Urinary Creatinine Excretion Rate and Mortality in Persons With Coronary Artery Disease. The Heart and Soul Study

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Urinary Creatinine Excretion Rate and Mortality in Persons With Coronary Artery Disease

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Background—In persons with coronary artery disease, low body mass index is associated with greater mortality; however, it is uncertain whether low muscle mass is a risk factor for mortality in this setting.

Methods and Results—In this study, 903 individuals with coronary artery disease provided 24-hour urine collections. We measured urine creatinine and volume and calculated creatinine excretion rate, a marker of muscle mass. Cox proportional-hazards models evaluated the association of creatinine excretion rate with mortality risk. Over a median follow-up of 6.0 years, 232 participants (26%) died. Compared with the highest sex-specific creatinine excretion rate tertile, the lowest tertile (<1068 mg/d in men, <766 mg/d in women) was associated with >2-fold risk of mortality (hazard ratio, 2.30; 95% confidence interval, 1.51 to 3.51) in models adjusted for age, sex, race, cystatin C–based estimated glomerular filtration rate, body mass index, traditional cardiovascular disease risk factors, and C-reactive protein levels. The association was essentially unaltered with further adjustment for physical fitness, left ventricular mass, left ventricular ejection fraction, or fasting insulin and glucose levels.

Conclusions—Lower creatinine excretion rate is strongly associated with mortality in outpatients with coronary artery disease, independently of conventional measures of body composition, kidney function, and traditional coronary artery disease risk factors. Future studies should determine whether low creatinine excretion rate may be a modifiable risk factor for mortality among persons with coronary artery disease, potentially through resistive exercise training or nutrition interventions. **(*Circulation*. 2010;121:1295-1303.)**

Key Words: cardiovascular diseases ■ creatinine ■ muscles ■ mortality

Although obesity is a risk factor for incident coronary artery disease (CAD), its significance in individuals with established CAD has recently been questioned. In a meta-analysis that included 40 studies and >250 000 individuals with CAD, there was a reverse J-shaped relationship between body mass index (BMI) and mortality: Individuals with a BMI <20.0 kg/m^2 had the greatest mortality risk, whereas obese (BMI, 30.0 to 34.9 kg/m^2) or severely obese (BMI >35 kg/m^2) individuals were not at greater risk than normal-weight individuals (BMI, 20.0 to 24.9 kg/m^2).[1] Because BMI does not discriminate between its relative contributions from adiposity or muscle, this finding has led many to hypothesize that the high death risk associated with low BMI may be due to deficiency in muscle rather than adiposity.[2–4] Implicit is the hypothesis that low muscle mass may be a risk factor for mortality in persons with established CAD. Yet, to the best of our knowledge, this association has not been studied in the setting of prevalent CAD.

Clinical Perspective on p 1303

It is estimated that >98% of creatinine comes from muscle,[5] where it is produced and secreted into serum at a continuous rate.[6] Once in serum, creatinine is almost exclusively excreted in the urine in individuals without severe kidney failure.[7,8] Because muscle mass does not change rapidly within individuals, elevations in serum creatinine typically reflect decrements in glomerular filtration rate (GFR). When the serum creatinine concentration is in steady state, however, regardless of its serum concentration, creatinine generation must equal creatinine excretion. Thus, the urinary creatinine excretion rate (CER) has been recognized as a marker of muscle mass for nearly a century.[9] Here, we evaluate the association of CER with all-cause mortality among a cohort of outpatients with stable CAD. On the basis of the relationship of low BMI with mortality reported elsewhere, we hypothesized that lower CER would be asso-

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ciated with mortality independently of traditional CAD risk factors and kidney function.

Methods

Study Participants

The Heart and Soul Study is an observational study designed to investigate the influence of psychosocial factors on the progression of CAD. Methods have been described previously.[10] Briefly, participants were recruited from outpatient clinics in the San Francisco Bay area if they met one of the following inclusion criteria: history of myocardial infarction, angiographic evidence of >50% stenosis in ≥1 coronary vessels, evidence of exercise-induced ischemia by treadmill or nuclear testing, history of coronary revascularization, or documented diagnosis of CAD by an internist or cardiologist. Participants were excluded if they were not able to walk 1 block, had experienced myocardial infarction within the past 6 months, or were likely to move out of the area within 3 years. The study protocol was approved by the Institutional Review boards of participating institutions, and all participants provided written informed consent.

Between September 2000 and December 2002, 1024 participants enrolled and underwent a day-long baseline study appointment that included a medical history, physical examination, and comprehensive health status questionnaire. Outpatient 24-hour timed urine collections and fasting (12-hour) morning venous blood samples were obtained. For the present analysis, we excluded 107 participants with missing timed urine collections and 20 individuals without complete covariate data, providing a final analytic sample of 903 participants. Participants were followed up for death through December 1, 2008. By this date, 38 (3.7%) participants had been lost to follow-up.

