

## Clinical Investigations

# Cystatin C Concentration as a Predictor of Systolic and Diastolic Heart Failure

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## ABSTRACT

**Background:** Risk factors for heart failure (HF) may differ according to ejection fraction (EF). Higher cystatin C, a marker of kidney dysfunction, is associated with incident HF, but previous studies did not determine EF at diagnosis. We hypothesized that kidney dysfunction would predict diastolic HF (DHF) better than systolic HF (SHF) in the Cardiovascular Health Study.

**Methods and Results:** Cystatin C was measured in 4453 participants without HF at baseline. Incident HF was categorized as DHF (EF  $\geq$  50%) or SHF (EF < 50%). We compared the association of cystatin C with the risk for DHF and SHF, after adjustment for age, sex, race, medications, and HF risk factors. During 8 years of follow-up, 167 participants developed DHF and 206 participants developed SHF. After adjustment, sequentially higher quartiles of cystatin C were associated with risk for SHF (competing risks hazard ratios 1.0 [reference], 1.99 [95% confidence interval 1.14–3.48], 2.32 [1.32–4.07], 3.17 [1.82–5.50],  $P$  for trend < .001). The risk for DHF was apparent only at the highest cystatin C quartile (hazard ratios 1.0 [reference], 1.09 [0.62–1.89], 1.08 [0.61–1.93], and 1.83 [1.07–3.11]).

**Conclusions:** Cystatin C levels are linearly associated with the incidence of systolic HF, whereas only the highest concentrations of cystatin C predict diastolic HF. (*J Cardiac Fail* 2008;14:19–26)

**Key Words:** Cystatin C, diastolic heart failure, ejection fraction, elderly, estimated glomerular filtration rate, heart failure, systolic heart failure.

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Renal dysfunction has been identified as a risk factor for the development of heart failure (HF).<sup>1–4</sup> Cystatin C concentration is a novel measure of kidney function that is less affected by age, sex, or muscle mass, and is a more sensitive indicator of early renal dysfunction.<sup>5,6</sup> Cystatin C has been shown to be superior to serum creatinine or estimated glomerular filtration rate (eGFR) in predicting incident HF in older adults in two studies, but neither study used measurement of left ventricular ejection fraction (EF) to differentiate incident cases of diastolic HF (DHF) or systolic HF (SHF).<sup>4,7</sup> Previous studies found a stronger cross-sectional association of kidney dysfunction with prevalent left ventricular diastolic dysfunction than with systolic dysfunction in patients without clinical HF,<sup>8,9</sup> but no previous study compared the associations of kidney dysfunction with incident DHF and SHF. Because chronic kidney dysfunction is associated with diastolic dysfunction,<sup>8</sup> left ventricular hypertrophy,<sup>8,10–12</sup> hypertension, and vascular stiffness,<sup>13–15</sup> we hypothesized that kidney

dysfunction may be a stronger predictor of DHF compared with SHF. We tested this hypothesis in the Cardiovascular Health Study (CHS) using baseline cystatin C measurements to estimate kidney function and point-of-diagnosis assessment of left ventricular EF to characterize systolic function at the time of HF onset.

