

Cystatin-C and mortality in elderly persons with heart failure

Michael G. Shlipak, Mark J. Sarnak, Ronit Katz, Linda Fried, Stephen Seliger, Anne Newman, David Siscovick, and Catherine Stehman-Breen
J. Am. Coll. Cardiol. 2005;45;268-271
doi:10.1016/j.jacc.2004.09.061

This information is current as of February 9, 2010

The online version of this article, along with updated information and services, is located on the World Wide Web at:
<http://content.onlinejacc.org/cgi/content/full/45/2/268>

JACC

JOURNAL *of the* AMERICAN COLLEGE *of* CARDIOLOGY



Cystatin-C and Mortality in Elderly Persons With Heart Failure

Michael G. Shlipak, MD, MPH,* Mark J. Sarnak, MD,† Ronit Katz, PhD,‡ Linda Fried, MD, MPH,§ Stephen Seliger, MD,|| Anne Newman, MD, MPH,¶ David Siscovick, MD, MPH# Catherine Stehman-Breen, MD, MS**

San Francisco and Thousand Oaks, California; Boston, Massachusetts; Seattle, Washington; and Pittsburgh, Pennsylvania

OBJECTIVES	We sought to evaluate cystatin-C, a novel measure of renal function, as a predictor of mortality in elderly persons with heart failure (HF) and to compare it with creatinine.
BACKGROUND	Renal function is an important prognostic factor in patients with HF, but creatinine levels, which partly reflect muscle mass, may be insensitive for detecting renal insufficiency.
METHODS	A total of 279 Cardiovascular Health Study participants with prevalent HF and measures of serum cystatin-C and creatinine were followed for mortality outcomes over a median of 6.5 years.
RESULTS	Median creatinine and cystatin-C levels were 1.05 mg/dl and 1.26 mg/l. Each standard deviation increase in cystatin-C (0.35 mg/l) was associated with a 31% greater adjusted mortality risk (95% confidence interval [CI] 20% to 43%, $p < 0.001$), whereas each standard deviation increase in creatinine (0.39 mg/dl) was associated with a 17% greater adjusted mortality risk (95% CI 1% to 36%, $p = 0.04$). When both measures were combined in a single adjusted model, cystatin-C remained associated with elevated mortality risk (hazard ratio 1.60, 95% CI 1.32 to 1.94), whereas creatinine levels appeared associated with lower risk (hazard ratio 0.73, 95% CI 0.57 to 0.95).
CONCLUSIONS	Cystatin-C is a stronger predictor of mortality than creatinine in elderly persons with HF. If confirmed in future studies, this new marker of renal function could improve risk stratification in patients with HF. (J Am Coll Cardiol 2005;45:268–71) © 2005 by the American College of Cardiology Foundation

Renal dysfunction is an important adverse prognostic factor in patients with heart failure (HF) (1–3). However, the standard clinical measures of renal function—serum creatinine and creatinine-based estimates of glomerular filtration rate (GFR)—may be less correlated with actual GFR in the elderly (4). Cystatin-C, a novel serum measure of renal function (5), is a serine protease inhibitor that is released from all functioning cells. Although studies suggest that cystatin-C may better approximate GFR than creatinine (5–7), their associations with HF outcomes have not been compared. In this pilot study, we compared cystatin-C with

creatinine and estimated GFR as mortality predictors in a cohort of elderly patients with HF.

METHODS

Participants. The Cardiovascular Health Study (CHS) is a community-based, longitudinal study of adults ≥ 65 years of age at entry. The objective of the study was to evaluate risk factors for the development and progression of cardiovascular disease (8). The original cohort of 5,201 study participants was recruited between 1989 and 1990, and an additional 687 African Americans were recruited in 1992 and 1993. Follow-up interviews to identify potential clinical events were done semi-annually.

This study includes the 279 participants with prevalent HF at the 1992 to 1993 visit of CHS. An expert panel adjudicated diagnoses of HF on the basis of published criteria (9,10). The study design was approved by the Institutional Review Board of the University of Washington.