Measurements

Urinary CER

The protocol used for timed urine collection has been described previously.[11] In brief, participants received detailed instructions on accurate urine collection and specimen refrigeration. Subjects were asked to void at the end of their study appointment and to begin the collection from that point forward. Research personnel arrived at the patient's home 24 hours after the timed collection was initiated to avoid overcollection or undercollection. If participants reported missing any urine or collections were <1 or >3 L, collections were repeated. When participants were unable to collect all urine for any reason, no data were recorded. Urine volume was recorded (mL), and creatinine was measured by the rate Jaffe method. CER was calculated in milligrams per day (urine volume [mL] times urine creatinine [mg/dL] divided by 100).

Mortality

Between the baseline examination and December 1, 2008, annual telephone interviews were conducted with study participants (or their proxy) for vital status. For any reported event, medical records, death certificates, and coroner's reports were retrieved. Date of death was recorded to provide time-to-event data from the baseline examination.

Other Participant Characteristics and Laboratory Tests

Age, sex, and race/ethnicity were determined by questionnaire. Weight and height were measured with subjects in light clothes and without shoes. BMI was calculated as weight in kilograms divided by height in meters squared. Waist and hip circumferences were measured with a flexible plastic measure to the nearest 0.1 cm. Waist circumference was measured midway between the lower rib margin and iliac crest. Hip circumference was measured at the level of the greater trochanters. Waist-to-hip ratio (WHR) was calculated. Serum cystatin C concentrations were measured with a particle-enhanced immunonephelometric assay[12] (N Latex Cystatin-C, Dade Behring, Inc, Deerfield, Ill) and used to calculate estimated GFR ($eGFR_{cys}$) with the following formula: $eGFR_{cys}=76.7\times\text{cystatin C}^{-1.19}$. This formula, which has been validated with comparison with iothalamate-measured GFR in a pooled cohort of kidney disease studies, showed little bias and provided a non–creatinine-based method to adjust for kidney function for this study.[13] History of smoking, hypertension, and diabetes mellitus was determined by questionnaire. Systolic and diastolic blood pressures were measured after 5 minutes of rest in subjects in the supine position. Total cholesterol and high-density lipoprotein (HDL) cholesterol were measured with standard clinical chemistry analyzers. High-sensitivity C-reactive protein (CRP) was measured with the Roche (Indianapolis, Ind) and the Beckman Extended Range (Galway, Ireland) assays.[14] Fasting glucose was measured by a standard clinical analyzer, and fasting insulin was measured by ELISA (Linco Research, St Charles, Mo). Participants provided rest transthoracic echocardiograms that were read by an expert cardiologist blinded to all clinical data as described previously.[15] Left ventricular (LV) mass was calculated with the truncated ellipsoid method[16] and indexed to body surface area. LV ejection fraction was determined by biplane method of disks.[17] Thereafter, subjects underwent exercise treadmill test by the modified Bruce protocol. The maximum number of metabolic equivalents (METs) and maximum heart rate achieved were recorded.

Statistical Analysis

Exploratory analyses demonstrated that the distribution of CER was approximately gaussian but differed substantially in men and women. Thus, for Kaplan–Meier survival estimates and Cox models, we evaluated sex-specific tertiles of CER as the primary predictor variable. In companion analyses, we evaluated CER as a continuous predictor, defined as 1-SD lower level in the unadjusted distribution of CER in our data set. Other secondary predictor variables measured on a continuous scale were also evaluated per 1-SD lower level to facilitate comparisons of their strengths of associations with mortality.

We used linear regression to evaluate age- and sex-adjusted association of key body composition variables, kidney function, and inflammatory markers with CER. Next, we explored the age- and sex-adjusted functional form of body composition measurements with CER using generalized additive models to fit cubic B-spline functions. The extreme 5% of CER measurements were excluded to avoid implausible extrapolations of the functional form from the extremes of the data distribution. Next, Kaplan–Meier survival curves were developed to explore the unadjusted association of CER tertiles with mortality. Subsequently, Cox proportional-hazards models were used to evaluate this association while adjusting for potential confounders. Sequential models were developed: model 1 was unadjusted; model 2 adjusted for age and sex; and model 3 adjusted for model 2 variables plus BMI. Sensitivity analyses were conducted to determine whether results were similar if weight, waist circumference, hip circumference, or WHR replaced BMI in model 3. A final model adjusted for the model 3 variables plus black race, eGFR, natural log of CRP, and traditional CAD risk factors (diabetes mellitus, hypertension, smoking, systolic blood pressure, diastolic blood pressure, and total and HDL cholesterol). The functional forms of each continuous variable with mortality were investigated, and when nonlinear associations were observed, appropriate categorizations were used to capture the observed functional form. We explored the functional form of CER with mortality in the fully adjusted model using a cubic B-spline function. To investigate whether low CER identifies individuals with occult systemic illness that may have led to higher short-term mortality risk, we evaluated a time interaction term, dichotomized at 3 years after baseline. Finally, we created multiplicative interaction terms to evaluate whether results were modified by sex, and analyses were stratified by sex. Results were similar, so only models combining both sexes are presented to maximize statistical power.

