



Published in final edited form as:

*Am J Kidney Dis.* 2007 March ; 49(3): 365–372. doi:10.1053/j.ajkd.2006.12.016.

## Association of Cystatin C With Poor Exercise Capacity and Heart Rate Recovery: Data From the Heart and Soul Study

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### Abstract

**Background**—Cystatin C, an alternative serum measure of kidney function, is a stronger predictor of cardiovascular events than creatinine or estimated glomerular filtration rate (eGFR). We hypothesized that serum cystatin C concentration would have a stronger more linear association with cardiovascular functional status than creatinine-based measures in outpatients with established coronary heart disease (CHD).

**Methods**—We measured serum cystatin C, serum creatinine, and eGFR in 906 outpatients with established CHD. We examined the association of these 3 measures of kidney function with treadmill exercise capacity (metabolic equivalent tasks achieved) and heart rate recovery (HRR) between peak and 1 minute after exercise by using linear and logistic regression.

**Results**—Higher cystatin C concentrations were associated linearly with worse treadmill exercise capacity and HRR. The proportion of participants with poor exercise capacity (metabolic equivalent tasks achieved < 5) was 45% (99 of 222 participants) among those with cystatin C levels in the highest quartile (>1.30 mg/L) compared with 12% (29 of 241 participants) among those with cystatin C levels in the lowest quartile (<0.92 mg/L; adjusted odds ratio, 3.2; 95% confidence interval, 1.6 to 6.5;  $P = 0.001$ ). The proportion of participants with poor HRR (<16 beats/min) was 42% (92 of 214 participants) among those with cystatin C levels in the highest quartile compared with 16% (37 of 238 participants) among those with cystatin C levels in the lowest quartile (adjusted odds ratio, 2.2; 95% confidence interval, 1.2 to 4.0;  $P = 0.01$ ). The lowest quartile of eGFR (<61.8 mL/min [ $<1.03$  mL/s]) was associated with decreased exercise capacity and prolonged HRR, but no difference was observed across the upper 3 quartiles of eGFR.

**Conclusion**—In patients with established CHD, cystatin C concentrations are associated linearly with worse exercise capacity and HRR. Cystatin C detects an association of impaired kidney function with decreased HRR and exercise capacity that is not fully captured using creatinine-based measurements.

## Keywords

Coronary artery disease; cystatin C; creatinine; renal function; exercise capacity; heart rate recovery

Cystatin C is a low-molecular-weight protein produced by nearly all nucleated cells, freely filtered by the glomerular membrane, and metabolized by the proximal tubule.<sup>1</sup> Increased serum cystatin C levels predict cardiovascular outcomes in outpatients with and without known coronary heart disease (CHD) and in patients presenting with acute coronary syndromes.<sup>2-6</sup> Cystatin C has a more linear association with cardiovascular mortality and adverse events than creatinine-based measurements.<sup>5</sup> A recent study defined elderly persons with increased cystatin C levels and estimated glomerular filtration rate (eGFR) greater than 60 mL/min (>1.00 mL/s) as having preclinical kidney disease and found this group to have increased risks of cardiovascular disease and incident chronic kidney disease (CKD).<sup>7</sup> No prior study evaluated the association of cystatin C level with cardiovascular functional status in patients with established CHD or compared it with creatinine-based measurements.

Treadmill exercise capacity and heart rate recovery (HRR) after exercise are objective measures of cardiac functional status that are well-validated independent predictors of cardiovascular and all-cause mortality.<sup>8-13</sup> Recovery of the heart rate immediately after exercise is thought to be a function of vagal reactivation. A delayed decrease in heart rate during the first minute after exercise likely reflects decreased vagal activity and is a powerful predictor of overall mortality.<sup>14</sup>

We hypothesized that cystatin C level would be associated strongly and linearly with exercise capacity and HRR and have a stronger association than creatinine-based measurements. To examine the association of cystatin C level with cardiovascular functional status, we measured serum cystatin C and creatinine, treadmill exercise capacity, and HRR after exercise in 906 outpatients with established CHD who were enrolled in the Heart and Soul Study.

