# Association between Renal Insufficiency and Inducible Ischemia in Patients with Coronary Artery Disease: The Heart and Soul Study

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*Abstract.* Chronic renal insufficiency (CRI) is a predictor of stroke, cardiovascular, and all-cause mortality, but the mechanisms responsible for these associations are unclear. Whether CRI was associated with severity of coronary artery disease (CAD) as measured by exercise stress echocardiography among outpatients with stable CAD was evaluated. This study is a cross-sectional analysis of the Heart and Soul study, a prospective cohort of patients with known CAD. Renal function was assessed by 24-h urine collection, and CRI was defined as measured creatinine clearance ≤60 ml/min. Exercise stress echocardiography was used to identify inducible ischemia, defined as any wall motion abnormality seen at stress but not at rest. Logistic regression was used to evaluate the association of CRI with exercise-induced ischemia after adjustment for cardiovascular risk factors. Participants with CRI composed 97 (23%) of the 431 participants and were characterized by older age, worse CAD, lower ejection fraction, greater left ventricular mass and higher C-reactive protein values. The prevalence of exercise-induced ischemia was also substantially greater in the participants with CRI (42% *versus* 23%; odds ratio [OR], 2.3; 95% confidence interval [CI], 1.4 to 3.8; $P < 0.001$). This association was minimally changed by adjustment for traditional cardiovascular risk factors and coronary disease history (OR, 2.0; 95% CI, 1.3 to 3.3; $P < 0.01$) and remained strong even after adjustment for C-reactive protein (OR, 2.3; 95% CI, 1.0 to 5.1; $P = 0.04$). CRI is strongly associated with exercise-induced ischemia in patients with CAD. The greater severity of atherosclerotic disease observed in patients with CRI may in part explain the association of CRI with increased cardiovascular risk among individuals with CAD.

Mild to moderate chronic renal insufficiency (CRI) is estimated to affect more than one fourth of people aged 65 and older in the United States (1) and is an independent predictor of stroke (2,3), cardiovascular (2–6), and all-cause mortality (2–5,7,8). In people with established coronary artery disease (CAD), CRI predicts recurrent events as strongly as other established cardiovascular risk factors such as diabetes and elevated BP (6). Whether the cardiovascular risk in the setting of CRI is due to increased atherosclerotic burden, higher risk of plaque rupture as a result of inflammation (9), or other mechanisms is unknown.

One method that can be used to determine the severity of CAD is exercise treadmill testing with stress echocardiography (10–12). To evaluate the association of CRI and inducible ischemia, we measured creatinine clearance (CrCl) and performed stress echocardiography in a cross-sectional study of 431 participants enrolled in the Heart and Soul study. We hypothesized that CRI would be associated with inducible ischemia independent of hypertension, diabetes, or other traditional cardiovascular risk factors. Because inflammatory biomarkers are known to be elevated in people with CRI, we also sought to determine whether inflammation was a mediator of this association (9).

## Materials and Methods

### *Participants*

The Heart and Soul study is a prospective cohort designed to investigate the influence of psychosocial factors on CAD progression. Methods have been described previously (13,14). Participants were recruited from outpatient clinics in the San Francisco Bay Area if they met one of the following inclusion criteria: (*1*) history of myocardial infarction, (*2*) angiographic evidence of >50% stenosis in one or more coronary vessels, (*3*) evidence of exercise-induced ischemia by treadmill or nuclear testing, (*4*) history of coronary revascularization, or (*5*) documented diagnosis of CAD by an internist or cardiologist. Participants were excluded when they were not able to walk one block or were likely to move out of the area within 3 yr. The study protocol

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was approved by the appropriate Institutional Review Boards, and all participants provided written, informed consent.

Between September 2000 and March 2002, 564 participants were enrolled. We excluded those who did not have 24-h urine collection data ($n = 7$) or who were unable to perform at least 3 min of exercise by the Bruce protocol ($n = 126$). This was done to ensure that a minimum level of exertion was attained to assess stress-induced ischemia. The study population therefore includes 431 participants.