Table 1. Characteristics of the Heart and Soul Cohort at Baseline

n	903
Age, y	67±11
Male, % (n)	82 (741)
Black, % (n)	15 (137)
Diabetes mellitus, % (n)	26 (237)
Hypertension, % (n)	71 (639)
Current smoking, % (n)	19 (175)
History of MI, % (n)	54 (483)
History of stroke, % (n)	14 (122)
History of coronary revascularization, % (n)	53 (538)
LV mass index, g/m^2	98±26
LV ejection fraction, %	62±10
Bruce treadmill data	
METS achieved	7.3±3.3
Maximum heart rate achieved, bpm	130±25
BMI, kg/m^2	28±5
Obese, % (n)	32 (286)
WHR	0.95±0.08
Total cholesterol, mg/dL	177±42
HDL cholesterol, mg/dL	45±14
Triglycerides, mg/dL	142±130
24-h Urine CrCl, mL/min	82±29
CKD_{CrCl} (CrCl <60 mL/min), % (n)	24 (220)
$eGFR_{Cys}$, mL · min^{-1} · 1.73 m^{-2}	71±23
CKD_{Cys} ($eGFR_{Cys}$ <60 mL · min^{-1} · 1.73 m^{-2}), % (n)	31 (277)
CER, mg/d	1197±412

MI indicates myocardial infarction; CrCl, creatine clearance; and CKD, chronic kidney disease. Data show means±SD or percent prevalence.

To determine whether any association between CER and mortality may be due to incomplete urine collections in patients with low CER, we performed a sensitivity analysis excluding participants whose measured 24-hour urinary creatinine clearance was >30% different from their $eGFR_{cys}$. This takes advantage of the fact that CER divided by serum creatinine equals creatinine clearance (in mL/min), an estimate of GFR.[18] $eGFR_{cys}$ provided another estimate of GFR, yet it is independent of the quality of the timed urine collection and of creatinine kinetics. Creatinine clearance was normalized to body surface area because $eGFR_{cys}$ is calculated as an estimate of GFR normalized to body surface area to facilitate comparison of the 2 GFR estimates.

Proportional-hazards assumptions were assessed by visually inspecting log-minus-log plots and plots of Schoenfeld residuals versus survival time. No evidence of violations was observed. Analyses were performed with STATA Statistical Software, version 9.2 (Stata Corp, College Station, Tex). Values of $P<0.05$ were considered statistically significant for all comparisons, including multiplicative interaction terms.

Results

Baseline characteristics of the study participants are shown in Table 1. The mean age of the 903 participants was 67±11 years; 32% were obese; and 31% had moderate chronic kidney disease determined by cystatin C. The mean CER was 1197±412 mg/d. Table 2 shows the age- and sex-adjusted associations of demographics, body composition, kidney function, physical fitness variables, LV mass, and LV ejection fraction with CER. As expected, younger participants and men had higher CER, and greater body mass by each measurement was associated with greater CER. When assessed by the relative difference in CER, the association was strongest for weight followed by BMI, whereas WHR had the weakest association with CER. Age- and sex-adjusted spline functions demonstrated that these associations were fairly linear across the distribution of body composition measures (Figure 1). Individuals achieving greater METs and maximum heart rate on the Bruce treadmill test had greater CER. Individuals with greater CER also had greater LV ejection fraction on average, although the association did not reach statistical significance. Lower $eGFR_{cys}$ was also associated with lower CER, but this association was modest in strength. Black race, CRP levels, and LV mass were not significantly associated with CER.

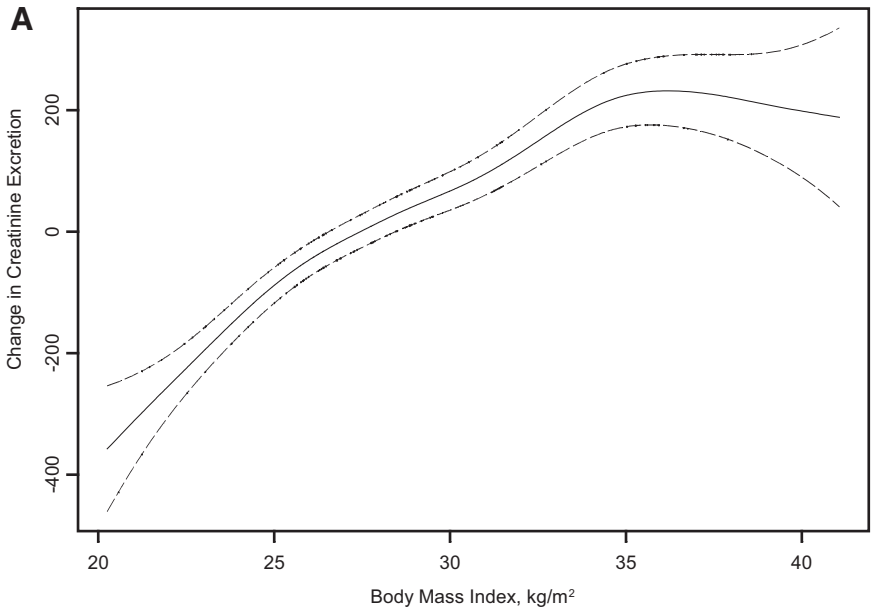
Table 2. Age- and Sex-Adjusted Associations of Variables With CER*