## Methods

### Participants and Study Design

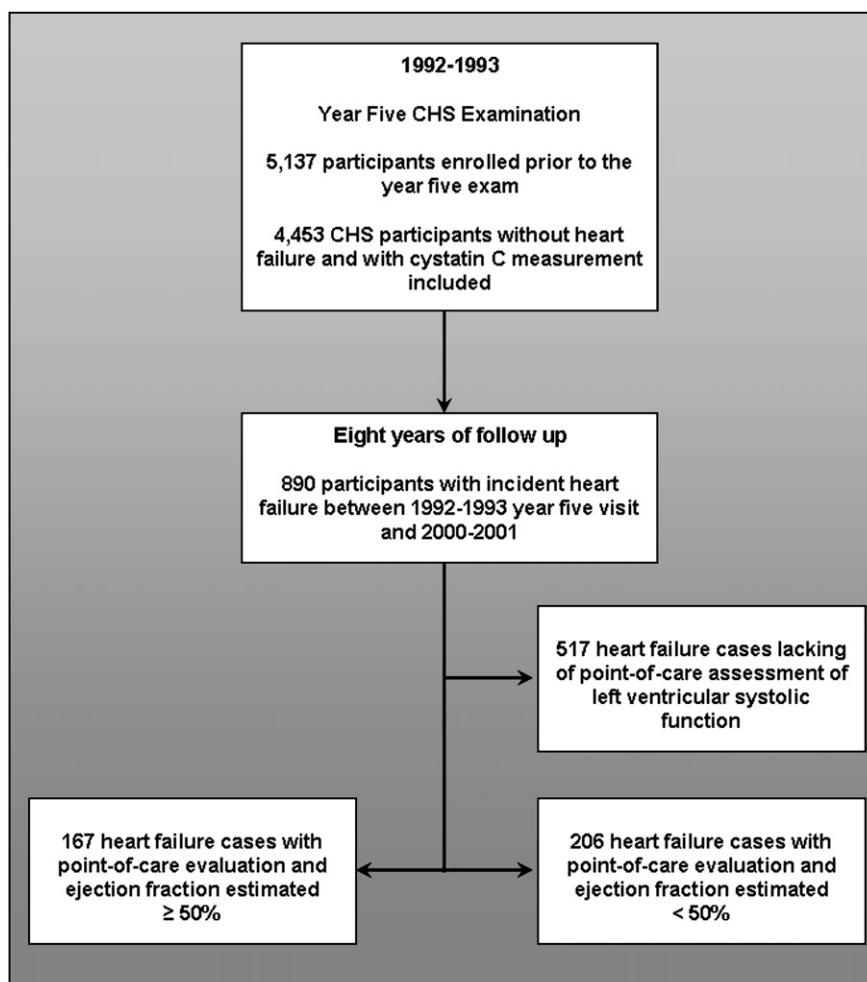
The CHS is a study of a 5888 adults aged 65 years or more who were recruited from four different communities in the United States (Forsyth County, North Carolina; Sacramento County, California; Allegheny County, Pennsylvania; and Washington County, Maryland). The purpose of the study was to evaluate risk factors for the development or progression of cardiovascular disease in the elderly. The study design, rationale, and examination details have been described in detail elsewhere.<sup>2,16</sup> The original CHS cohort of 5201 participants was recruited from 1989 to 1990, and a second cohort of African Americans was added from 1992 to 1993.<sup>16</sup>

This study is a longitudinal analysis of predictors of SHF and DHF subsequent to the 1992 to 1993 clinical visit of CHS, the baseline for this analysis, and the point at which serum cystatin C and creatinine were measured in the CHS (Fig. 1). Participants

were included if they had no diagnosis of HF before the 1992 to 1993 clinical visit. This report describes incident HF events with a recorded EF at the time of diagnosis from 1992 to 2000.

### Predictors

Cystatin C is a commercially available blood test for kidney function available in the United States and the European Union. Cystatin C assays were performed on serum that was drawn in the morning and stored at  $-70^{\circ}\text{C}$ . A BNII nephelometer (Dade Behring, Inc., Deerfield, Illinois) measured cystatin C with a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade-Behring, Inc.).<sup>17</sup> Polystyrene particles were coated with monoclonal antibodies to cystatin C that agglutinate in the presence of antigen (cystatin C) and increase the intensity of the scattered light. The amount of cystatin C in a sample is proportional to the increase in scattered light. The assay range is 14.6 to 549.0 nmol/L (0.195–7.330 mg/L); the reference range for young, healthy individuals ranges from 40 to 71 nmol/L (0.53–0.95 mg/L). The intra-assay coefficient of variation ranges from 2.0% to 2.8%, and the interassay coefficient of variation ranges from 2.3% to 3.1%.<sup>17</sup> Serum creatinine was measured using a colorimetric method by a Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, New York). Glomerular filtration rate (GFR) was estimated as  $\text{GFR} = 186.3 \times (\text{serum creatinine concentration})^{-1.154} \times (\text{age})^{-0.203} \times 1.212$  (if black)  $\times 0.742$



**Fig 1.** Selection of participants included from the CHS.

(if female).<sup>18</sup> eGFR was dichotomized at the cut point of 60 mL/min per 1.73 m<sup>2</sup> because of published guidelines regarding the definition of chronic kidney disease<sup>19</sup> and because of the poor discriminatory power of GFR estimates greater than 60 mL/min per 1.73 m<sup>2</sup> in predicting HF<sup>4</sup> and other cardiovascular events.<sup>20</sup>