### *Measurements*

**Primary Predictor Variable.** Presence or absence of CRI was determined by 24-h urine collection for all participants. At the intake appointment, participants were provided with a 3-L collection jug and instructed to save all urine between the end of their intake appointment and the time when a researcher recovered the urine. Participants were instructed to keep the urine collections refrigerated at all times. Research personnel arrived at the participants' home 24 h after their inception appointments to ensure accurately timed specimens. At that time, participants were asked about the time of their first and last voids. When more than 1 h had passed since their last void, participants were instructed to void at that time to complete the collection. All participants were asked whether they were able to collect all urine or whether some fraction had been inadvertently discarded. When the sample was reported to be incomplete, participants were asked to repeat the collection, and research personnel returned 24 h later to re-collect the urine. When the 24-h urine volume was <1 L, participants were asked to repeat the collection to ensure an adequately collected specimen. Similarly, when the 3-L collection jug was completely full, participants were given two new jugs and asked to repeat the collection to ensure that no urine was inadvertently discarded. When participants were unable to collect all urine for any reason or had urinary incontinence, their samples were deemed inadequate and no data were recorded for these participants. CrCl was calculated using the following formula: urine creatinine (mg/dl) * 24-h urine volume (dl)/serum creatinine (mg/dl) * 1440 (min/d). *A priori*, we defined CRI as measured CrCl of ≤60 ml/min (15).

**Secondary Predictor Variables.** Age; race; smoking status; and medical history of diabetes, hypertension, myocardial infarction, and coronary revascularization were determined by self-report. We measured weight and height and calculated body mass index (kg/m$^2$). Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. After a 12-h fast, serum samples were obtained for measurement of creatinine, total cholesterol, HDL, LDL, albumin, and hematocrit.

To explore the role of inflammation as a potential mediator of the association between CRI and ischemia, we measured C-reactive protein (CRP) in 118 participants with exercise-induced ischemia and in a random sample of 111 participants without ischemia. We used the Roche Integra assay, an enhanced immunoturbidimetric assay that uses latex particles that are coated with monoclonal anti-CRP antibodies to measure CRP with high sensitivity. The assay has been standardized against the World Health Organization reference and has been compared with the Dade nephelometric method with a correlation coefficient of 0.997. The interassay coefficient of variation is 3.2%, and the lowest detectable measurement with this assay is 0.025 mg/dl. For this analysis, we considered high CRP levels as >0.38 mg/dl, based on cut points used in previous studies (13,16).

**Outcome Variable.** The primary outcome was the presence or absence of exercise-induced ischemia (17). We performed a symptom-limited graded exercise treadmill test according to the Standard Bruce Protocol for all participants at their inception appointment. Participants were asked to walk on a treadmill beginning at a workload of 20 to 30 W and increased by 20 to 30 W every 3 min until they reached dyspnea, symptom-limited fatigue, chest discomfort, or electrocardiographic changes suggestive of ischemia. Continuous electrocardiographic monitoring with 12-lead electrocardiography was performed throughout exercise.

Doppler echocardiography just before exercise was used to obtain a complete resting two-dimensional echocardiogram, including imaging and Doppler in all standard views and subcostal imaging of the inferior vena cava. Standard two-dimensional parasternal short-axis and apical two- and four-chamber views obtained during held inspiration were planimetered using a computerized digitization system (Tom Tec Corporation, Boulder, CO) to determine left ventricular volume, ejection fraction, stroke volume, cardiac output, and mass. At peak exercise, apical two- and four-chamber views were obtained to detect the development of right or left ventricular dilation or wall motion abnormalities. We defined exercise-induced ischemia as the presence of new wall motion abnormalities not visualized on the baseline rest echocardiogram. An experienced echocardiographer who was without knowledge of electrocardiograms, renal function status, or additional diagnostic tests analyzed all echocardiograms.