Correlate	Difference in CER, mg/d	95% CI	P
Age (per 11 y greater)†	−161	−184–−138	<0.001
Male sex	421	360–481	<0.001
Black (vs all other races)	22	−44–87	0.52
Weight (per 18 kg greater)†	169	148–191	<0.001
Height (per 9 cm greater)†	112	86–138	<0.001
BMI (per 5.4 kg/m^2 greater)†	139	118–161	<0.001
Waist circumference (per 15 cm greater)†	129	107–151	<0.001
Hip circumference (per 14 cm greater)†	120	97–142	<0.001
WHR (per 0.8 greater)†	70	44–96	<0.001
Maximum heart rate on Bruce treadmill test (per 25 bpm greater)†	37	12–62	0.004
METS achieved on Bruce treadmill test (per 3.34 METS greater)†	32	5–58	0.02
LV ejection fraction (per 10% greater)†	21	−3–44	0.08
$eGFR_{Cys}$ (per 22 mL · min^{-1} · 1.73 m^{-2} greater)†	13	10–15	<0.001
ln(CRP) (per 1.3 greater)†	8	−15–32	0.48
LV mass index (per 26.3 g/m^2 greater)†	−3	−26–21	0.82

*Evaluated with linear regression.
†SD difference.

Association of CER With Mortality

Participants were followed up for a median of 6.0 years (interquartile range, 4.6 to 6.1 years), during which time, 232 participants (26%) died. Figure 2 shows Kaplan–Meier survival estimates by sex-specific CER tertiles. In the highest CER tertile, 37 deaths (12%) occurred compared with 69 (23%) among persons in the middle tertile and 126 (42%) among persons in the lowest tertile. Accordingly, compared with the highest CER tertile, subjects in the



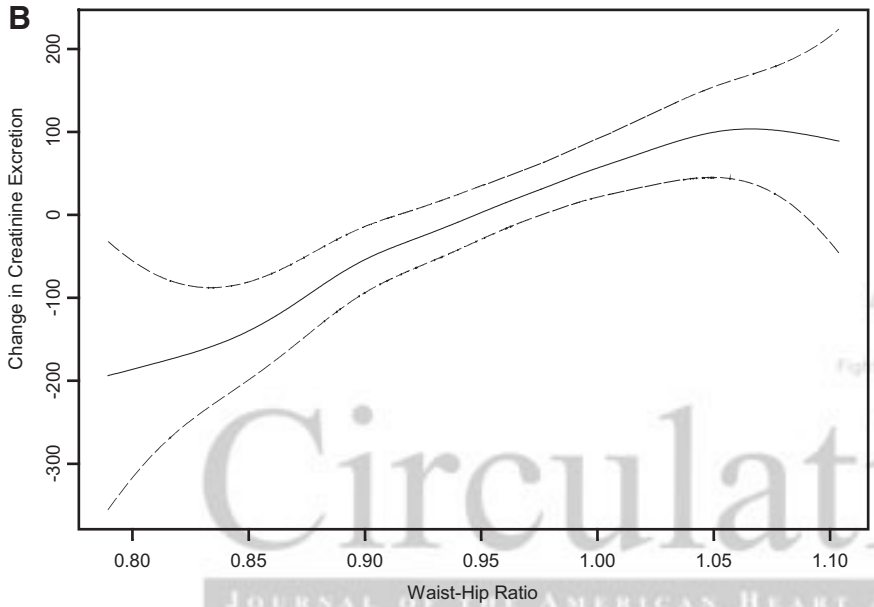


Figure 1. Age- and sex-adjusted spline functions demonstrating the cross-sectional association of BMI (A) and WHR (B) with creatinine excretion rate in persons with CAD. Solid line represents beta coefficients; dotted lines, 95% CIs. The extreme 5% of the data distribution was excluded to avoid implausible extrapolation from the extremes of the data.