## METHODS

### Participants

The Heart and Soul Study is a prospective cohort study designed to evaluate the influence of psychosocial factors on health outcomes in outpatients with CHD. Details regarding recruitment procedures and inclusion and exclusion criteria were published previously.<sup>15</sup> In brief, we used administrative databases to identify outpatients with stable CHD at 2 Department of Veterans Affairs Medical Centers, 1 university medical center, and 9 public health clinics in the San Francisco Bay Area. Patients were eligible to participate if they met 1 of the following inclusion criteria: history of myocardial infarction, angiographic evidence of greater than 50% stenosis in 1 or more coronary vessel, evidence of exercise-induced ischemia by treadmill testing, or history of coronary revascularization. We excluded patients who were unable to walk 1 block, had a myocardial infarction in the preceding 6 months, or were planning to move out of the local area within 3 years.

Between September 2000 and December 2002, a total of 1,024 participants completed a baseline study appointment that included a medical history interview, physical examination, and comprehensive health status questionnaire. Of these, 84 participants were not able to perform the exercise treadmill test and 34 participants were not able to provide a serum sample. The remaining 906 participants constituted the analytic sample for the present cross-sectional analysis. This protocol was approved by the appropriate institutional review boards, and all participants provided written informed consent.

## Predictor Variables

Cystatin C was measured from fasting serum samples collected between September 2000 and December 2002 and stored at  $-70^{\circ}\text{C}$  using a BNII nephelometer (Dade Behring Inc, Deerfield, IL) with a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring Inc).<sup>16</sup> Monoclonal antibodies to cystatin C were coated on polystyrene particles that agglutinate to increase the intensity of scattered light in proportion to cystatin C concentration. The assay range is 0.195 to 7.330 mg/L. The detection limit of the assay is 0.05 mg/L, analytical sensitivity is 0.005 mg/L, and the reference range for healthy persons is 0.53 to 0.95 mg/L. Interassay and intra-assay coefficients of variation are less than 3.1%.<sup>7</sup> Serum creatinine was determined by using the Jaffé reaction from venous samples obtained during the study visit.<sup>7</sup> We used the 4-variable Modification of Diet in Renal Disease equation to calculate eGFR<sup>17</sup>:  $\text{eGFR} = (186 \times [\text{serum creatinine}/88.4] - 1.154) \times (\text{age}) - 0.203 \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$ . Kidney function was categorized into quartiles by using cystatin C, eGFR, or serum creatinine. We also used both eGFR and cystatin C level to categorize participants as having CKD (eGFR < 60 mL/min [ $<1.00 \text{ mL/s}$ ]), preclinical kidney disease (pre-CKD; eGFR > 60 mL/min [ $>1.00 \text{ mL/s}$ ] and cystatin C  $\geq 1.0 \text{ mg/L}$ ), or normal kidney function (eGFR > 60 mL/min [ $>1.00 \text{ mL/s}$ ] and cystatin C < 1.0 mg/L).

## Outcomes

Each participant underwent a symptom-limited graded exercise treadmill test according to a standard Bruce protocol.<sup>18</sup> To achieve maximum heart rate, participants who were unable to continue the standard Bruce protocol (for orthopedic or other reasons) were switched to slower settings on the treadmill and encouraged to exercise for as long as possible. Continuous 12-lead electrocardiographic monitoring was performed throughout the testing, and exercise capacity was calculated as total metabolic equivalent tasks (METs) achieved at peak exercise (1 MET = 3.5 mL of oxygen uptake per kilogram of body weight per minute). For participants who required modification of the Bruce protocol, exercise capacity was determined as total METs achieved at peak exercise. These patients were included in all analyses. We defined poor (<5 METs) exercise capacity according to previously published criteria.<sup>9</sup> After achieving maximal workload, subjects were immediately placed supine. Heart rate was measured exactly 1 minute after termination of exercise to compensate for the effects of physiological venous blood redistribution in the immediate postexercise period. HRR was calculated as the difference between maximal heart rate during exercise and heart rate 1 minute into recovery. For purposes of analysis, we categorized poor HRR as the lowest quartile compared with the upper 3 quartiles of HRR.<sup>19</sup>

## Potential Confounding Variables

Age, ethnicity, education, income, marital status, smoking, alcohol use, angina frequency, and physical activity were determined by means of questionnaire. Medical history was determined by self-report. Resting heart rate was obtained as part of the intake physical examination, and body mass index was calculated as weight in kilograms divided by the square of height in meters. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Hemoglobin and albumin were measured from venous blood samples.

