Item S1. Detailed methods and tables *a-d*.

Detailed 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.[1] Participants were recruited from HCFA Medicare eligibility lists at 4 locations: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. To be eligible, participants were required to be community-dwelling, aged 65 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 1992–1993.

For our study, we excluded participants with prevalent HF (N=275), missing baseline creatinine (N=72) or cystatin C (N=623), those who were missing measures of galectin-3 or sST2 at baseline due to insufficient serum (N=1,510). We also excluded participants with missing follow-up measures of cystatin C or creatinine (N=645), leaving a final analytic sample of N=2,763. Characteristics of participants included vs. excluded in our analyses are described in **Table S1**.

The CHS study was approved by the institutional review boards of the University of Washington and each of the participating centers.

Exposures

Galectin-3 was measured in serum using an enzyme-linked immunosorbent assay (BG Medicine, Waltham, MA). The lower limit of quantification is 1.32 ng/mL, upper assay range is 94.8 ng/mL, and the FDA-approved cutoff is 17.8 ng/mL. Analyte stability has been demonstrated for at least 9 freeze-thaw cycles in serum and for at least 2 years when stored at -70CSoluble. Soluble ST2 (sST2) was measured from previously frozen serum (-70° Celsius) collected in 1992-1993 and 1995-1996 (main CHS cohort) or 1995-1996 and 1998-1999 (supplemental CHS African American Cohort) using the FDA approved Presage ST2 assay (Critical Diagnostics). The FDA approved prognostic cut point for this assay is 35 ng/mL. References ranges for sST2 have been reported as 8.6-49.3 ng/mL in males and 7.2-33.5 ng/mL in females[2] or 4-31 ng/mL in males and 2-21 ng/mL in females.[3] Analyte stability has been demonstrated for at least 1.5 years from previously frozen samples.[4]

Outcomes

Our primary outcomes were: (1) rapid kidney function decline, defined as an eGFR decline $\geq$30% (a definition used by the FDA as a clinically important decline in kidney function[5]) over 3 to 4 years (2) incident eGFR<60 ml/min/1.73m^2 over 7 years and (3) continuous percent decline in eGFR Rapid kidney function decline was determined by measures of kidney function at baseline and year 3 for the initial cohort and year 3 and year 7 for the additional African-American cohort. (for a range of 3-4 years of follow-up). Incident eGFR<60 ml/min/1.73m^{2}was determined by all available measures of kidney function – 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). To meet criteria for incident eGFR<60 ml/min/1.73m^2, participants had to have met the following criteria: eGFR>60 ml/min/1.73 m2 at baseline

(N=548 excluded), at least 1 ml/min/1.73 m^2 decline in eGFR per year in follow-up and eGFR <60 ml/min/1.73 m^2 at a follow-up visit. We chose these criteria to capture participants with clinically significant eGFR decline. Finally, continuous percent decline in eGFR was calculated as the percent change from baseline eGFR.

Estimated glomerular filtration rate (eGFR) was determined from the 2012 combined cystatin C-creatinine equation.[6] All renal function assays were performed at the University of Vermont in May and June 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%.[7] Serum creatinine, measured using a colorimetric method (Ektachem700, Eastman Kodak, Rochester, NY) was calibrated to isotope dilution mass spectrometry, and the intra-assay coefficient of variation was 1.9%.

Covariates

Clinical characteristics were obtained from the baseline CHS study visit and included: demographic characteristics (age, sex and race) and comorbid diseases (diabetes, cardiovascular disease). Cardiovascular disease (CVD) was defined as history of coronary heart disease (CHD) or stroke. 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 blood pressure, body mass index in kg/m^2) and laboratory values (LDL cholesterol, HDL cholesterol, triglycerides) were considered in the analysis. Medication use (anti-hypertensive [including ACE inhibitors/ARBs and diuretics] medications) was determined by participant pill bottles and were recorded by study personnel.

NT-proBNP was measured at baseline on the Elecsys 2010 system (Roche Diagnostics, Indianapolis, Indiana) [8]. The coefficient of variation for the NT-proBNP assay was 2% to 5% during the testing period, and the analytical measurement range for NT-proBNP was 5 to 35,000 pg/ml [8]. Troponin T concentrations were measured at baseline with highly sensitive reagents on an Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, Indiana), with an analytical measurement range of 3 to 10 000 pg/mL [9].

Statistical methods

Characteristics of the study population were compared across quartiles of galectin-3 and across categories of soluble ST2. We performed a series of nested logistic regression models to examine the association of galectin-3 and soluble ST2 in quartiles with odds of 30% decline in eGFR (e.g. rapid kidney function decline) and linear regression to examine the association with continuous percent change in eGFR. Estimated GFR decline was calculated as (last eGFR-first eGFR)/first eGFR x 100% and reported as a dichotomous outcome ($\geq$30%) or continuous (per 1% decline). We chose covariates to adjust for a priori that may be important confounders. We adjusted for demographic characteristics (age, sex, race), baseline eGFR, other important covariates (systolic blood pressure, BMI, diabetes mellitus, smoking, LDL cholesterol, HDL cholesterol, anti-hypertensive medications, and prevalent cardiovascular). In a final model, we adjusted for NT-proBNP and troponin T to determine whether the observed associations were independent of these two well-established cardiac biomarkers.