lowest tertile were at ≈4-fold risk of death in unadjusted analysis (Table 3). This association was attenuated to ≈3-fold when adjusted for age and sex (mean±SD age, 61±10, 67±10, and 71±11 years for the highest, middle, and lowest tertiles, respectively). Adjustment for BMI was complex; the association of BMI with mortality was not linear. In age- and sex-adjusted models, subjects in the lowest BMI quintile (<24.1 kg/m^2) were at 1.5-fold greater risk for mortality (P=0.03) compared with subjects in the second quintile, and mortality risk was similar across quintiles 2 through 5 (Figure 3). Therefore, we categorized BMI by the lowest quartile versus quartiles 2 through 5. With this adjustment, the lowest CER tertile remained associated with an ≈3-fold mortality risk (Table 3). Results were similar when each quintile of BMI was modeled as separate indicator variables, when BMI was modeled continuously, and when BMI plus a quadratic term (BMI^2) was modeled concurrently. Results were also similar when weight, height, waist circumference, hip circumference, or WHR replaced BMI (data not shown). When the model was further adjusted for traditional CAD risk factors, kidney function, and CRP, the association was modestly further attenuated, but the lowest CER tertile remained at 2-fold greater risk of mortality compared with the highest tertile. The functional form of the relationship of CER with mortality was linear throughout the distribution of CER values in the final multivariable model (Figure 4). Results were similar when men and women were evaluated separately (interaction P=0.21).

Table 4 shows hazard ratios (HRs) for mortality for each predictor variable in the final model. When continuous predictor variables per 1-SD change were compared, only age (per SD, 11 years) was clearly more strongly associated with mortality than CER. The associations of CER, eGFR, and

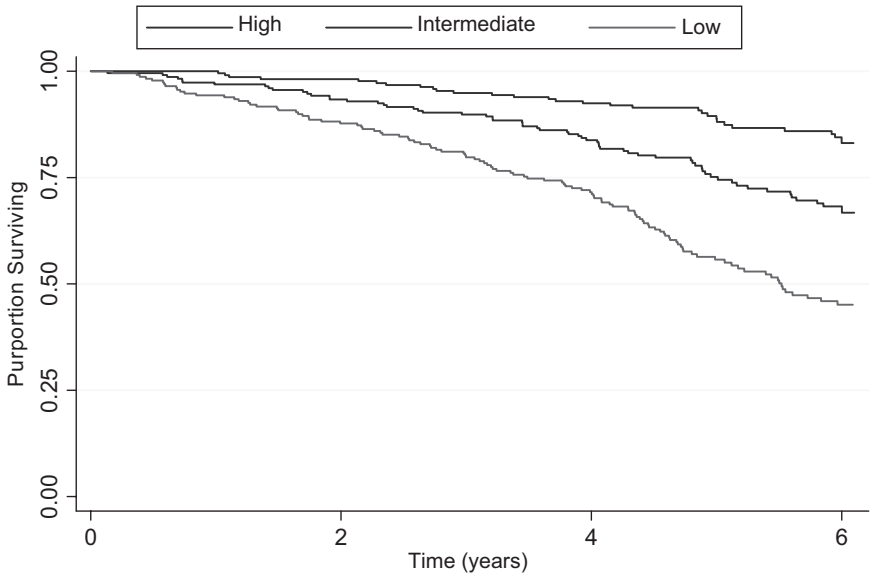


Figure 2. Kaplan–Meier survival curve demonstrating the unadjusted association of creatinine excretion tertiles with mortality in persons with CAD.

CRP with mortality were of similar strength. Associations of the remainder of the continuously predictors were more modest or altogether absent. Compared with the binary risk factors, 1-SD lower CER was weaker than male sex and current smoking, similar in strength to diabetes mellitus, and stronger than the lowest quintile of BMI, hypertension, or black race.

Evaluation of Potential Mechanisms

Table 5 shows the result of further adjustment of the multivariable model for variables that might mediate the association of CER with mortality. Additional adjustment for maximum heart rate and METs achieved on the Bruce exercise treadmill had little effect on the association of CER with mortality. Results were also similar with adjustment for LV mass index and ejection fraction, prior CVD history, or fasting blood glucose and insulin levels. To evaluate whether low CER may be a marker of occult illness and might therefore be more strongly associated with short-term mortality, we evaluated whether the association differed in individuals who died ≤3 versus >3 years after their baseline visit. Results were similar. In this model, each 1-SD lower CER was associated with an HR of 1.39 (95% confidence interval [CI], 1.03 to 1.85) in participants who died ≤3 years (n=80) and 1.35 (95% CI, 1.09 to 1.69) in those who died >3 years later (interaction $P=0.91$).

Sensitivity Analyses

To investigate potential misclassification bias introduced by undercollected or overcollected urine specimens, we excluded participants whose measured urinary creatinine clearance was discrepant with $eGFR_{cys}$ by >30% (n=267, 30%). Among those excluded, creatine clearance overestimated $eGFR_{cys}$ in 136 and underestimated $eGFR_{cys}$ in 131 individuals. The association of CER with mortality was similar in the remaining 636 participants compared with the entire sample. Participants with CER in the lowest tertile were at 3-fold mortality risk compared with the highest tertile (HR, 2.99; 95% CI, 1.59 to 5.62), and 1-SD lower CER was associated with 40% greater mortality risk