### *Statistical Analyses*

Differences in baseline characteristics between participants with and without CRI were compared using $\chi^2$ tests for dichotomous variables and *t* tests (or nonparametric equivalent) for continuous variables. We used forward stepwise multivariate logistic regression to determine the independent association of CRI with exercise-induced ischemia. Certain variables were forced into the multivariate model because of their strong association with cardiovascular or renal disease in previous studies (age, diabetes, hypertension, angiotensin-converting enzyme inhibitor use, HDL, and LDL). Other candidate variables that were associated with exercise-induced ischemia at $P < 0.2$ were also retained in our multivariate models. Candidate variables included gender; race; history of congestive heart failure, myocardial infarction, angioplasty, coronary bypass surgery, angina, or smoking status; ejection fraction, left ventricular mass, body mass index, serum levels of total cholesterol, triglycerides, hematocrit, and albumin; and medical therapy with HMG-CoA reductase inhibitors, aspirin, and $\beta$ blockers. Finally, to determine whether inflammation attenuates the association between CRI and ischemia, we performed further multivariate adjustment for CRP in the subset of participants for whom CRP values were available. Analyses were performed using the Statistical Analysis Software (version 8; SAS Institute, Inc, Cary, NC).

## Results

### *Baseline Characteristics*

Among the 431 participants, 97 (23%) had CRI. Of these, 68 participants had CrCl between 40 and 60 ml/min, 27 participants had CrCl between 20 and 40 ml/min, and two participants had CrCl <20 ml/min. Compared with participants who had normal renal function, those who had CRI were older and more often had a history of myocardial infarction or coronary

artery bypass surgery (Table 1). They had a lower mean ejection fraction and greater left ventricular mass. Participants with CRI also had lower body mass index, hematocrit, and albumin levels and higher CRP measurements. They were more likely to be taking statins and less likely to be taking aspirin.

### *Association of Renal Insufficiency and Exercise-Induced Ischemia*

CRI was strongly associated with exercise-induced ischemia (Figure 1, Table 2). Among participants with CRI, 42% had inducible ischemia, compared with 23% of those with normal renal function (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.4 to 3.8; $P < 0.01$). After multivariate adjustment, CRI remained strongly associated with exercise-induced ischemia (OR, 2.0; 95% CI, 1.2 to 3.3; $P = 0.01$). After further adjustment for CRP, the adjusted association was essentially unchanged (OR, 2.3; 95% CI, 1.0 to 5.1).

### *Test for Interaction*

In stratified analysis, we observed similar associations between CRI and inducible ischemia in participants with and without diabetes ($P = 0.67$ for interaction). The OR for CRI as a predictor of exercise-induced ischemia was 2.7 (95% CI, 1.1 to 7.1) in participants with diabetes and 2.1 (95% CI, 1.2 to 3.7) in those without diabetes. Similarly, there was no interaction with hypertension. The odds of CRI as a predictor of ischemia was 2.3 (95% CI, 1.2 to 4.3) for participants with hypertension and 1.7 (0.6 to 4.6) in those without hypertension ($P$ 0.93 for interaction). Likewise, we did not observe any significant interactions between CRI

*Table 1.* Baseline characteristics of the 431 participants by presence of chronic renal insufficiency

