarkers and the development of ESRD in patients with type 2 diabetes mellitus, anemia, and CKD. *Am J Kidney Dis* 58: 717–728, 2011
29. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A: The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1: 263–276, 1991
30. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL: Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 304: 2494–2502, 2010
31. deFilippi CR, Christenson RH, Gottdiener JS, Kop WJ, Seliger SL: Dynamic cardiovascular risk assessment in elderly people. The role of repeated N-terminal pro-B-type natriuretic peptide testing. *J Am Coll Cardiol* 55: 441–450, 2010
32. FDA: GFR decline as an endpoint for clinical trials in CKD. In: *FDA Workshop Conference Report*, Bethesda MD, FDA, 2012
33. Shlipak MG, Katz R, Kestenbaum B, Fried LF, Newman AB, Siscovick DS, Stevens L, Sarnak MJ: Rate of kidney function decline in older adults: a comparison using creatinine and cystatin C. *Am J Nephrol* 30: 171–178, 2009
34. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 367: 20–29, 2012
35. Erlandsen EJ, Randers E, Kristensen JH: Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. *Scand J Clin Lab Invest* 59: 1–8, 1999
36. de Ruijter W, Westendorp RG, Macfarlane PW, Jukema JW, Assendelft WJ, Gussekloo J: The routine electrocardiogram for cardiovascular risk stratification in old age: the Leiden 85-plus study. *J Am Geriatr Soc* 55: 872–877, 2007
37. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography: Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 18: 1440–1463, 2005
38. Gore MO, Seliger SL, Defilippi CR, Nambi V, Christenson RH, Hashim IA, Hoogeveen RC, Ayers CR, Sun W, McGuire DK, Ballantyne CM, de Lemos JA: Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. *J Am Coll Cardiol* 63: 1441–1448, 2014
39. Shlipak MG, Katz R, Kestenbaum B, Fried LF, Siscovick D, Sarnak MJ: Clinical and subclinical cardiovascular disease and kidney function decline in the elderly. *Atherosclerosis* 204: 298–303, 2009
40. Park M, Shlipak MG, Katz R, Agarwal S, Ix JH, Hsu CY, Peralta CA: Subclinical cardiac abnormalities and kidney function decline: the multi-ethnic study of atherosclerosis. *Clin J Am Soc Nephrol* 7: 1137–1144, 2012
41. Patel UD, Garg AX, Krumholz HM, Shlipak MG, Coca SG, Sint K, Thiessen-Philbrook H, Koyner JL, Swaminathan M, Passik CS, Parikh CR; Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) Consortium: Preoperative serum brain natriuretic peptide and risk of acute kidney injury after cardiac surgery. *Circulation* 125: 1347–1355, 2012
42. Yasuda K, Kimura T, Sasaki K, Obi Y, Iio K, Yamato M, Rakugi H, Isaka Y, Hayashi T: Plasma B-type natriuretic peptide level predicts kidney prognosis in patients with predialysis chronic kidney disease. *Nephrol Dial Transplant* 27: 3885–3891, 2012
43. Spanaus KS, Kronenberg F, Ritz E, Schlapbach R, Fliser D, Hersberger M, Kollerits B, König P, von Eckardstein A; Mild-to-Moderate Kidney Disease Study Group: B-type natriuretic peptide concentrations predict the progression of nondiabetic chronic kidney disease: the Mild-to-Moderate Kidney Disease Study. *Clin Chem* 53: 1264–1272, 2007
44. Ho JE, Hwang SJ, Wollert KC, Larson MG, Cheng S, Kempf T, Vasan RS, Januzzi JL, Wang TJ, Fox CS: Biomarkers of cardiovascular stress and incident chronic kidney disease. *Clin Chem* 59: 1613–1620, 2013
45. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R: Cardiorenal syndrome. *J Am Coll Cardiol* 52: 1527–1539, 2008
46. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH: Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 53: 589–596, 2009
47. House AA: Cardiorenal syndrome: new developments in the understanding and pharmacologic management. *Clin J Am Soc Nephrol* 8: 1808–1815, 2013
48. Hatamizadeh P, Fonarow GC, Budoff MJ, Darabian S, Kovesdy CP, Kalantar-Zadeh K: Cardiorenal syndrome: pathophysiology and potential targets for clinical management. *Nat Rev Nephrol* 9: 99–111, 2013

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