### Covariates

Covariates measured at the 1992 to 1993 CHS visit are described in detail elsewhere.<sup>2,4,16</sup> Covariates obtained in interviews included demographic characteristics (age, sex, education, income, and self-described race) and use of blood pressure medications (including diuretics, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin II receptor blockers, and  $\beta$ -blockers). History of chronic obstructive pulmonary disease, atrial fibrillation, or coronary heart disease was adjudicated both by self-report of physician diagnosis and by review of medical records. Participants were asked to describe their general health status as excellent, very good, good, fair, or poor. Measured risk factors for cardiovascular disease were body mass index (kilograms per meters squared), systolic and diastolic blood pressure (measured using a Hawksley random-zero sphygmomanometer), smoking (never, former, or current), diabetes (defined by fasting glucose level  $\geq 6.99$  mmol/L [ $\geq 126$  mg/dL], or use of insulin or hypoglycemic agent), left ventricular hypertrophy determined by electrocardiogram, fasting glucose, fasting low-density lipoprotein (estimated with the Friedewald equation), and high-density lipoprotein cholesterol. Hypertension was defined by a systolic blood pressure  $\geq 140$  mm Hg, a diastolic blood pressure  $\geq 90$  mm Hg, a clinical history of hypertension, or the use of antihypertensive medications. Pulmonary function was assessed using the forced expiratory volume in 1 second.

### Incident Heart Failure Outcomes

The primary outcomes of this analysis were incident cases of HF with a time of diagnosis estimate of EF by echocardiogram ( $n = 310$ ), multiple gated cardiac blood pool imaging ( $n = 7$ ), cardiac catheterization ( $n = 47$ ), or other modality ( $n = 9$ ). HF cases did not require hospitalization and were identified at semiannual visits and adjudicated according to an established protocol.<sup>2,21,22</sup> Physician diagnosis or participant self-report of HF were followed by review of the participant's medical records. Incident HF was confirmed by the CHS Cardiovascular Events Committee on the basis of physician diagnosis and consideration of signs, symptoms, chest radiographic findings, and treatment for HF (current prescription for diuretic agent, digitalis, or a vasodilator). For participants with an echocardiogram, multiple gated cardiac blood pool imaging, or cardiac catheterization performed at the time of their incident HF diagnosis from the 1992 to 1993 clinical visit up to June of 2000, the estimated EF was obtained from the original cardiologist's reading. These reports, but not the imaging studies they were based on, were subsequently reviewed by four independent CHS investigators who were blinded to participants' baseline creatinine and cystatin C levels.

### Echocardiography from the 1994 to 1995 CHS Examination

Left ventricular EF was qualitatively assessed in all participants from a two-dimensional echocardiogram and scored as normal, borderline, or subnormal at the 1994 to 1995 examination, 2 years after the baseline visit for this analysis.<sup>2</sup>

### Statistical Methods

The distributions of baseline demographic characteristics, cardiovascular disease risk factors, and medication use of participants with no incident HF, and each type of HF (SHF, DHF, or unknown EF) were compared using analysis of variance or chi-square testing. In addition, the baseline characteristics of participants with incident DHF were compared with those of participants diagnosed with SHF using chi-square tests or *t* tests. Cystatin C concentration was divided into quartiles and modeled by quartile and as a continuous predictor. Unadjusted incidence rates were calculated per 1000 person-years and plotted by type of HF, quartile of cystatin C, and eGFR  $< 60$  or  $\geq 60$  mL/min per 1.73 m<sup>2</sup>.

All participants were considered to be at risk for an initial diagnosis of HF with either an impaired EF or normal EF. Because a participant could not initially have both outcomes, we assumed that incident HF with an EF  $\geq 50\%$  (DHF), incident HF with an EF  $< 50\%$  (SHF), and incident HF with an unknown EF were competing risks: The occurrence of one type of HF was presumed to be noninformative for the risk of occurrence of the other. We used a Cox proportional hazards regression in a competing risks context.<sup>23,24</sup> This approach stratifies on event type and allows simultaneously for estimation of the separate associations of each risk factor with the relative hazard of each outcome under a proportional hazards assumption. All models included cystatin C (or eGFR) and were adjusted for the major predictors of HF identified in an earlier analysis of incident HF in CHS:<sup>2</sup> age, sex, race, self-reported health status, systolic blood pressure, diastolic blood pressure, C-reactive protein, diabetes, left ventricular hypertrophy, prevalent coronary heart disease, forced expiratory volume in 1 second, ACEI or angiotensin II receptor blocker use, and diuretic use. Adding a variable for history of atrial fibrillation did not appreciably change the results, so atrial fibrillation was not included in the final model. Participants who developed HF but lacked a measurement of EF at the time of diagnosis were censored. The proportional hazards assumption was verified using tests and graphs based on the Schoenfeld residuals. To determine statistically whether kidney function has a significantly different association with DHF and SHF, we used interaction terms (cystatin C \* HF category and eGFR \* HF category) in Cox proportional hazards models that pooled both DHF and SHF cases. HF type was used as a covariate in the analysis, and we tested for its interaction with cystatin C.