| Variable | Creatinine Clearance | | *P* Value |
|---|---|---|---|
| | ≥60 ml/min ($n = 334$) | <60 ml/min ($n = 97$) | |
| Age | 67 ± 10.4 | 72 ± 9.2 | <0.001 |
| Male | 90% | 92% | 0.57 |
| Race | | | |
| white | 61% | 63% | 0.71 |
| black | 13% | 12% | 0.90 |
| other | 26% | 25% | 0.75 |
| Medical history | | | |
| hypertension | 65% | 75% | 0.07 |
| diabetes | 20% | 26% | 0.23 |
| CHF | 15% | 22% | 0.09 |
| myocardial infarction | 54% | 70% | 0.01 |
| angioplasty | 44% | 51% | 0.27 |
| CABG | 41% | 53% | 0.03 |
| angina | 61% | 68% | 0.19 |
| current smoker | 16% | 14% | 0.67 |
| LV ejection fraction | 0.63 ± 0.10 | 0.59 ± 0.11 | <0.01 |
| LV mass | 185 ± 55 | 198 ± 64 | 0.04 |
| Body mass index | 28 ± 4 | 27 ± 4 | 0.02 |
| Serum measurements | | | |
| total cholesterol | 178 ± 41 | 172 ± 39 | 0.15 |
| LDL | 103 ± 32 | 100 ± 30 | 0.48 |
| HDL | 47 ± 14 | 46 ± 16 | 0.60 |
| triglycerides | 154 ± 175 | 124 ± 60 | 0.10 |
| hematocrit | 41 ± 4 | 39 ± 4 | <0.01 |
| albumin | 4.0 ± 0.3 | 3.8 ± 0.4 | <0.01 |
| CRP levels (median) | 1.4 | 2.3 | 0.04 |
| high CRP (>0.38 mg/dl) | 19% | 29% | 0.14 |
| Medications | | | |
| ACE inhibitor or ARB | 29% | 31% | 0.76 |
| statin | 40% | 54% | 0.01 |
| aspirin | 85% | 75% | 0.03 |
| β blocker | 55% | 57% | 0.74 |

CHF, congestive heart failure; CABG, coronary artery bypass surgery; LV, left ventricular; CRP, C-reactive protein; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

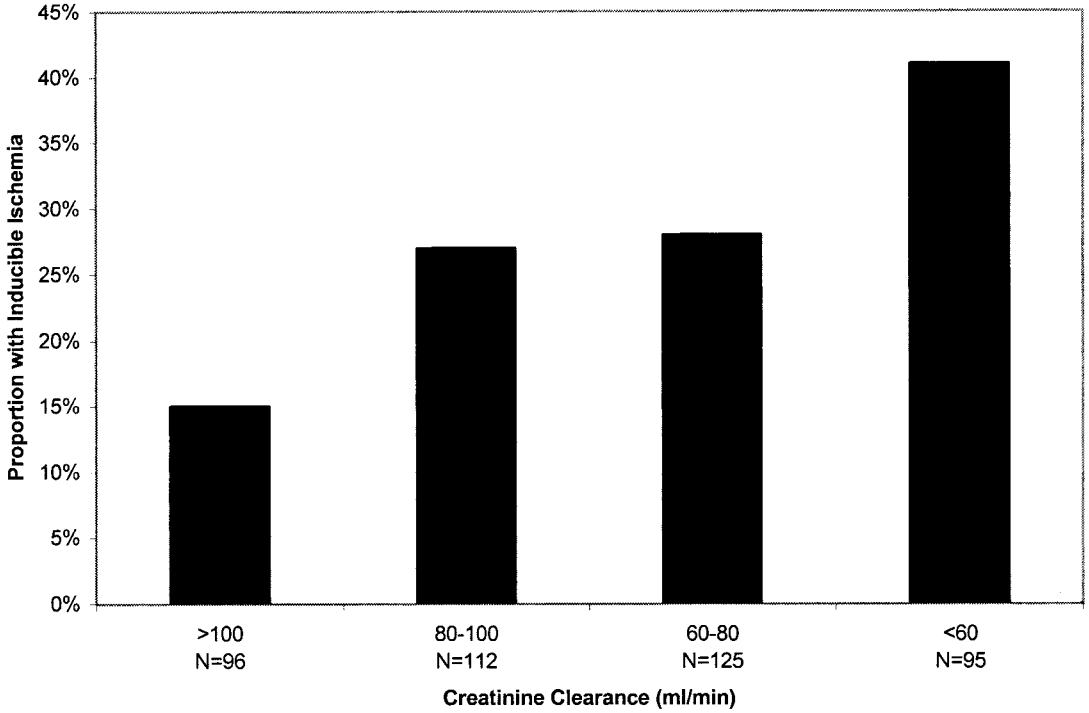


*Figure 1.* Percentage of participants with inducible ischemia by subgroup of measured creatinine clearance. The prevalence of inducible ischemia increased significantly as creatinine clearance decreased ($P < 0.001$ for trend).