Systolic and diastolic blood pressures were measured with the patient at rest by trained study personnel using a calibrated sphygmomanometer. A complete resting 2-dimensional echocardiogram, including all standard views, was used to determine left ventricular ejection fraction. We calculated wall motion score index immediately postexercise as our measure of ischemia. The wall motion score index represents the sum of wall motion scores from 16 possible wall segments divided by the number of segments visualized.<sup>20</sup> Thus, a normally

contracting left ventricle received a wall motion score index of 1 (16/16 = 1), and higher scores indicate worse contractility.

### Statistical Analysis

Differences in baseline characteristics between participants with and without poor exercise capacity (METs < 5) were compared by using *t*-tests for continuous variables that were normally distributed, Wilcoxon tests for continuous variables that were not normally distributed, and chi-square tests (or Fisher exact test) for dichotomous variables. We examined the 3 measures of kidney function (cystatin C level, eGFR, and serum creatinine level) and the 2 measures of cardiac function (exercise capacity and HRR) as both continuous and categorical variables. We first compared the association of each kidney function measure categorized in quartiles with continuous measures of exercise capacity and HRR by using linear regression. Next, we entered each kidney function measure as a continuous predictor variable and determined areas under the receiver operating characteristic (ROC) curves for predicting poor exercise capacity and HRR as dichotomous outcome variables. We calculated 95% confidence intervals (CIs) for ROC areas by using DeLong's formula for SEs.

Finally, we used multivariate logistic regression to evaluate the association of kidney function categories with poor exercise capacity or HRR as dichotomous outcome variables. Multivariate analyses were adjusted for all variables listed in Table 1.

Analyses were performed using Statistical Analysis Software (version 9.1; SAS Institute Inc, Cary, NC).

## RESULTS

Of 906 participants, 218 (24%) had poor exercise capacity (METs < 5). Compared with participants who achieved METs of 5 or greater, those with poor exercise capacity were older and less likely to have attained a high school education, had lower income, and were less likely to be married (Table 1). They were more likely to have hypertension, congestive heart failure, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, and a history of stroke, but less likely to have undergone prior revascularization. Participants with poor exercise capacity had greater body mass index, but lower ejection fraction, albumin level, hemoglobin level, and diastolic blood pressure. Participants with poor exercise capacity also were more likely to be using a renin-angiotensin inhibitor and less likely to be using aspirin or a statin (Table 1).

In linear regression analyses, increasing quartiles of cystatin C levels were associated with progressively worse exercise capacity. After multivariate analysis, participants with cystatin C concentrations in quartiles III and IV had 1.0 and 1.7 METs lower exercise capacity than those with cystatin C concentrations in the lowest quartile (Table 2). Quartiles II and III of eGFR and creatinine were associated with less substantial decreases in exercise capacity, and only the fourth quartile of eGFR was significantly different from the first quartile in multivariate analysis. When entered as continuous variables, areas under the ROC curve for predicting poor exercise capacity (METs < 5) were 0.71 (95% CI, 0.67 to 0.75) for cystatin C level, 0.59 (95% CI, 0.54 to 0.63) for serum creatinine level, and 0.62 (95% CI, 0.58 to 0.66) for eGFR.

Results were similar for HRR. In adjusted analyses, the third and fourth quartiles of cystatin C were associated with slower HRR ( $P = 0.06$  and  $0.001$ ); whereas only the fourth quartiles of creatinine level and eGFR were statistically significant (Table 3). Areas under the ROC curves for predicting poor HRR (<16 beats/min) were 0.66 (95% CI, 0.62 to 0.70) for cystatin

C level, 0.59 (95% CI, 0.54 to 0.63) for serum creatinine level, and 0.62 (95% CI, 0.57 to 0.66) for eGFR.