To investigate the possibility that the presence of an impaired EF at baseline may have influenced the association of cystatin C with each type of HF, we repeated our analysis after exclusion of all participants with an echocardiogram from the 1994 to 1995 CHS examination showing borderline or subnormal left ventricular function ( $N = 52$ ).<sup>2,25</sup> This sensitivity analysis used the 1994 to 1995 visit as the baseline, so all incident HF cases between 1992 and 1995 were also excluded ( $N = 52$ ).

A *P* value of less than .05 was considered statistically significant. Statistical analyses were performed using S-Plus (release 6.1, Insightful Inc, Seattle, Washington) and SPSS statistical software (release 14.0.2, SPSS Inc., Chicago, Illinois).

## Results

### Baseline Characteristics of the Participants

A total of 4453 CHS participants without a history of HF were included in this analysis. During 8 years of follow-up,

**Table 1.** Baseline Characteristics of the 4453 Participants Included in the Analysis Categorized by Heart Failure Category: The Cardiovascular Health Study

	No HF (n = 3563)	HF EF $\geq$ 50% (n = 167)	HF EF < 50% (n = 206)	HF Unknown EF (n = 517)	Overall P Value*
Age (y)	74 (5)	76 (6)	76 (5)	76 (6)	<.001
Male	39%	41%	61%	46%	<.001
African-American	17%	17%	18%	16%	.888
Height (cm)	164 (10)	164 (10)	167 (9)	165 (10)	<.001
Weight (lbs)	159 (32)	164 (33)	168 (34)	164 (35)	<.001
BMI (kg/m <sup>2</sup> )	26.7 (4.6)	27.8 (4.8)	27.2 (4.9)	27.4 (5.3)	<.001
Systolic BP (mm Hg)	135 (21)	140 (22)	144 (23)	141 (23)	<.001
Diastolic BP (mm Hg)	72 (11)	69 (12)	72 (13)	71 (13)	.008
Hypertension <sup>‡</sup>	38%	52%	53%	51%	<.001
Smoking status					.455
Never	46%	50%	45%	43%	
Former	44%	44%	43%	46%	
Current	10%	7%	12%	12%	
Diabetes <sup>§</sup>	13%	25%	24%	22%	<.001
Glucose (mg/dL)	106 (32)	121 (53)	116 (43)	115 (45)	<.001
LDL (mg/dL) <sup>  </sup>	128 (34)	127 (29)	127 (35)	126 (34)	.485
HDL (mg/dL) <sup>  </sup>	54 (15)	50 (12)	49 (14)	52 (14)	<.001
Hemoglobin (g/L)	13.7 (1.4)	13.6 (1.4)	13.8 (1.4)	13.7 (1.4)	.626
C-reactive protein (mg/L)	2.41 (1.14–5.46)	3.48 (1.65–6.91)	3.38 (1.52–6.40)	3.41 (1.53–7.91)	<.001
ACEI or angiotensin II receptor blocker	9%	13%	15%	13%	.001
Diuretic	22%	35%	31%	34%	<.001
FEV <sub>1</sub>	2.0 (0.66)	1.9 (0.61)	2.0 (0.84)	2.0 (0.67)	<.001
Chronic obstructive pulmonary disease	11%	14%	14%	17%	.001
Atrial fibrillation	2%	7%	4%	6%	<.001
Left ventricular hypertrophy	4%	9%	11%	9%	<.001
History of coronary heart disease	16%	30%	35%	28%	<.001
Cystatin C concentration	1.08 (0.31)	1.19 (0.32)	1.23 (0.35)	1.20 (0.41)	<.001
Creatinine concentration	0.99 (0.35)	1.06 (0.34)	1.14 (0.41)	1.08 (0.56)	<.001
eGFR	72.4 (17.8)	69.3 (20.0)	68.1 (21.7)	69.9 (20.4)	<.001
EF at HF diagnosis (%)	NA	60 (8)	34 (9)	NA	<.001

BMI, Body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FEV<sub>1</sub>, forced expiratory volume in 1 second; EF, ejection fraction; HF, heart failure; eGFR, estimated glomerular filtration rate (in mL/min per 1.73 m<sup>2</sup>); ACEI, angiotensin-converting enzyme inhibitor.

Data are means (standard deviations) or proportions, except C-reactive protein, expressed as median (interquartile range).

\*P values are from analysis of variance tests (for continuous variables) or chi-square tests (for categorical variables).