Table 3. Association of CER With Mortality in Persons With CAD*

	Creatinine Excretion Tertiles, per 412 mg/d*				
Model	Highest	Middle	Lowest	Per 412 mg/d†	*P*
Events/No. at risk (%)	37/301 (12)	69/301 (23)	126/301 (42)		
Unadjusted	1.00	2.05 (1.37–3.05)	4.10 (2.84–5.92)	1.59 (1.38–1.84)	<0.001
Age and sex adjusted	1.00	1.68 (1.12–2.53)	3.05 (2.06–4.52)	1.61 (1.36–1.91)	<0.001
Age, sex, and BMI adjusted‡	1.00	1.66 (1.10–2.50)	2.89 (1.91–4.35)	1.55 (1.30–1.86)	<0.001
Fully adjusted§	1.00	1.50 (0.99–2.28)	2.30 (1.51–3.51)	1.38 (1.15–1.66)	0.001

Values are HR (95% CI) unless otherwise indicated.

*Highest=men (n=758) ≥1423, women (n=165) ≥1014; middle=men 1068–1422, women 766–1013; lowest=men <1068, women <766. Evaluated with Cox proportional-hazards models.

†412 mg/d represents 1-SD lesser creatinine excretion rate.

‡BMI dichotomized at the lowest quintile (<24.1 kg/m^2).

§Adjusted for age, sex, race, BMI (lowest quintile), diabetes mellitus, hypertension, current smoking, systolic and diastolic blood pressures, total cholesterol, HDL cholesterol, eGFR, and ln(CRP).

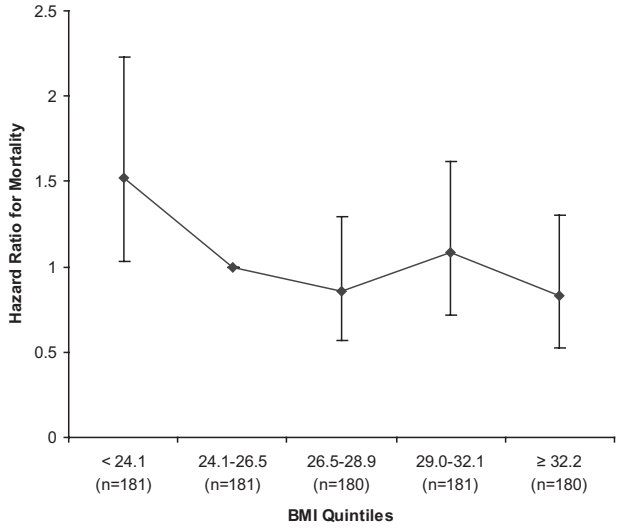


Figure 3. Association of body mass index with mortality. Models adjusted for age and sex. The second BMI quintile (24.1 to 26.5 kg/m^2) served as the reference category. Error bars reflect 95% CIs.

(HR, 1.40; 95% CI, 1.03 to 1.90) in the fully adjusted model.

Discussion

We demonstrated that lower CER is strongly associated with mortality in outpatients with stable CAD. The association showed a dose-response relationship and was independent of BMI, WHR, kidney function, inflammatory biomarkers, or traditional CAD risk factors. Adjustment for markers of physical fitness, LV structure and function, and insulin resistance rendered the association effectively unaltered. The association was approximately equal in strength to that of kidney function and CRP, which are 2 of the strongest risk factors for mortality in the secondary prevention setting.[19] These findings have important implications for individuals with prevalent CAD.

Table 4. Mutually Adjusted Relative Strength of Association of Risk Factors for Mortality in Persons With CAD

Risk Factor	HR	95% CI	*P*
Age, per 11 y greater*	1.51	1.25–1.83	<0.001
eGFR, per 22 mL · min^{-1} · 1.73 m^{-2} lower*	1.40	1.19–1.65	<0.001
CER, per 412 mg/d lower*	1.38	1.15–1.66	0.001
ln(CRP), per 1.3 greater*	1.33	1.16–1.53	<0.001
Total cholesterol, per 42 mg/dL greater*	1.08	0.93–1.24	0.32
DBP, per 11 mm Hg greater*	0.93	0.77–1.12	0.46
HDL cholesterol, per 14 mg/dL greater*	0.94	0.81–1.10	0.45
SBP, per 21 mm Hg greater*	0.99	0.82–1.20	0.94
Male sex	1.97	1.19–3.19	0.008
Current smoking	1.88	1.31–2.69	0.001
Diabetes mellitus	1.36	1.03–1.88	0.03
BMI <24.1 kg/m^2	1.28	0.93–1.78	0.13
Hypertension	0.87	0.65–1.20	0.43
Black race	0.96	0.62–1.42	0.76

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.
*Per SD change.