We evaluated the association of cystatin C level quartiles with poor exercise capacity, defined as achieved METs less than 5. The prevalence of poor exercise capacity ranged from 12% in the lower 2 quartiles to 45% in the highest quartile (Table 4). After multivariate adjustment, the fourth quartile retained a 3-fold odds of poor exercise capacity compared with the first quartile. The prevalence of poor HRR increased across quartiles of cystatin C levels from 16% to 42%. In adjusted analysis, the highest quartile had a 2-fold odds of poor HRR compared with the lowest quartile.

We repeated these logistic regression analyses using kidney function categories that incorporated both eGFR and cystatin C level (Table 5). Compared with participants who had normal kidney function, those with pre-CKD had a 2.2-fold odds of poor exercise capacity and a 1.7-fold odds of poor HRR in adjusted analyses. Participants with CKD had a 2.8-fold odds of poor exercise capacity and a 2.2-fold odds of poor HRR in multivariate analyses.

## DISCUSSION

We found that greater concentrations of cystatin C had nearly linear associations with poor exercise capacity and HRR in patients with CHD. Compared with participants who had cystatin C concentrations in the lowest quartile, those in the upper 3 quartiles had progressively worse tread-mill exercise capacity and HRR after exercise. Conversely, associations of serum creatinine level and eGFR with poor cardiac function were limited to those in the worst quartile of kidney function. When combining cystatin C level and eGFR, participants who had pre-CKD (cystatin C  $\geq$  1.0 mg/L and normal eGFR) had significantly worse exercise capacity and HRR compared with persons who had normal cystatin C level (<1.0 mg/L) and normal eGFR. Our findings suggest that cystatin C level is an independent correlate of poor cardiovascular functional status in persons with established CHD.

Prior studies of the relation between cystatin C levels and major cardiovascular outcomes evaluated either outpatient populations without preexistent CHD or patients presenting with acute coronary syndrome. No prior study examined the association of cystatin C level with severity of cardiovascular functional status in patients with established CHD. Moreover, no prior study compared cystatin C levels with creatinine-based measurements of renal function as a predictor of cardiovascular functional status. We found that cystatin C levels were distributed over a range similar to that seen in prior studies and was associated inversely with 2 established measures of cardiovascular functional status: exercise capacity and HRR. Cystatin C levels also had more linear associations with these end points than creatinine-based measurements. HRR and exercise capacity had similar distributions in this population compared with prior studies of patients with CHD.

Cystatin C level was reported to be superior to creatinine-based measurements in predicting incident cardiovascular disease, heart failure, and mortality.<sup>2-5</sup> The distinction between the 2 filtrating markers is pronounced in persons with eGFR greater than 60 mL/min (>1.00 mL/s); cystatin C level retains a strong association with cardiovascular risk in persons with eGFR greater than 60 mL/min (>1.00 mL/s), whereas creatinine level and eGFR have no significant association.<sup>21</sup> We previously showed that CKD, defined as creatinine clearance less than 60 mL/min (<1.00 mL/s), was associated with a 6-fold odds of poor exercise capacity in the Heart and Soul cohort compared with the highest creatinine clearance.<sup>22</sup> Our current study extends these findings by detecting a broader association of cystatin C level with decreased exercise capacity and poor HRR that extends to persons with pre-CKD. Because prior data suggest that cystatin C level more accurately reflects mild decreases in GFR than creatinine-based

measurements, our results suggest that even mildly impaired kidney function is associated with greater severity of functional cardiovascular disease.<sup>23</sup>

Mechanisms for the association of cystatin C level with severity of cardiovascular functional capacity are not well understood. One possibility is that anemia associated with kidney disease may lead to poor cardiovascular function.<sup>22</sup> However, adjustment for hemoglobin level did not affect the association of cystatin C with exercise capacity or HRR. Another possibility is that volume overload may lead to poor exercise capacity or HRR. However, adjustment for left ventricular ejection fraction, history of congestive heart failure, and resting heart rate did not change the association of cystatin C level with cardiovascular functional capacity. A third possibility is that the poor nutritional status and frailty associated with kidney disease may lead to decreased cardiovascular conditioning.<sup>24-27</sup> Nonetheless, adjustment for albumin level, body mass index, and medical comorbidities did not eliminate the association of cystatin C level with these outcomes. Another possibility is that decreasing GFR, captured better with cystatin C than creatinine level, is a manifestation of cumulative exposure to cardiovascular risk factors and is linked to decreased cardiovascular functional capacity by residual confounding.