*Table 2.* Univariate and multivariate association of chronic renal insufficiency with exercise-induced ischemia

| | No. with Ischemia with Normal Renal Function | No. with Ischemia with CRI | Odds Ratio | 95% CI | *P* Value |
|---|---|---|---|---|---|
| Unadjusted analysis ($n = 431$) | 79 | 39 | 2.3 | 1.4–3.8 | <0.01 |
| Adjusted analysis[a] ($n = 409$) | — | — | 2.0 | 1.2–3.3 | 0.01 |
| Adjusted analysis[a] including CRP[b] ($n = 190$) | 59 | 31 | 2.3 | 1.0–5.1 | 0.04 |

[a] Adjusted for age, diabetes, hypertension, ACE inhibitor/ARB use, history of myocardial infarction, serum HDL and LDL levels, history of angioplasty, and history of coronary bypass graft surgery.
[b] Includes 118 participants with inducible ischemia and 111 randomly selected participants without inducible ischemia.

and levels of hematocrit ($P = 0.31$ for interaction), CRI and congestive heart failure ($P = 0.30$ for interaction), or CRI and elevated CRP ($P = 0.25$ for interaction).

## Discussion

Our analysis demonstrates that CRI is strongly associated with exercise-induced ischemia as assessed by stress echocardiography in participants with established CAD. The association was substantial and independent of other known risk factors such as hypertension or diabetes. As stress echocardiograms have been shown to predict CAD risk and atherosclerotic burden (10–12), our findings indicate that even among participants with known CAD, the presence of CRI is associated with increased atherosclerosis. These results add to the growing body of evidence suggesting that CRI predicts high cardiovascular risk in individuals with established CAD (4–6).

The increased cardiovascular risk for individuals with CRI was explained only in part by their increased prevalence and severity of diabetes and hypertension. Other renal-specific mechanisms likely contribute to the increased risk and are poorly understood. The proinflammatory state described in CRI has been proposed as one potential mediator (9). The current analysis, along with previous work from our group (9), establishes that CRP levels are elevated in individuals with CRI. However, CRP did not seem to substantially mediate the association of CRI with inducible ischemia in this study. Multiple other factors have also been proposed, including elevated levels of fibrinogen (9) and homocysteine (18), altered lipid metabolism (19–21), and markers of increased coagulability and fibrinolysis (9). Their relative contributions should be addressed in future studies.

The findings of our study indicate that individuals with stable CAD and CRI may benefit from more aggressive car-

diovascular screening and prevention. We found that individuals at particularly high risk can be identified with stress echocardiography, a noninvasive test readily available at most medical centers. Individuals with inducible ischemia might benefit from more intensive medical therapy for established and modifiable cardiovascular risk factors. The importance of such therapy is reinforced by multiple previous studies that have shown that use of cardioprotective medications is lower in individuals with CRI than in those with normal renal function (7,22).

A particular strength of our study is the use of a direct measure of renal function with 24-h urine collections. Most previous studies have relied on one-time measurements of serum creatinine to estimate CrCl. We believe that our study therefore more accurately quantifies the association of CRI with inducible ischemia and CAD risk. However, several limitations should also be considered in interpreting our results. Although our findings demonstrate that CRI is associated with exercise-induced ischemia, we cannot determine the direction of the association because of the cross-sectional design. In addition, although our hypothesis is that CRI leads to accelerated atherosclerosis and coronary disease instability, it is possible that an unmeasured risk factor was a predictor of both CRI and exercise-induced ischemia. However, to explain the twofold odds of the observed association, any lurking confounder would need to be highly prevalent in the cohort and strongly associated with both CRI and inducible ischemia. Furthermore, our study participants were mostly men, and our results therefore may not be generalizable to women. Finally, our study did not include anatomic measures of coronary disease; thus, we were not able to determine whether CRI is associated with ischemia because of greater anatomic disease burden or through other mechanisms (23,24,25).