Predictors. RENAL FUNCTION. Cystatin-C was measured from samples collected at the 1992 to 1993 visit and stored at -70°C , using a BNII nephelometer (Dade Behring Inc., Deerfield, Illinois) and a particle-enhanced immunonephelometric assay (N Latex Cystatin-C, Dade Behring) (11).

Serum creatinine was measured using the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, New York), a colorimetric method. We used the simplified Modification of Diet in Renal Disease (MDRD) equation to estimate GFR from serum creatinine.

From the *General Internal Medicine Section, Veterans Affairs Medical Center, and Departments of Medicine, Epidemiology, and Biostatistics, University of California, San Francisco, California; †Division of Nephrology, Department of Medicine, Tufts-New England Medical Center, Boston, Massachusetts; ‡Collaborative Health Studies Coordinating Center, Seattle, Washington; §Renal Section, Medical Service, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania; ||Nephrology Division, University of Washington School of Medicine, Seattle, Washington; ¶Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, and Division of Geriatric Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; #Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, Washington; and **Amgen Inc., Thousand Oaks, California. Dr. Shlipak is supported by the National Heart, Lung and Blood Institute (NHLBI) Grant R01 HL073208 (National Institutes of Health [NIH], Bethesda, Maryland), RWJF Generalist Physician Faculty Scholars Award, and AFAR Paul Beeson Physician Faculty Scholars Award. The Cardiovascular Health Study (CHS) is supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, and N01-HC-15103 from the NHLBI of the NIH. A full list of participating CHS investigators and institutions can be found at <http://www.chs-nhlbi.org>.

Manuscript received July 26, 2004; revised manuscript received September 14, 2004, accepted September 28, 2004.

Abbreviations and Acronyms

CHS = Cardiovascular Health Study
CI = confidence interval
GFR = glomerular filtration rate
HF = heart failure
HR = hazard ratio
MI = myocardial infarction

COVARIATES. Candidate variables for adjustment included demographic characteristics (age, gender, race, and education level); medical history (diabetes, hypertension, smoking status, alcohol intake, body mass index, myocardial infarction [MI] [before 1992 to 1993 visit], stroke, coronary revascularization procedure, claudication, and cancer [all before 1992 to 1993 visit]; chronic obstructive pulmonary disease [from the 1989 to 1990 visit]); fibrinogen, C-reactive protein, lipid, and hemoglobin levels from the 1992 to 1993 visit; electrocardiographic findings (left ventricular hypertrophy and atrial fibrillation); and medication use (aspirin, diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, and calcium antagonists).

Outcome. The outcomes of interest were all-cause mortality. Follow-up began at the 1992 to 1993 visit and continued until June 30, 2001.

Analysis. We compared participants with HF who survived with those who died during follow-up. To evaluate measures of renal function as predictors of mortality, cystatin-C and creatinine were evaluated as continuous variables per standard deviation. We used multivariate Cox proportional hazards models that were adjusted for all the aforementioned characteristics as candidate predictors. Covariates whose entry into the model changed the coefficient of cystatin-C by 5% were retained and included in the final models for cystatin-C, creatinine, and estimated GFR. The adjustment variables were age, gender, body mass index, previous stroke, cancer, hypertension, anemia, and lipid-lowering medications. Hypertension was defined as systolic blood pressure >140 mm Hg, and anemia was defined as hemoglobin <12 g/dl for men and <13 g/dl for women. We also evaluated models that included both cystatin-C and creatinine. We did not evaluate estimated GFR as a continuous variable because of the implications of modeling ratios in regression analyses, in particular, problems with spurious correlations and the loss of scientific interpretation of the coefficient by adjusting for GFR (12).

We evaluated the association of quartiles of estimated GFR, cystatin-C, and creatinine as predictors of mortality. Creatinine quartiles were gender-specific to ensure adequate representation of men and women within each. We determined the unadjusted and multivariate-adjusted risk for quartiles 2 through 4 compared with quartile 1. Multivariate analyses were done using the covariates selected for continuous variable analyses.