Several limitations must be considered in interpreting our results. First, we evaluated the association of cystatin C level and exercise capacity in a population of largely older white men; thus, our results may not generalize to other groups of patients. Second, the cross-sectional design of our analysis does not allow us to determine the direction of association or allow for causal inference. Third, as stated, we cannot exclude the possibility that the association of cystatin C level with exercise capacity and HRR was confounded by unmeasured factors.

In summary, we found that greater cystatin C levels were associated independently with decreased exercise capacity and HRR in patients with CHD. We found that cystatin C level had more linear associations with poor exercise capacity and HRR than creatinine-based measures. Our findings suggest that CKD, as well as pre-CKD, is associated with worse cardiovascular functional capacity among outpatients with established CHD. Poor functional capacity may contribute to the increased risk of cardiovascular events associated with elevated cystatin C levels and CKD.

## Acknowledgments

Support: The Heart and Soul Study was supported by grants from the Department of Veterans Affairs (Epidemiology Program), the Robert Wood Johnson Foundation, the American Federation for Aging Research, and the National Institutes of Health (R01 HL079235). J.H.I. was supported by the UCSF Academic Senate Individual Investigator Program. The cystatin C assays were supported by Dade-Behring, Inc. None of these funding sources had any role in the collection of data, interpretation of results, or preparation of this manuscript.

## REFERENCES

1. Randers E, Ivarsen P, Erlandsen EJ, et al. Plasma cystatin C as a marker of renal function in patients with liver cirrhosis. *Scand J Clin Lab Invest* 2002;62:129–134. [PubMed: 12004928]
2. Jernberg T, Lindahl B, James S, Larsson A, Hansson LO, Wallentin L. Cystatin C: A novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. *Circulation* 2004;110:2342–2348. [PubMed: 15477399]
3. Shlipak MG, Katz R, Fried LF, et al. Cystatin-C and mortality in elderly persons with heart failure. *J Am Coll Cardiol* 2005;45:268–271. [PubMed: 15653026]
4. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005;352:2049–2060. [PubMed: 15901858]
5. Sarnak MJ, Katz R, Stehman-Breen CO, et al. Cystatin C concentration as a risk factor for heart failure in older adults. *Ann Intern Med* 2005;142:497–505. [PubMed: 15809461]