<sup>‡</sup>Hypertension was defined by systolic blood pressure  $\geq$  140 mm Hg, diastolic blood pressure  $\geq$  90 mm Hg, or taking antihypertensive medications.

<sup>§</sup>Diabetes mellitus was defined by self-report or the current use of insulin or an oral hypoglycemic medication.

<sup>||</sup>To convert milligrams/deciliter of high-density lipoprotein or low-density lipoprotein cholesterol to millimolars, divide by 39.

there were 890 participants with new-onset HF, of whom 167 (19%) developed DHF, 206 (23%) developed SHF, and 517 (58%) had HF without an EF measurement at the point of diagnosis (Fig. 1; Table 1). The mean EF was 60% for participants diagnosed with DHF and 34% for participants diagnosed with SHF. The distribution of baseline characteristics of CHS participants by categories of cystatin C are published elsewhere.<sup>4</sup> Compared with participants diagnosed with DHF, participants diagnosed with SHF were more likely to be male ( $\chi^2$ ,  $P \leq .001$ ) and have a higher mean diastolic blood pressure ( $t$  test,  $P \leq .01$ ) but did not differ significantly regarding other baseline characteristics (Table 1). Cystatin C concentrations were higher and eGFRs were lower in the participants diagnosed with HF. The percentage of participants hospitalized for their initial presentation with DHF was 86%, whereas 91% of participants diagnosed with SHF and 87% of participants with HF with an unmeasured EF were hospitalized at the time of first diagnosis ( $\chi^2$ ,  $P = .17$ ).

The 517 participants who developed HF but lacked a point-of-diagnosis estimated EF did not differ from the included participants with an estimated EF regarding age,

sex, race/ethnic category, socioeconomic status, general health, medication use, cardiovascular risk factors, or medical history. Participants with unclassified HF had cystatin C concentrations that were intermediate between participants diagnosed with DHF and SHF.

### Incidence Rates of Heart Failure

Among participants with HF who had an estimation of EF at the time of hospitalization for HF, SHF was more common than DHF (seven vs. five HF events per 1000 person-years, Fig. 2). When participants were categorized by baseline cystatin C, the incidence of both types of HF increased from the lowest to highest quartiles of cystatin C (Table 2; Fig. 2). The association of cystatin C with risk for SHF appeared linear across quartiles of cystatin C and slightly stronger at the highest categories of cystatin C, whereas the lower three quartiles of cystatin C had similar risks for DHF. Participants with an eGFR  $\geq$  60 mL/min per 1.73 m<sup>2</sup> had an equal likelihood of developing DHF or SHF, whereas participants with an eGFR < 60 mL/min per 1.73 m<sup>2</sup> had a greater likelihood of developing SHF (Table 2; Fig. 2).

**Table 2.** Incidence Rates (% Per Year) for Heart Failure with an Ejection Fraction  $\geq 50\%$  or  $< 50\%$ : The Cardiovascular Health Study 1992 to 2000

		EF $\geq$ 50%			EF $<$ 50%		
	N	Person-years at Risk	No. of Events	Rate (% per Year)	Person-years at Risk	No. of Events	Rate (% per Year)
Cystatin C quartiles (mg/L)							
$\leq 0.92$	1064	9003	31	0.3	9003	25	0.3
0.92–1.05	1097	8967	41	0.5	8967	51	0.6
1.06–1.22	920	7224	32	0.4	7224	54	0.7
$\geq 1.23$	855	5415	63	1.2	5415	76	1.4
eGFR							
$\geq 60$	3070	24701	115	0.5	24701	134	0.5
$< 60$	806	5478	48	0.9	5478	67	1.2

EF, ejection fraction; eGFR, **estimated** glomerular filtration rate (in mL/min per 1.73 m<sup>2</sup>).

### Competing Risks Analysis

We compared the association of quartiles of cystatin C with risk for DHF and SHF (Table 3; Fig. 3). The risk for SHF increased with each sequentially higher level of cystatin C. Compared with the lowest quartile, the highest quartile of cystatin C was associated with an approximately fourfold higher risk of incident SHF after adjustment for age, sex, and race. After adjustment for demographic factors, HF risk factors, medication use, and forced expiratory volume in 1 second, each ascending quartile of cystatin C remained significantly associated with SHF ( $P$  for trend  $< .001$ ). In contrast, only the highest quartile of cystatin C ( $> 1.23$  mg/L) was associated with DHF in either the model adjusted for age, sex, and race/ethnic category or the fully adjusted model.