For the outcome of incident eGFR<60 ml/min/1.73m^2, we tested the association between biomarker categories and the incidence rate ratio for eGFR<60 ml/min/1.73m^2using Poisson regression models, adjusting for demographics, baseline eGFR, systolic blood pressure, BMI,

diabetes mellitus, smoking, LDL cholesterol, HDL cholesterol, anti-hypertensive medications, and prevalent CVD. In the final model, we also adjusted for baseline NT-proBNP and troponin T.

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

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Table *a*. Characteristics of CHS study population included vs. excluded in our analyses

	Included	Excluded	Whole cohort
Number of Participants	2763	3125	5888
Demographics			
Age (years) ± SD	72 ± 5	74 ± 6	73 ± 6
Female n(%)	1740 (63)	1653 (53)	3393 (58)
Black race n(%)	443 (16)	481 (15)	924 (16)
Prevalent Cardiovascular Disease			
History of CHD n(%)	452 (16)	702 (23)	1154 (20)
CVD Risk Factors			
Hypertension n(%)	1610 (58)	1847 (59)	3457 (59%)
SBP (mmHg) ± SD	136 ± 21	137 ± 22	137 ± 22
Hypertension medications	1271 (46)	1518 (49)	2789 (47)
Diabetes n(%)	436 (16)	517 (17)	953 (16)
Smoking			
Never n (%)	1311 (48)	1427 (46)	2738 (47)
Former n(%)	1159 (42)	1285 (41)	2444 (42)
Current n(%)	291 (11)	409 (13)	700 (12)
Body mass index (kg/m^2) ± SD	26.7 ± 4.6	26.6 ± 4.8	26.7 ± 4.7
LDL cholesterol (mg/dl) ± SD	131 ± 35	129 ± 37	130 ± 36
HDL cholesterol (mg/dl) ± SD	55 ± 16	53 ± 16	54 ± 16
Kidney Function			
eGFR* ($ml/min/1.73m^2$) ± SD	74 ± 17	70 ± 19	72 ± 18
eGFR_Cr	74 (17)	71 (18)	72 ± 18
eGFR-CysC	74 (18)	68 (19)	71 ± 19

*eGFR Creatinine Cystatin C (CKD Epi)

Table *b*. Characteristics of study population by baseline Galectin-3 concentration (N=2,763)

	Galectin-3 Quartiles				
	All	**<12.77**	**12.77 – 15.63**	**15.64 – 19.18**	**> 19.18**
Number of Participants	2763	746	723	692	602
Demographics					
Age (years) ± SD	72 ± 5	71 ± 5	71 ± 5	72 ± 5	73 ± 6
Female n(%)	1740 (63)	382 (51)	458 (63)	479 (69)	421 (70)
Black race n(%)	443 (16)	118 (16)	128 (18)	100 (15)	97 (16)
Prevalent Cardiovascular Disease					
History of CVD n(%)	515 (19)	125 (17)	122 (17)	125 (18)	143 (24)
CVD Risk Factors					
Hypertension n(%)	1610 (58)	392 (53)	419 (58)	407 (59)	392 (65)
SBP (mmHg) ± SD	136 ± 21	136 ± 21	136 ± 21	136 ± 21	136 ± 22
Hypertension medications	1271 (46)	277 (37)	313 (43)	336 (49)	345 (57)
Diabetes n(%)	436 (16)	130 (17)	101 (14)	104 (15)	101 (17)
Smoking					
Never n (%)	1311 (48)	331 (44)	334 (46)	355 (51)	291 (48)
Former n(%)	1159 (42)	337 (45)	300 (42)	272 (39)	250 (42)
Current n(%)	291 (11)	77 (10)	89 (12)	64 (9)	61 (10)
Body mass index (kg/m^2) ± SD	26.7 ± 4.6	26.2 ± 4.1	26.6 ± 4.5	26.9 ± 4.8	27.3 ± 5.0
LDL cholesterol (mg/dl) ± SD	131 ± 35	128 ± 33	131 ± 34	132 ± 34	130 ± 38
HDL cholesterol (mg/dl) ± SD	55 ± 16	56 ± 16	56 ± 16	55 ± 15	54 ± 16
Troponin (pg/ml), med[IQR]	4.51 [2.99, 8.73]	4.39 [2.99, 7.94]	4.04 [2.99, 8.04]	4.36 [2.99, 8.58]	5.80 [2.99, 11.02]
NT-proBNP (pg/mL), med[IQR]	102 [54, 197]	90 [47, 172]	89 [50, 168]	105 [57, 201]	137 [75, 271]
ST-2 ± SD	24.6 ± 9.7	24.8 ± 9.3	24.0 ± 8.8	23.8 ± 8.6	25.9 ± 11.9
Kidney Function					
eGFR* (ml/min/1.73m^2) ± SD	74 ± 17	81 ± 14	77 ± 15	73 ± 16	63 ± 19
eGFR_Cr	74 (17)	79 (14)	76 (16)	73 (17)	65 (20)
eGFR-CysC	74 (18)	82 (15)	77 (16)	72 (16)	62 (19)