6. Ix JH, Shlipak MG, Chertow GM, Whooley MA. Association of cystatin C with mortality, cardiovascular events, and incident heart failure among persons with coronary heart disease: Data from the Heart and Soul Study. *Circulation* 2007;115:173–179. [PubMed: 17190862]
7. Ix JH, Chertow GM, Shlipak MG, Brandenburg VM, Ketteler M, Whooley MA. Fetuin-A and kidney function in persons with coronary artery disease—Data from the Heart and Soul Study. *Nephrol Dial Transplant* 2006;21:2144–2151. [PubMed: 16644775]
8. Mora S, Redberg RF, Cui Y, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: A 20-year follow-up of the lipid research clinics prevalence study. *JAMA* 2003;290:1600–1607. [PubMed: 14506119]
9. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;346:793–801. [PubMed: 11893790]
10. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995;273:402–407. [PubMed: 7823386]
11. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med* 2000;132:552–555. [PubMed: 10744592]
12. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. *J Am Coll Cardiol* 2003;42:831–838. [PubMed: 12957428]
13. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA* 2000;284:1392–1398. [PubMed: 10989401]
14. Messinger-Rapport B, Snader CE, Pothier, Blackstone EH, Yu D, Lauer MS. Value of exercise capacity and heart rate recovery in older people. *J Am Geriatr Soc* 2003;51:63–68. [PubMed: 12534847]
15. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: The Heart and Soul Study. *JAMA* 2003;290:215–221. [PubMed: 12851276]
16. Newman DJ, Thakkar H, Edwards RG, et al. Serum cystatin C measured by automated immunoassay: A more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 1995;47:312–318. [PubMed: 7731163]
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–470. [PubMed: 10075613]
18. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: Summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol* 2002;40:1531–1540. [PubMed: 12392846]
19. Spies C, Otte C, Kanaya A, Pipkin SS, Schiller NB, Whooley MA. Association of metabolic syndrome with exercise capacity and heart rate recovery in patients with coronary heart disease in the Heart and Soul Study. *Am J Cardiol* 2005;95:1175–1179. [PubMed: 15877989]
20. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358–367. [PubMed: 2698218]
21. Shlipak MG, Katz R, Sarnak MJ, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med* 2006;145:237–246. [PubMed: 16908914]
22. Odden MC, Whooley MA, Shlipak MG. Association of chronic kidney disease and anemia with physical capacity: The Heart and Soul Study. *J Am Soc Nephrol* 2004;15:2908–2915. [PubMed: 15504944]

23. Bokenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J. Cystatin C—A new marker of glomerular filtration rate in children independent of age and height. *Pediatrics* 1998;101:875–881. [PubMed: 9565418]
24. Johansen KL, Chertow GM, da Silva M, Carey S, Painter P. Determinants of physical performance in ambulatory patients on hemodialysis. *Kidney Int* 2001;60:1586–1591. [PubMed: 11576377]
25. Johansen KL, Chertow GM, Ng AV, et al. Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney Int* 2000;57:2564–2570. [PubMed: 10844626]
26. Harris LE, Luft FC, Rudy DW, Tierney WM. Clinical correlates of functional status in patients with chronic renal insufficiency. *Am J Kidney Dis* 1993;21:161–166. [PubMed: 8430676]
27. Shlipak MG, Stehman-Breen C, Fried LF, et al. The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kidney Dis* 2004;43:861–867. [PubMed: 15112177]



Table 1

Characteristics of 906 Participants With CHD Divided According to Exercise Capacity

Variables	Poor Exercise Capacity (METs < 5) (n = 218)	Normal Exercise Capacity (METs ≥ 5) (n = 688)	P
<b>Demographic</b>			
Age (y)	71 ± 11	65 ± 10	<0.0001
Men	173 (79)	577 (84)	0.12
White	146 (67)	408 (59)	0.05
High school graduate	178 (82)	614 (90)	0.002
Annual income < \$20,000	139 (64)	281 (41)	<0.0001
Married	73 (33)	319 (47)	0.0007
<b>Medical history:</b>			
Hypertension	167 (77)	465 (68)	0.01
Myocardial infarction	113 (53)	369 (54)	0.80
Coronary revascularization	113 (52)	428 (62)	0.007
Congestive heart failure	53 (24)	97 (14)	0.0005
Stroke	44 (20)	74 (11)	0.0003
Diabetes mellitus	73 (33)	157 (23)	0.002
Chronic pulmonary disease	16 (7)	15 (2)	0.0003
Peripheral vascular disease	25 (14)	49 (8)	0.03
Current angina (any v none)	46 (21)	115 (17)	0.14
<b>Kidney function:</b>			
Serum cystatin C (mg/L)	1.4 ± 0.75	1.1 ± 0.39	<0.0001
Modification of Diet in Renal Disease eGFR (mL/min)	69.6 ± 23.8	78.9 ± 21.6	<0.0001
Serum creatinine (mg/dL)	1.3 ± 0.83	1.1 ± 0.42	<0.0001
<b>Other characteristics:</b>			
Regular alcohol use	58 (27)	211 (31)	0.22
Current smoking	49 (22)	130 (19)	0.26
Body mass index (kg/m <sup>2</sup> )	29 ± 6	28 ± 5	0.0003
Hemoglobin (g/dL)	13.5 ± 1.5	14 ± 1.3	<0.0001
Albumin (g/dL)	3.8 ± 0.4	3.9 ± 0.3	<0.0001
<b>Cardiac function:</b>			
Resting heart rate (beats/min)	69 ± 12	67 ± 12	0.10
Systolic blood pressure (mm Hg)	134 ± 19	131 ± 19	0.05
Diastolic blood pressure (mm Hg)	72 ± 11	75 ± 10	0.003
Ejection fraction (%)	61 ± 1	62 ± 1	0.02
Wall motion score index	1.2 ± 0.4	1.2 ± 0.4	0.12
<b>Medication use:</b>			
β-Blocker	131 (60)	391 (57)	0.40
Statin	122 (56)	470 (68)	0.0008
Renin-angiotensin inhibitor	129 (59)	337 (49)	0.009
Aspirin	159 (73)	552 (80)	0.02