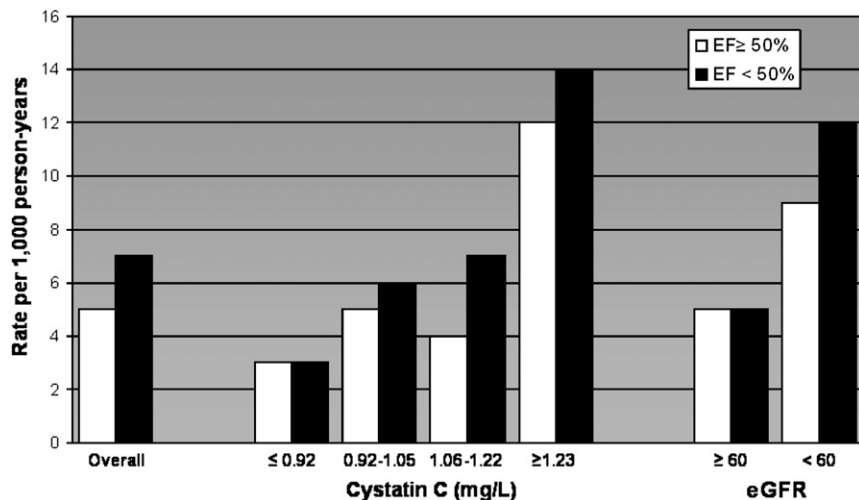
When an interaction term for HF type (SHF or DHF) was inserted into a fully adjusted standard Cox proportional hazards model with HF with either type of EF as the outcome, the association of continuous cystatin C with SHF was significantly greater than the association of cystatin C with DHF ( $P$  value for interaction  $< .001$ ). The association of eGFR

and SHF compared with DHF was weaker ( $P$  value for interaction = .06 for the fully adjusted model).

Ascending quartiles of cystatin C were associated with increasing adjusted risk for the development of “unclassified” HF, defined by the absence of a point-of-care EF measurement. The magnitude of the fully adjusted hazard ratios for the association between cystatin C and risk of unclassified HF were intermediate between those described for DHF and SHF (hazard ratios [95% confidence intervals] for each higher quartile of cystatin C 1.00 [reference], 1.12 [0.80–1.57], 1.84 [1.34–2.51], 2.18 [1.58–3.00]).

### Sensitivity Analysis

Exclusion of the 52 participants with evidence of impaired left ventricular function at the 1994 to 1995 clinical examination and the 52 participants diagnosed with HF before the 1994 to 1995 examination did not appreciably change the unadjusted or adjusted risks predicted by cystatin C during 6 years of follow-up. In these analyses restricted to participants with a normal baseline EF, the fully adjusted hazard ratio for HF at the highest quartile

**Fig 2.** Incidence rates for HF categorized by EF and kidney function from 1992 to 2000 in the CHS. EF, ejection fraction; eGFR, estimated glomerular filtration rate (mL/min per 1.73 m<sup>2</sup>). EF, ejection fraction.



**Table 3.** Risk of Systolic (Ejection Fraction < 50%) or Diastolic (Ejection Fraction ≥ 50%) Heart Failure (Hazard Ratios [95% Confidence Intervals]) by Levels of Cystatin C and Estimated Glomerular Filtration Rate: The Cardiovascular Health Study 1992 to 2000

	EF ≥ 50%		EF < 50%	
	Adjusted for Age, Gender, and Race	Fully Adjusted*	Adjusted for Age, Gender, and Race	Fully Adjusted*
Cystatin C quartiles (mg/L)				
≤0.92	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.92–1.05	1.06 (0.61–1.84)	1.09 (0.62–1.89)	1.98 (1.14–3.46)	1.99 (1.14–3.48)
1.06–1.22	1.12 (0.63–1.99)	1.08 (0.61–1.93)	2.44 (1.39–4.28)	2.32 (1.32–4.07)
≥1.23	2.25 (1.33–3.80)	1.83 (1.07–3.11)	3.95 (2.29–6.83)	3.17 (1.82–5.50)
eGFR				
≥60	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
<60	1.44 (0.95–2.19)	1.34 (0.88–2.03)	1.81 (1.28–2.57)	1.68 (1.18–2.40)

EF, Ejection fraction; eGFR, estimated glomerular filtration rate (in mL/min per 1.73 m<sup>2</sup>).