We compared the adjusted mortality risk of participants with cystatin-C levels above and below the median value

after stratifying the cohort by the median creatinine and estimated GFR levels. S-Plus (release 6.1, Insightful Inc., Seattle, Washington) and SPSS statistical software (release 12.0.0, SPSS Inc., Chicago, Illinois) were used for the analyses.

RESULTS

During a median follow-up time of 6.5 years (range 0.1 to 9.1), 182 patients (65%) died, and the annual mortality risk was 11.1%. Characteristics associated with mortality include advanced age, male gender, reduced body mass index, and previous stroke (Table 1). Mean cystatin-C and creatinine levels were significantly higher and estimated GFR was lower among the participants who died during follow-up.

A change of one standard deviation in cystatin-C (0.34 mg/l) was associated with a mortality risk in unadjusted analyses (hazard ratio [HR] 1.31, 95% confidence interval [CI] 1.20 to 1.43), and this association was unchanged after multivariate adjustment (HR 1.31, 95% CI 1.17 to 1.47). A change of one standard deviation in creatinine (0.39 mg/dl) was less strongly associated with mortality risk (HR 1.23, 95% CI 1.12 to 1.36), and the point estimate was attenuated somewhat by multivariate adjustment (HR 1.17, 95% CI 1.01 to 1.36). When both measures were combined in a single adjusted model, cystatin-C remained associated with elevated mortality risk (HR 1.60, 95% CI 1.32 to 1.94), whereas creatinine levels appeared associated with lower risk

Table 1. Baseline Characteristics of Participants With Heart Failure by Survival During Follow-Up

Characteristic	Alive (n = 97)	Dead (n = 182)	p Value
Age (yrs)	74 ± 5	78 ± 6	< 0.0001
Male	37 (38%)	101 (56%)	0.01
African American	22 (23%)	28 (15%)	0.13
High school graduate	63 (65%)	106 (58%)	0.45
Body mass index (kg/m ²)	29 ± 5	27 ± 5	< 0.0001
Diabetes	25 (26%)	54 (30%)	0.49
Previous MI	40 (41%)	75 (41%)	1.00
Previous stroke	8 (8%)	36 (20%)	0.01
Previous revascularization	16 (17%)	17 (9%)	0.08
Cancer	14 (15%)	36 (22%)	0.19
Systolic blood pressure (mm Hg)	136 ± 25	136 ± 24	0.96
Diastolic blood pressure (mm Hg)	68 ± 13	68 ± 14	0.86
Total cholesterol (mg/dl)	203 ± 40	195 ± 40	0.12
LDL cholesterol (mg/dl)	122 ± 36	118 ± 33	0.34
HDL cholesterol (mg/dl)	49 ± 13	49 ± 14	0.91
CRP (mg/dl)	9.0 ± 16.8	8.4 ± 13.3	0.76
Hemoglobin (g/dl)	13.4 ± 1.5	13.2 ± 1.7	0.17
Atrial fibrillation	7 (7%)	22 (12%)	0.20
Left ventricular hypertrophy	8 (8%)	13 (14%)	0.20
Cystatin-C (mg/l)	1.18 ± 0.29	1.46 ± 0.53	< 0.0001
Creatinine (mg/dl)	1.03 ± 0.33	1.24 ± 0.48	< 0.0001
Estimated GFR (ml/min/1.73 m ²)	70 ± 18	62 ± 22	0.001

Data are presented as the mean value ± SD or number (%) of subjects.

CRP = C-reactive protein; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.