In summary, we found that among individuals with CAD, the presence of CRI is strongly associated with exercise-induced ischemia. We believe that all patients with CRI merit aggressive cardiovascular risk factor management. Those with exercise-induced ischemia are likely at highest risk and might be considered for further diagnostic investigation. Finally, although we found individuals with CRI to have higher CRP values, the association of CRI with inducible ischemia did not seem to be mediated solely through inflammation.

## References


1. Clase CM, Garg AX, Kiberd BA: Prevalence of low glomerular filtration in nondiabetic Americans: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol* 13: 1338–1349, 2002
2. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB: Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 137: 555–562, 2002
3. Shulman NB, Ford CE, Hall WD, et al: Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension* 13[5 Suppl]: I80–I93, 1989
4. Ruilope LM, Salvetti A, Jamerson K, et al: Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol* 12: 218–225, 2001
5. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134: 629–636, 2001
6. Muntner P, He J, Hamm L, Loria C, Whelton PK: Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 13: 745–753, 2002
7. Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Furberg CD; Heart and Estrogen/progestin Replacement Study (HERS) Investigators: Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J Am Coll Cardiol* 38: 705–711, 2001
8. Fried LF, Shlipak MG, Crump C, Bleyer AJ, Gottdiener JS, Kronmal RA, Kuller LH, Newman AB: Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol* 41: 1364–1372, 2003
9. Wolfe RA, Port FK, Webb RL, et al: Excerpts from the United States Renal Data System, 1998. Annual data report: V. Patient mortality and survival. *Am J Kidney Dis* 32[Suppl 1]: 269–280, 1998
10. Ridker PM, Hennekens CH, Buring JE, Rifai N: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 342: 836–843, 2000
11. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM: Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 107: 87–92, 2003
12. Cortigiani L, Eugenio P, Coletta C, Chiarella F, Mathias W, Gandolfo N, De Alcantara M, Mazzoni V, Gensini GF, Landi P; Echo Persantine International Cooperative (EPIC) Study Group; Echo Dobutamine International Cooperative (EDIC) Study Group: Safety, feasibility, and prognostic implications of pharmacologic stress echocardiography in 1482 patients evaluated in an ambulatory setting. *Am Heart J* 141: 621–629, 2001
13. Olmos LI, Dekik H, Gordon R, Dunn JK, Verani MS, Quinones MA, Zoghbi WA: Long-term prognostic value of exercise echocardiography compared with exercise 201Tl ECG, and clinical variables in patients evaluated for coronary artery disease. *Circulation* 98: 2679–2686, 1998
14. Arruda AM, McCully RB, Oh JK, Mahoney DW, Seward JB, Pellikka PA: Prognostic value of exercise echocardiography in patients after coronary artery bypass surgery. *Am J Cardiol* 87: 1069–1073, 2001
15. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis* 39: S1–S246, 2002
16. Chauveau P, Chadefaux B, Coude M, et al: Hyperhomocysteinemia, a risk factor for atherosclerosis in chronic uremic patients. *Kidney Int* 43: S72–S77, 1993
17. Appel G: Lipid abnormalities in renal disease. *Kidney Int* 39: 169–183, 1991
18. Attman P, Samuelsson O, Alaupovic P: Lipoprotein metabolism and renal failure. *Am J Kidney Dis* 21: 573–592, 1993

19. Kimak E, Solski J, Janicka L, Zagojska M: Lipid and lipoprotein ratios as risk factors of atherosclerosis in patients with chronic renal insufficiency. *Int Urol Nephrol* 31: 263–267, 1999
20. Tonelli M, Bohm C, Pandeya S, Gill J, Levin A, Kiberd BA: Cardiac risk factors and the use of cardioprotective medications in patients with chronic renal insufficiency. *Am J Kidney Dis* 37: 484–489, 2001
21. Rifai N, Ridker PM: Proposed cardiovascular risk assessment algorithm using high sensitivity C-reactive protein and lipid screening. *Clin Chem* 47: 28–30, 2001
22. Beattie MS, Shlipak MG, Liu H, Browner WS, Schiller NB, Whooley MA: CRP and ischemia in users and nonusers of beta blockers and statins: Data from The Heart and Soul Study. *Circulation* 107: 245–250, 2003