Note: Values expressed as mean ± SD or number (percent). METS achieved on exercise treadmill testing. To convert GFR in mL/min to mL/s, multiply by 0.01667; serum creatinine in mg/dL to μmol/L, multiply by 88.4; serum albumin and hemoglobin in g/dL to g/L, multiply by 10.

Table 2

$\beta$  Coefficients for Poor Exercise Capacity (METs < 5) by Quartile of Kidney Function

	Quartile								
	I		II		III		IV		
		$\beta$ Coefficient	P	$\beta$ Coefficient	P	$\beta$ Coefficient	P	$\beta$ Coefficient	P
Cystatin C (mg/L)	0.35-0.92								
Range									
Unadjusted		-0.82	0.005	-2.2	1.07-1.28	-3.5	<0.0001	>1.29	<0.0001
Adjusted		-0.30	0.26	-1.0	0.0002	-1.7	0.0002		<0.0001
eGFR (mL/min)									
Range	>90								
Unadjusted		-0.67	0.03	-0.90	62.5-76.1	-2.3	0.003	8.1-62.4	<0.0001
Adjusted		-0.01	0.96	-0.10	0.72	-6.5	0.72		0.03
Creatinine (mg/dL)	0.5-0.9								
Range									
Unadjusted		+0.13	0.68	-0.51	1.1-1.2	-1.5	0.07	>1.3	<0.0001
Adjusted		-0.22	0.43	-0.46	0.08	-0.75	0.08		0.01

Note: Adjusted for all variables in Table 1 (except kidney function variables). To convert GFR in mL/min to mL/s, multiply by 0.01667; serum creatinine in mg/dL to  $\mu$ mol/L, multiply by 88.4.

Table 3

$\beta$  Coefficients for Poor HRR (<16 beats/min) by Quartile of Kidney Function

	Quartile			
	I	II	III	IV
		$\beta$ Coefficient	P	$\beta$ Coefficient
Cystatin C (mg/L)				
Range	0.35-0.92			
Unadjusted	-0.88	0.93-1.06	0.45	1.07-1.28
Adjusted	+0.62		0.62	
eGFR (mL/min)				
Range	>90	76.2-89.9		62.5-76.1
Unadjusted	-2.10	-2.8	0.08	-2.8
Adjusted	-1.20	-1.5	0.36	-1.5
Creatinine (mg/dL)				
Range	0.5-0.9	<0.9-1.0		1.1-1.2
Unadjusted	-0.15	-0.15	0.90	-2.4
Adjusted	-0.59	-0.59	.66	-1.8

Note: Adjusted for all variables in Table 1 (except kidney function variables). To convert GFR in mL/min to mL/s, multiply by 0.01667; serum creatinine in mg/dL to  $\mu$ mol/L, multiply by 88.4.