First, although it is frequently hypothesized that decreased muscle mass is associated with mortality in persons with CAD,[1,20] to the best of our knowledge, this hypothesis has not previously been evaluated. Because creatinine is a byproduct of muscle and is excreted almost exclusively in the urine, CER is a surrogate for muscle mass, regardless of serum creatinine concentrations.[9] For example, in a sample of 664 community-living individuals (mean urinary creatinine clearance, 105±32 mL/min) in Minnesota, depending on log transformation and correction for body surface area, between 37% and 62% of the variance in CER was accounted for by muscle mass determined by dual-energy x-ray absorptiometry (Andrew Rule, MD, personal communication, 2009).[21] In another study among 25 young healthy volunteers, middle arm muscle area by computed tomography accounted for 88% of the variance in CER (r=0.94, R^2=0.88).[22] In patients

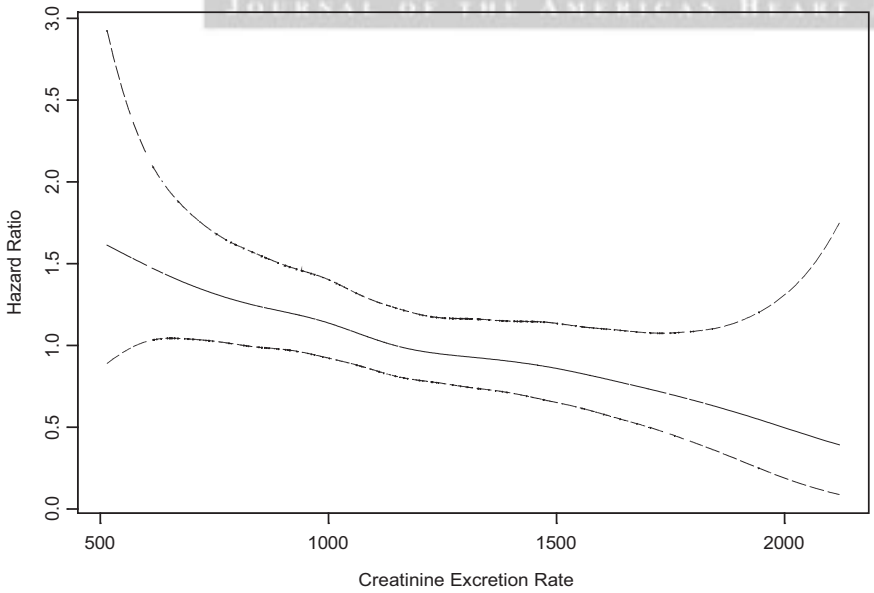


Figure 4. Natural piecewise cubic spline function demonstrating that the adjusted association of CER with mortality was fairly linear in persons with CAD. Solid line represents HRs; dotted lines, 95% CIs. The extreme 5% of the data distribution was excluded to avoid implausible extrapolation from the extremes of the data. *The spline function was adjusted for age, sex, race, BMI (lowest vs greater quintile), diabetes mellitus, hypertension, current smoking, systolic and diastolic blood pressures, total cholesterol, HDL cholesterol, eGFR, and ln(CRP).

Table 5. Adjustment for Potential Mediators on the Association of CER (per SD Decrease*) With Mortality

Model	HR (95% CI)	P
Fully adjusted model†	1.38 (1.15–1.66)	0.001
Fully adjusted model† plus METS and maximum heart rate	1.39 (1.14–1.68)	0.001
Fully adjusted model† plus LV mass index and LV ejection fraction	1.37 (1.14–1.65)	0.001
Fully adjusted model† plus history of MI, stroke, or revascularization	1.39 (1.16–1.68)	<0.001
Fully adjusted model† plus fasting glucose and insulin	1.39 (1.16–1.67)	<0.001

MI indicates myocardial infarction.

*412 mg/day represents 1-SD lesser creatinine excretion rate.

†Adjusted for age, sex, race, BMI (lowest quintile vs greater), diabetes mellitus, hypertension, current smoking, systolic and diastolic blood pressures, total cholesterol, HDL cholesterol, eGFR, and ln(CRP).

with end-stage renal disease, muscle mass measured by bioelectric impedance accounted for 85% of the variances in total (residual renal plus dialysis) creatinine clearance (r=0.92, r^2=0.85).[23] Thus, the most likely explanation for the data presented here is that low muscle mass is a strong risk factor for mortality in persons with established CAD.

The mechanisms responsible for this association, however, remain uncertain. Oterdoom and colleagues[24] recently conducted a study evaluating the association of CER with mortality among community-living Europeans predominantly without CVD and demonstrated that low CER was strongly associated with mortality, a finding similar to the data presented here. Because skeletal muscle is the main site for insulin-mediated glucose disposal, these investigators hypothesized that low CER may be associated with insulin resistance. In their study, adjustment for fasting glucose and insulin had little effect on the association of CER with mortality, results that we confirm here and can extend to populations with CAD. Oterdoom et al suggested that CER may be a marker of physical inactivity and/or protein calorie malnutrition, yet they lacked measurement of these factors and suggested that these hypotheses be studied elsewhere. Here, we observed that individuals with lower CER achieved lower METs and heart rate on the Bruce protocol; however, accounting for these measurements had virtually no effect on the association of CER with mortality. Moreover, adjustment for LV mass and ejection fraction had little effect. Therefore, although the mechanisms responsible for the association of CER with mortality remain unknown, our data suggest that low CER is more than a marker of physical fitness or of cardiovascular structure or function and might therefore provide complementary risk information above and beyond traditional markers of disease severity among persons with CAD.