\*Adjusted for age, gender, race, self-reported health, systolic blood pressure, diastolic blood pressure, C-reactive protein, diabetes, electrocardiographic evidence of left ventricular hypertrophy, prevalent coronary heart disease, forced expiratory volume in 1 second, ACEI or angiotensin II receptor blocker use, and diuretic use.

of cystatin C was 4.5 (95% CI 2.25–9.00) for SHF and 2.1 (95% CI, 1.12–3.85) for DHF.

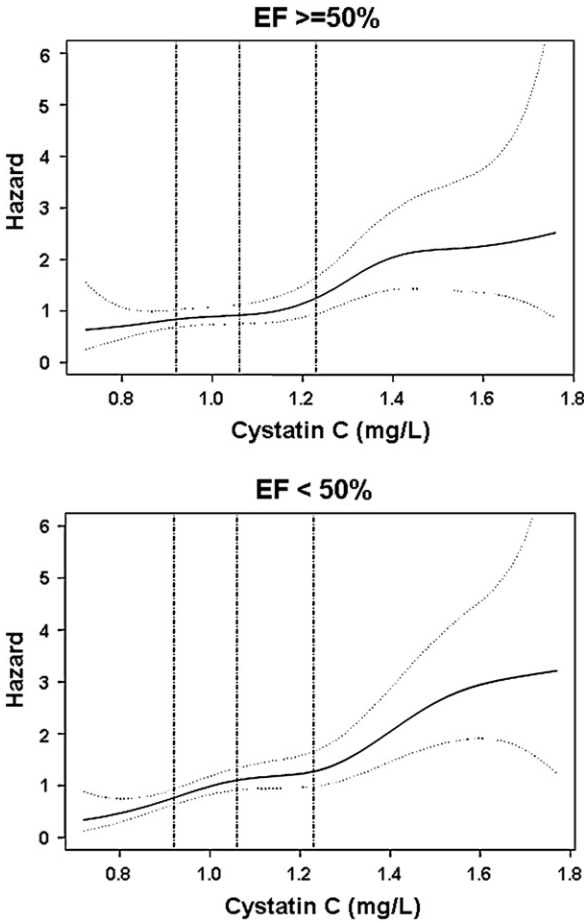
**Discussion**

We studied a large cohort of community-dwelling older adults and found differing associations of baseline elevated cystatin C concentrations with incident DHF and SHF during 8 years of follow-up. Cystatin C concentration had a linear association with risk for SHF, whereas only the highest quartile of cystatin C (> 1.2 mg/L) was associated with the risk for incident DHF. These patterns of association of cystatin C with each type of HF persisted after adjustment for age, blood pressure, left ventricular hypertrophy, history of coronary heart disease or diabetes, medication use, and other potential confounders. Even when the analysis was restricted to participants with a documented normal EF at baseline, cystatin C concentrations still predisposed patients to SHF. As would be expected, cystatin C had intermediate associations with “unclassified” HF, because such patients were a mix of those with DHF and those with SHF.

Several past studies have found that markers of kidney dysfunction predict incident HF,<sup>1–4</sup> but none have examined point-of-diagnosis measures of left ventricular systolic function to distinguish kidney dysfunction as a predictor of DHF and SHF. In a previous study by our group, Sarnak et al.<sup>4</sup> determined that an elevated cystatin C was an independent predictor of HF after adjusting for traditional and nontraditional risk factors for HF, but that study did not differentiate the EF at HF diagnosis. Ix et al.<sup>9</sup> found that higher cystatin C had a stronger association with diastolic compared with systolic dysfunction in the Heart and Soul Study, and Stewart et al.<sup>8</sup> found that a reduced eGFR was associated with echocardiographic evidence of diastolic dysfunction, but not impaired left ventricular function; however, both studies were cross-sectional and did not include participants with clinical HF.

Early in the pathogenesis of HF, increased left atrial filling pressures trigger the release of atrial natriuretic peptide

and inhibition of vasopressin, which leads to decreased renal sympathetic tone and diuresis.<sup>26</sup> Even mild kidney dysfunction blunts these compensatory mechanisms<sup>27</sup> and may lead to sodium and water retention and extracellular



**Fig 3.** Competing risks hazards (95% confidence intervals) for incident HF with an EF ≥ 50% or < 50% by serum cystatin C concentration in the CHS 1992–2000. Data are splines adjusted for age, sex, and race with 2.5% of the data removed from both ends. Vertical dotted lines delineate cystatin C quartiles (≤0.92, 0.92–1.05, 1.06–1.22, ≥1.23 mg/L). EF, ejection fraction.

fluid volume expansion, which can accelerate the progression of clinical HF.<sup>26,28</sup> Kidney dysfunction is also associated with diastolic dysfunction,<sup>8</sup> left ventricular hypertrophy<sup>8,10–12</sup> and vascular stiffness.<sup>13–15</sup> With these mechanisms in mind, we initially hypothesized that kidney dysfunction would increase the risk for DHF to a greater degree than for SHF. Our findings, in contrast, suggest that even relatively small decrements in kidney function contribute to the risk of SHF, whereas the risk of DHF increases only with a substantial reduction in kidney function.