Table 4

Association of Cystatin C With Poor Exercise Capacity (METs < 5) and Poor HRR (lowest quartile < 16 beats/min)

Cystatin C Quartile	Proportion with Low Exercise Capacity (%)	Unadjusted Odds Ratio (95% CI)	P	Adjusted Odds Ratio* (95% CI)	P
I (<0.92 mg/L)	12	1.0 (0.6-1.8)	0.94	1.0 (0.3-1.5)	—
II (0.92-1.07 mg/L)	12	2.8 (1.7-4.5)	<0.0001	1.8 (0.9-3.6)	0.41
III (1.07-1.30 mg/L)	28	5.9 (3.7-9.4)	<0.0001	3.2 (1.6-6.5)	0.09
IV (>1.30 mg/L)	45				0.001

  

Cystatin C Quartile	Proportion With Poor HRR (%)	Unadjusted Odds Ratio (95% CI)	P	Adjusted Odds Ratio* (95% CI)	P
I (<0.92 mg/L)	16	1.2 (0.8-2.0)	0.40	0.9 (0.5-1.6)	0.60
II (0.92-1.07 mg/L)	29	2.1 (1.4-3.4)	0.001	1.5 (0.9-2.8)	0.14
III (1.07-1.30 mg/L)	28	3.9 (2.5-6.1)	<0.0001	2.2 (1.2-4.0)	0.01
IV (>1.30 mg/L)	42				

\* Adjusted for all variables in Table 1 (except kidney function variables). Odds ratios for other variables associated with poor exercise capacity (at  $P < 0.10$ ) were: age, 1.1 (95% CI, 1.05 to 1.1); white, 1.5 (95% CI, 0.9 to 2.3); low income, 3.8 (95% CI, 2.4 to 6); prior revascularization, 0.6 (95% CI, 0.4 to 0.9); prior heart failure, 2.1 (95% CI, 1.2 to 3.6); prior stroke, 1.9 (95% CI, 1.1 to 3.3); statin use, 0.5 (95% CI, 0.3 to 0.8); smoking, 2.4 (95% CI, 1.4 to 4.3); body mass index, 1.1 (95% CI, 1.0 to 1.1); albumin level, 0.5 (95% CI, 0.3 to 0.9); systolic blood pressure, 1.0 (95% CI, 0.99 to 1.0); diastolic blood pressure, 0.96 (95% CI, 0.94 to 0.99); and diabetes, 1.6 (95% CI, 1.0 to 2.5). Odds ratios for other variables associated with poor HRR (at  $P < 0.10$ ) were: age, 1.1 (95% CI, 1.0 to 1.1); high school graduate, 1.8 (95% CI, 1.0 to 3.2); prior revascularization, 0.7 (95% CI, 0.5 to 1.1); prior heart failure, 1.7 (95% CI, 1.1 to 2.7);  $\beta$ -blocker use, 1.6 (95% CI, 1.0 to 2.3); body mass index, 1.0 (95% CI, 1.0 to 1.1); resting heart rate, 1.03 (95% CI, 1.01 to 1.05); and smoking, 2.9 (95% CI, 1.8 to 4.8).

Association of Preclinical Kidney Disease and CKD<sup>†</sup> With Poor Exercise Capacity (METs < 5) and Poor HRR (<16 beats/min)

	Normal Kidney Function		Pre-CKD		CKD	
		P		P		P
Poor exercise capacity	—					
Unadjusted OR (95% CI)*	—		3.7 (2.4-5.5)	<0.0001	5.1 (3.2-7.9)	<0.0001
Adjusted OR (95% CI)	—		2.2 (1.3-3.9)	0.005	2.8 (1.5-5.3)	0.002
Poor HRR	—					
Unadjusted OR (95% CI)*	—		2.5 (1.7-3.6)	<0.0001	3.5 (2.3-5.3)	<0.0001
Adjusted OR (95% CI)	—		1.7 (1.0-2.7)	0.04	2.2 (1.3-3.9)	0.004

\* Adjusted for all variables in Table 1 (except kidney function variables).

<sup>†</sup> Normal kidney function defined as eGFR greater than 60 mL/min (>1.00 mL/s) and cystatin C level less than 1.0 mg/L. Pre-CKD defined as eGFR greater than 60 mL/min (>1.00 mL/s) and cystatin C level of 1.0 mg/L or greater. CKD defined as eGFR less than 60 mL/min (<1.00 mL/s).