Table 2. Quartiles of Renal Function and Mortality Risk in Elderly Patients With Heart Failure

	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Cystatin-C				
Range	≤1.03	1.04–1.26	1.27–1.55	≥1.56
n	69	71	70	69
Annual risk	7%	10%	12%	19%
Unadjusted HR	1.00	1.49 (0.94–2.37)	1.89 (1.21–2.96)	3.35 (2.17–5.17)
Adjusted HR*	1.00	1.04 (0.64–1.70)	1.18 (0.70–1.99)	2.15 (1.30–3.54)
Creatinine				
Range in women	0.45–0.75	0.85	0.95–1.05	1.15–4.05
Range in men	0.75–0.95	1.05–1.25	1.35–1.45	1.55–3.05
n	77	70	54	78
Annual risk	9%	11%	10%	16%
Unadjusted HR	1.00	1.32 (0.87–2.00)	1.19 (0.75–1.89)	2.01 (1.36–2.98)
Adjusted HR*	1.00	0.97 (0.61–1.54)	1.01 (0.62–1.64)	1.38 (0.88–2.16)
Estimated GFR				
Range	>80.96	61.80–80.96	49.28–61.79	≤49.27
n	70	69	71	69
Annual risk	7%	12%	10%	17%
Unadjusted HR	1.00	1.64 (1.05–2.55)	1.37 (0.87–2.14)	2.67 (1.75–4.09)
Adjusted HR*	1.00	1.20 (0.74–1.95)	0.77 (0.47–1.26)	1.62 (1.01–2.59)

*Adjusted for age, gender, body mass index, previous stroke, cancer, hypertension, anemia, and lipid-lowering medication.
GFR = glomerular filtration rate; HR = hazard ratio.

(HR 0.73, 95% CI 0.57 to 0.95). However, we cannot exclude colinearity as an explanation for this finding, as the correlation of the two measures was high ($r = 0.80$).

After multivariate adjustment, the highest quartile of cystatin-C (>1.55 mg/l) was associated with a two-fold mortality risk, whereas the lower three quartiles had similar risk (Table 2). We repeated the analyses with the inclusion of all candidate covariates and found that the results were essentially unchanged: HRs of 1.00 and 0.92 (95% CI 0.51 to 1.69), 1.37 (95% CI 0.70 to 2.68), and 2.16 (95% CI 1.17 to 4.00) for quartiles 1 through 4. Although the highest quartile of creatinine had elevated mortality risk on unadjusted analysis, this association was not significant on adjusted analysis. After multivariate adjustment, the highest quartile of estimated GFR was associated with a 60% greater mortality risk than the lowest quartile (Table 2).

We evaluated the association of cystatin-C levels above and below the median value (1.26 mg/l) with mortality after stratifying by the median creatinine (1.05 mg/dl) and estimated GFR levels (61 ml/min/1.73 m²) (Fig. 1). Participants with cystatin-C levels above the median value were at similarly elevated mortality risk, regardless of whether their creatinine or estimated GFR levels were above or below the median value.

DISCUSSION

Cystatin-C was an independent predictor of mortality in elderly persons with HF. Persons with cystatin-C levels in the highest quartile (>1.55 mg/l) had a two-fold adjusted mortality risk compared with those in the lowest quartile. Although creatinine levels were associated with mortality in a linear model, the association of cystatin-C with mortality was greater in magnitude and persisted even after adjustment for creatinine. This novel measure of renal function

could potentially improve the risk stratification of elderly patients with HF.

Previous studies have found that renal dysfunction, measured by creatinine or estimated GFR, is a strong predictor of mortality in the setting of HF (1–3). Because creatinine levels are influenced heavily by muscle mass, estimated GFR is recommended by the National Kidney Foundation as the appropriate renal function measure for clinicians (13). However, estimates of GFR may not be optimal in persons with normal creatinine levels (14). Cystatin-C may overcome some of the limitations of creatinine and estimated GFR, as