*eGFR Creatinine Cystatin C (CKD Epi)

Table *c*. Characteristics of study population by baseline ST-2 concentration (N=2,763)

	ST-2Quartiles				
	All	**<18.84**	**18.84 – 23.62**	**23.63 – 29.72**	**>29.72**
Number of Participants	2763	761	724	684	594
Demographics					
Age (years) ± SD	72 ± 5	71 ± 5	72 ± 5	72 ± 5	73 ± 5
Female n(%)	1740 (63)	589 (77)	497 (69)	395 (58)	259 (44)
Black race n(%)	443 (16)	102 (13)	119 (16)	111 (16)	111 (19)
Prevalent Cardiovascular Disease					
History of CVD n(%)	515 (19)	122 (16)	142 (20)	117 (17)	134 (23)
CVD Risk Factors					
Hypertension n(%)	1610 (58)	389 (51)	415 (57)	421 (62)	385 (65)
SBP (mmHg) ± SD	136 ± 21	133 ± 21	135 ± 21	137 ± 21	138 ± 22
Hypertension medications	1271 (46)	294 (39)	323 (45)	341 (50)	313 (53)
Diabetes n(%)	436 (16)	67 (9)	93 (13)	120 (18)	156 (26)
Smoking					
Never n (%)	1311 (48)	365 (48)	368 (51)	306 (45)	272 (46)
Former n(%)	1159 (42)	294 (39)	294 (41)	304 (45)	267 (45)
Current n(%)	291 (11)	102 (13)	62 (9)	72 (11)	55 (9)
Body mass index (kg/m^2) ± SD	26.7 ± 4.6	26.3 ± 4.6	26.8 ± 4.4	26.9 ± 4.7	27.0 ± 4.7
LDL cholesterol (mg/dl) ± SD	131 ± 35	133 ± 34	131 ± 33	131 ± 35	126 ± 36
HDL cholesterol (mg/dl) ± SD	55 ± 16	57 ± 16	56 ± 15	55 ± 16	53 ± 16
Troponin (pg/ml), med[IQR]	4.51 [2.99, 8.73]	2.99 [2.99, 637]	3.94 [2.99, 7.44]	4.92 [2.99, 9.58]	7.14[2.99,12.95]
NT-proBNP (pg/mL), med[IQR]	102 [54, 197]	86 [44, 155]	102 [53, 185]	115 [64, 218]	116 [56, 246]
Galectin-3 ± SD	16.2 ± 6.2	16.0 ± 5.7	16.2 ± 5.5	16.1 ± 6.0	16.6 ± 7.8
Kidney Function					
eGFR* ($ml/min/1.73m^2$) ± SD	74 ± 17	77 ± 16	75 ± 16	73 ± 18	71 ± 18
eGFR_Cr	74 ± 17	76 ± 17	75 ± 16	72 ± 18	71 ± 18
eGFR-CysC	74 ± 17	77 ± 17	75 ± 17	73 ± 19	71 ± 19

*eGFR Creatinine Cystatin C (CKD Epi)

Table *d*. Association of baseline Galectin-3 and ST-2 with continuous percent decline of kidney function among participants in the Cardiovascular Health Study (N=2,763)

Biomarker	Unadjusted	Model 1	Model 2
Galectin-3	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
Continuous (per SD = 6)	-0.22 (-0.81, 0.38)	0.08 (-0.54, 0.70)	0.02 (-0.60, 0.64)
Quartiles			
<12.77	1.00 (ref)	1.00 (ref)	1.00 (ref)
12.77 - 15.63	-0.24 (-1.87, 1.40)	0.04 (-1.57, 1.64)	0.09 (-1.51, 1.69)
15.64 – 19.18	-0.46 (-2.11, 1.19)	-0.05 (-1.71, 1.60)	-0.09 (-1.74, 1.56)
>19.18	-0.45 (-2.17, 1.26)	0.34 (-1.48, 2.16)	0.19 (-1.63, 2.00)
ST-2			
Continuous (per SD = 10)	-0.02 (-0.62, 0.58)	-0.23 (-0.85, 0.38)	-0.44 (-1.06, 0.18)
Quartiles			
<18.84	1.00 (ref)	1.00 (ref)	1.00 (ref)
18.84 – 23.62	0.92 (-0.70, 2.54)	0.55 (-1.04, 2.13)	0.34 (-1.24, 1.92)
23.63 – 29.72	1.42 (-0.23, 3.06)	0.69 (-0.95, 2.33)	0.28 (-1.37, 1.92)
> 29.72	0.98 (-0.74, 2.69)	0.29 (-1.47, 2.05)	-0.25 (-2.03, 1.53)

Model 1: adjusted for age, gender, race, baseline estimated glomerular filtration rate (eGFR), body mass index (BMI), systolic blood pressure, hypertension medications, diabetes, smoking, LDL cholesterol, HDL cholesterol, prevalent cardiovascular disease (defined as coronary heart disease and stroke)
Model 2: Model 1 + NTproBNP and troponin T
* $p<0.05$