The mechanisms explaining the development of SHF in persons with mild kidney dysfunction warrant additional study. One possibility is that sodium retention and increased extracellular fluid volume in the setting of kidney dysfunction more rapidly lead to cardiac dilatation and relative cardiac ischemia. Thus, after decompensation, the patient with HF who has kidney dysfunction may present with systolic dysfunction. Cystatin C's strong association with SHF could potentially be confounded by its association with diffuse vascular disease and risk for ischemic heart disease.<sup>29,30</sup> Alternatively, having a reduced EF before a clinical diagnosis of HF could lead to impaired renal blood flow and activation of the renin-angiotensin-aldosterone system, which could result in elevated cystatin C. This reverse causality explanation seems less likely in our study because our sensitivity analysis demonstrated that the association of cystatin C with SHF remained after exclusion of participants with an asymptomatic reduced EF measured at baseline.

This study is another reminder of the importance of kidney dysfunction as both an etiologic and complicating factor in HF incidence and progression. A recent meta-analysis<sup>31</sup> summarized the association of kidney dysfunction with increased mortality in patients with HF. Given the poor prognosis of patients with combined kidney disease and HF and the challenges of managing the combined conditions,<sup>32</sup> HF prevention strategies are critical for patients with kidney dysfunction. The Studies of Left Ventricular Dysfunction prevention trial demonstrated that ACEIs reduced mortality and delayed the onset of symptomatic HF in asymptomatic patients with a reduced EF.<sup>33</sup> ACEIs and angiotensin II receptor blockers have also been shown to prevent the progression of chronic kidney disease.<sup>34–37</sup> More recently, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial investigators reported that thiazide diuretics prevent clinical HF in patients diagnosed with hypertension.<sup>38</sup> In patients with early signs of kidney disease (microalbuminuria or increased cystatin C concentration), intervention with ACEIs, angiotensin II receptor blockers, and/or diuretics could potentially delay or prevent the onset of HF. Our results suggest that this hypothesis merits investigation.

### Limitations

Our study has limitations. Our study relied on cystatin C and eGFR as measures of kidney function. We did not have

a direct measure of GFR, such as iothalamate clearance, or measures of urine albumin excretion (another measure of early kidney disease). We also lacked measurement of either plasma brain type natriuretic peptide or N-terminal fragment pro-brain type natriuretic peptide, which may have led to misclassification of HF cases at the point of diagnosis. Neither cystatin C nor eGFR directly measure which aspect of the kidney's complex physiology is the causal link between kidney dysfunction and HF—specifically, neither variable directly measures the kidney's capacity to regulate salt and water balance. The conclusion that the association between kidney dysfunction and HF is causal is further limited by the fact that CHS measured cystatin C and creatinine at baseline, but not at the time of HF diagnosis. Left ventricular EF was measured at numerous point-of-care sites using a variety of imaging modalities, and therefore the EF measurements used in this analysis likely lack the accuracy of EF measured in a standardized core laboratory. A large proportion of HF cases were missing an estimate of EF, and baseline characteristics of these participants varied slightly from the other participants with HF. We found that the association between cystatin C and unclassified HF was intermediate between the associations shown for DHF and SHF, which suggests that this group was composed of both types. We chose to group participants with HF into two EF categories, whereas other investigators used three EF categories to avoid misclassification.<sup>39</sup> Misclassification could bias the results toward uniform effects; this is less of a concern in our study because there was a significant difference in the main outcome between the two groups. However, DHF was defined on the basis of EF, not on echocardiographic assessment of compliance or filling, which may have led to the inclusion of more patients incorrectly diagnosed with HF in the DHF group compared with the SHF group, and biasing the results to show no association of cystatin C with DHF. The association of elevated cystatin C with HF may be a marker for the severity of other risk factors for HF.

### Conclusions

We found that kidney dysfunction independently predicted the incidence of both SHF and DHF in the CHS. Cystatin C had a linear association with risk for SHF throughout its distribution, whereas only the highest levels of cystatin C were associated with the risk for DHF. Identifying interventions to prevent the development of HF in persons with kidney dysfunction should be a high priority for future investigation.

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