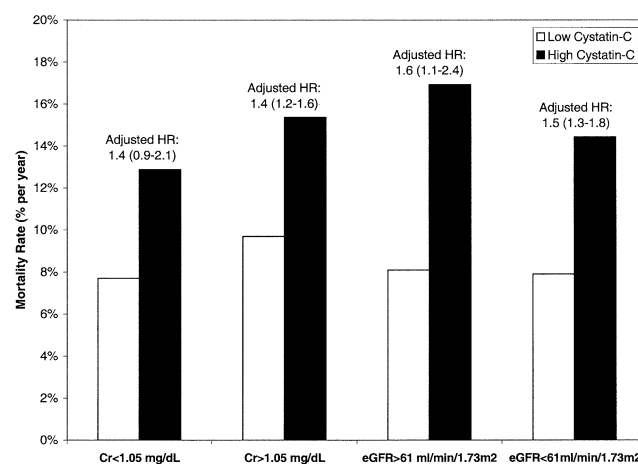


Figure 1. Association of cystatin-C levels with mortality in elderly persons with heart failure, stratified by creatinine (Cr) and estimated glomerular filtration rate (eGFR) levels. The figure displays the annual mortality risk for participants with cystatin-C levels above (high) or below (low) the median of 1.26 mg/l. The adjusted hazard ratios (HR) compare high versus low cystatin-C levels among subgroups of participants with high creatinine (above median value of 1.05 mg/dl) or low creatinine (<1.05 mg/dl), as well as by high eGFR (>61 ml/min/1.73 m²) or low eGFR (<61 ml/min/1.73 m²).

it does not appear to be dependent on age, gender, or body mass.

Study limitations. This study has certain important limitations. The small sample size of participants with HF limited the power to detect differences across the lower quartiles of each renal function measure or to conduct subgroup analyses by gender and race. This is a sample of elderly subjects with HF, so we do not know whether cystatin-C would have advantages over creatinine in younger patients or those with different diagnoses. In addition, although we presume that the association of cystatin-C with mortality is caused by its correlation with GFR, we cannot exclude the possibility that circulating cystatin-C levels either have directly harmful effects or reflect another pathologic process distinct from renal function.

Conclusions. Independent of both creatinine and traditional risk factors, cystatin-C is a strong predictor of mortality in persons with HF. Further study will be needed to confirm this finding and to determine whether measurement of cystatin-C would have clinical benefits in the care of elderly patients with HF.

Reprint requests and correspondence: Dr. Michael G. Shlipak, General Internal Medicine Section (111A-1), Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, California 94121. E-mail: shlip@itsa.ucsf.edu.

REFERENCES

1. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001;38:955–62.
2. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000;35:681–9.
3. Shlipak MG, Smith GL, Rathore SS, Massie BM, Krumholz HM. Renal function, digoxin therapy and heart failure outcomes: evidence from the Digoxin Intervention Group trial. *J Am Soc Nephrol* 2004;15:2195–203.
4. Lamb EJ, O’Riordan SE, Webb MC, Newman DJ. Serum cystatin C may be a better marker of renal impairment than creatinine. *J Am Geriatr Soc* 2003;51:1674–5.
5. Fliser D, Ritz E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am J Kidney Dis* 2001;37:79–83.
6. 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;47:312–8.
7. 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;101:875–81.
8. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;1:263–76.
9. Psaty BM, Kuller LH, Bild D, et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. *Ann Epidemiol* 1995;5:270–7.
10. Gottdiener JS, McClelland RL, Marshall R, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002;137:631–9.
11. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. *Scand J Clin Lab Invest* 1999;59:1–8.
12. Kronmal RA. Spurious correlation and the fallacy of the ratio standard revisited. *J Royal Stat Soc A* 1993;156:379–92.
13. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Kidney Disease Outcome Quality Initiative*. *Am J Kidney Dis* 2002; 39:S1–246.
14. Verhave JC, Gansevoort RT, Hillege HL, De Zeeuw D, Curhan GC, De Jong PE. Drawbacks of the use of indirect estimates of renal function to evaluate the effect of risk factors on renal function. *J Am Soc Nephrol* 2004;15:1316–22.