It remains possible that factors other than muscle mass may also influence CER, although their contributions are thought to be smaller.[6,25,26] Among these, dietary consumption of meat (particularly undercooked meat) may be the most important. We lack diet data; thus, future studies are required to determine the relative contributions of muscle mass versus diet to CER and mortality in the secondary prevention setting. Infections, fever, trauma, and exercise may also modestly increase CER.[27–31] Because each is associated with greater CER and would more likely also be associated with greater rather than lesser mortality risk, these factors are unlikely to explain the inverse association of CER with mortality demonstrated here. These observations suggest, however, that CER may be influenced not only by muscle mass but also may reflect muscle health and function. Thus, future studies should evaluate the relative contributions of muscle quantity and quality to CER, as well as the independent associations of muscle quantity and quality to health outcomes.

It is common to statistically adjust for BMI as a surrogate for body composition in studies evaluating risk factors for CAD. Here, low CER and BMI were each independently associated with mortality. Similarly, adjustment for body weight, height, or WHR did not meaningfully attenuate the association of CER with mortality. These data suggest that adjustment for standard measures of body composition will not account for possible confounding by differences in muscle mass. If our findings are confirmed, future studies should consider measuring and adjusting for CER or other measures of muscle mass when evaluating risk factors for CAD and its consequences. Beyond minimizing confounding, such studies may also identify new pathways influencing prognosis in CAD.

To the best of our knowledge, this study is the first to evaluate the health consequences of CER in persons with CAD. CER has important advantages and disadvantages in this setting. While our CER measurements were collected in a research setting, timed urine collections in clinical practice are frequently overcollected or undercollected.[18] At the outset, it was possible that participants with a greater burden of comorbidity might have differentially undercollected their urine and that this feature may have biased our results. We took advantage of the fact that dividing CER by serum creatinine concentration calculates creatinine clearance (an estimate of GFR).[18] In a sensitivity analysis, we excluded persons whose creatinine clearance differed >30% from GFR calculated from a cystatin C–based equation, which is independent of creatinine kinetics and of the accuracy of the timed urine collections. In this analysis, we found that the association of CER with mortality was similar to that observed in the entire cohort. These data provide reassurance that inaccurate timed collections were unlikely to have led to our results. Our study has additional limitations. Although prior studies have demonstrated that CER is correlated with muscle mass, we lacked other measures of muscle mass to determine their relative strength with mortality compared with CER. Our study participants were mostly older men, and all had prevalent CAD. Results may differ in other populations.

CER also has important advantages over other measures of muscle mass. Timed urine collection and creatinine measurement are inexpensive and can be readily obtained even in resource-limited healthcare settings, where dual-energy x-ray absorptiometry scans or other measures of muscle mass may not be routinely available or feasible. With the growing burden of CAD worldwide,[32] if our findings are confirmed, CER may provide a cost-effective and readily available

mechanism to identify individuals at particularly high risk for death in the secondary prevention setting. Moreover, the American Heart Association has recommended the prescription of resistive exercise interventions for individuals with established CAD.[20,33] It is possible that CER measurement might ultimately be useful to identify individuals who might benefit most from resistive exercise interventions and/or to monitor the response to such interventions.

Conclusions

Low CER is strongly associated with mortality in outpatients with prevalent CAD. Adjustment for conventional measures of body composition did not materially attenuate this association. If confirmed, CER may represent a novel, potentially modifiable, readily available, and inexpensively measured risk factor for mortality in the secondary prevention setting.

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CLINICAL PERSPECTIVE

Recent studies have demonstrated that low body mass index is associated with mortality in individuals with coronary artery disease, whereas higher body mass index is not. Lower body mass index may reflect low muscle mass rather than low fat. When serum creatinine is in steady state, urinary creatinine excretion rate is proportional to muscle mass. In 903 outpatients with stable coronary artery disease, we collected 24-hour urine collections and evaluated the relation of creatinine excretion rate with mortality over 6 years. Individuals within the lowest tertile of creatinine excretion rate were at >2-fold mortality risk compared with the highest tertile independently of body mass index, waist-to-hip ratio, traditional coronary artery disease risk factors, inflammatory biomarkers, and kidney function. Timed urine collection may provide an inexpensive and readily available method to measure muscle mass in outpatients with coronary artery disease and to garner additional information on mortality risk independently of conventional measures of body composition or traditional coronary artery disease risk factors. Future studies are required to determine whether resistive exercise and/or nutritional interventions can improve creatinine excretion rate and whether such improvements in creatinine excretion rate are associated with demonstrable improvements in health outcomes.