Cystatin-C and mortality in elderly persons with heart failure

Michael G. Shlipak, Mark J. Sarnak, Ronit Katz, Linda Fried, Stephen Seliger, Anne Newman, David Siscovick, and Catherine Stehman-Breen

J. Am. Coll. Cardiol. 2005;45:268-271

doi:10.1016/j.jacc.2004.09.061

This information is current as of February 9, 2010

Updated Information & Services	including high-resolution figures, can be found at: http://content.onlinejacc.org/cgi/content/full/45/2/268
References	This article cites 13 articles, 5 of which you can access for free at: http://content.onlinejacc.org/cgi/content/full/45/2/268#BIBL
Citations	This article has been cited by 12 HighWire-hosted articles: http://content.onlinejacc.org/cgi/content/full/45/2/268#otherarticles
Rights & Permissions	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://content.onlinejacc.org/misc/permissions.dtl
Reprints	Information about ordering reprints can be found online: http://content.onlinejacc.org/misc/reprints.dtl

REFERENCES

1. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *J Am Coll Cardiol* 2004; 43:900–21.
2. Kessler KM. All opinions are not equal (letter). *Circulation* 2003;107:2979–86.

REPLY

I appreciate Dr. Kessler's interest in our guidelines (1) and his thoughtful comments about the importance of data to support evidence-based clinical recommendations. This is precisely why the expert panel assigned a class and level of evidence to express the strength of the recommendation and the amount of data to support it. Although I agree that recommendations for drug interventions, such as hormone therapy, should be supported by randomized controlled trials, I do not agree that basic lifestyle recommendations such as not smoking, engaging in regular physical activity, eating a primarily plant-based diet, and maintaining a healthy weight, require randomized controlled trials to be given our strongest recommendation for clinical practice. As noted, such research may not be feasible or ethical. Moreover, a class I recommendation has not historically precluded further research.

Dr. Geoffrey Rose, a founding father of modern cardiovascular epidemiology, established the principle that randomized controlled trials are not necessary for interventions that restore us to our evolutionary norms. Given the burgeoning epidemic of obesity and the well-documented adverse consequences of smoking in our society, I hope Dr. Kessler would agree that interventions to restore individuals to a heart-healthy lifestyle should be a top priority for clinical practice and for public health.

***Lori Mosca, MD, MPH, PhD**

*Medicine/Cardiology
Columbia University
622 West 168th Street
PH 10-203B
New York, NY 10032
E-mail: ljm10@columbia.edu

doi:10.1016/j.jacc.2004.12.006

REFERENCE

1. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *J Am Coll Cardiol* 2004; 45:900–21.

CORRECTION

Shlipak MG, Katz R, Fried LF, Swords Jenny N, Stehman-Breen CO, Newman AB, Siscovick D, Psaty BM, Sarnak MJ. Cystatin-C and Mortality in Elderly Persons With Heart Failure. *J Am Coll Cardiol* 2004;45:268–71. As per the authors, the author group was incorrectly printed. The correct author list and their affiliations are:

Michael G. Shlipak, MD, MPH,* Ronit Katz, PhD,† Linda F. Fried, MD, MPH,‡ Nancy Swords Jenny, MD,§ Catherine O. Stehman-Breen, MD, MS,|| Anne B. Newman, MD, MPH,¶ David Siscovick, MD, MPH,# Bruce M. Psaty, MD, PhD,# Mark J. Sarnak, MD**

From the *General Internal Medicine Section, Veterans Affairs Medical Center, and Departments of Medicine, Epidemiology, and Biostatistics, University of California, San Francisco, California; †Collaborative Health Studies Coordinating Center, Seattle, Washington; ‡Renal Section, Medical Service, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania; §Department of Pathology, College of Medicine, University of Vermont, Burlington, Vermont; ||Amgen Inc., Thousand Oaks, California; ¶Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, and Division of Geriatric Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; #Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, Washington; and the **Division of Nephrology, Department of Medicine, Tufts-New England Medical Center, Boston, Massachusetts.

doi:10.1016/j.jacc.2005.01.007