Association of High Serum Creatinine and Anemia Increases the Risk of Coronary Events: Results from the Prospective Community-Based Atherosclerosis Risk in Communities (ARIC) Study

CLAUDINE T. JURKOVITZ, JEROME L. ABRAMSON, L. VIOLA VACCARINO, WILLIAM S. WEINTRAUB, and WILLIAM M. MCCLELLAN
Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia

Abstract. Coronary heart disease (CHD) is a major cause of morbidity and mortality in patients with chronic kidney disease or anemia. The purpose of this study was to examine whether the association between renal function and risk of CHD is modified by hemoglobin (Hgb) status. Analyses were based on data from the Atherosclerosis Risk in Communities study, a community-based study of risk factors for CHD in middle-aged people. People with known CHD at baseline were excluded from the analysis. Participants were followed for 9 yr for the occurrence of CHD. Anemia was defined as Hgb <13 g/dl in men and <12 g/dl in women. Cox proportional hazards models were used to assess the relative risk (RR) of CHD occurrence according to Hgb status, after adjusting for other risk factors (demographics, lipids, diabetes, hypertension, smoking, body mass index, and carotid intima-media thickness). A total of 13,329 participants were included. The interaction between Hgb concentration and serum creatinine (Scr) was significant (P = 0.02). Among people with anemia, a Scr ≥1.2 mg/dl in women or ≥1.5 mg/dl in men was associated with a higher risk of CHD (RR, 2.74; 95% confidence interval, 1.42 to 5.28) than those with normal Scr. In contrast, among those without anemia, this association was not noted (RR, 1.20; 95% confidence interval, 0.86 to 1.67). In conclusion, this study indicates that high Scr is associated with almost a threefold risk of CHD among middle-aged people with anemia, whereas no increased risk is found in people with high Scr in the absence of anemia.

Cardiovascular disease (CVD) mortality rates in ESRD are approximately 15 times higher than in the general population (1). Many studies examining the association between ESRD and cardiovascular mortality (2,3) have found that ESRD is an independent predictor of cardiovascular death. However, it is unclear whether moderate renal insufficiency is also associated with cardiovascular events. Previous studies conducted in patients at high risk of CVD have suggested that mild renal insufficiency may be an independent risk factor for cardiovascular events (4–8). However, in analyses of population-based cohorts (9,10), there was no independent association between moderate renal insufficiency and cardiovascular mortality or nonfatal cardiovascular events after adjustment for traditional risk factors.

Anemia is a frequent complication of chronic kidney disease (CKD) and is primarily due to failure of erythropoietin production to respond to decreased hemoglobin (Hgb) concentration (11,12). In chronic anemia, long-lasting flow/volume overload and increased cardiac work lead to progressive cardiac enlargement and left ventricular hypertrophy (13). The risk of coronary heart disease (CHD) increases when the anemia is not treated, and recent studies have indicated that anemia in patients with CKD may predispose to ischemic heart disease, heart failure, and premature death (14–16). Therefore, the risk of CHD may be distinctly higher in people with renal insufficiency and concomitant anemia, when compared with people with renal insufficiency but without anemia and with people with normal renal function. We examined this hypothesis in the Atherosclerosis Risk in Communities (ARIC) study, a large population-based cohort study of risk factors for CVD. We specifically hypothesized that the association between renal function and CHD incidence is modified by anemia status with highest risk being observed in people with renal insufficiency and concomitant anemia.

Materials and Methods
Population Sample

The sample population for this study was drawn from the ARIC Study cohort, which was composed of population-based samples from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. The design of ARIC has been published previously (17). In brief, 15,792 men and women, aged 45 to 64 at recruitment, were enrolled from 1986 to 1989 and followed for up to 9 yr for the occurrence of cardiovascular events. To focus on first
coronary events as the initial manifestation of CHD, we excluded from our analyses 1168 subjects who had either prevalent CHD (defined by history of physician-diagnosed myocardial infarction [MI], previous MI by electrocardiogram, or previous coronary artery bypass surgery or coronary angioplasty) or missing data on prevalent CHD. We further excluded 1295 participants with missing serum creatinine or Hgb levels or missing data on any of the control variables at baseline. This left 13,329 subjects in the cohort for our analysis.

Variables

Serum creatinine (Scr) was measured at baseline using a modified kinetic Jaffe method on frozen serum samples in the ARIC central laboratory as described previously (17,18). Subjects were stratified according to two levels of Scr, normal or high (≥1.2 mg/dl for women and ≥1.5 mg/dl for men). These cut-points correspond to the gender-specific 95th percentiles for Scr levels in this population. Moreover, these cut-points were described as being equivalent to an inulin creatinine clearance of < 60 ml/min (19).

Hgb was determined in hospital-based independent laboratories within 24 h after venipuncture at 4°C, using automated particle counters (Coulter Diagnostics, Hialeah, FL): in Jackson, Coulter S+IV, calibration S-Cal; in Washington County, at two laboratories, both using Coulter S+IV, calibration S-Cal; in Minneapolis, at one laboratory using two different counters, Coulter S+III and Coulter S+IV, calibration S-Cal; in Forsyth County, Technicon H-6000 (Technicon Corporation, Tarrytown, NY), calibration Fisher ("Copmutrol") (20,21). Anemia was defined as Hgb <12 g/dl in women and <13 g/dl in men, according to the World Health Organization criteria (22).

Other baseline characteristics considered in this analysis included patient demographics (age, race, gender, education level [<12 yr of education, ≥12 yr]), medical history and CHD risk factors (hypertension, diabetes, current smoking, body mass index, LDL and HDL cholesterol, insulin, fibrinogen), and carotid intima-media thickness (IMT) as a measure of subclinical CHD. Blood tests for lipids and fibrinogen were measured in the ARIC central laboratories as described previously (17,23). Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, or treatment for hypertension in the last 2 wk. Diabetes was defined as a blood glucose ≥200 mg/dl for a casual sample or blood glucose ≥126 mg/dl if fasting, or a known personal history of diabetes or use of medications for diabetes in the last 2 wk. Carotid IMT was measured by B-mode ultrasonography (17).

Ascertainment of CHD Incidence and Mortality

CHD was defined by definite or probable MI or definite CHD death. ARIC participants were contacted annually by telephone for identification of all hospitalizations and deaths, and discharge summaries and hospital records were reviewed for coronary events by trained abstractors. Deaths were identified from death certificates, and out-of-hospital fatal CHD events were investigated by interviewing one or more next of kin or other informants, and by the completion of a questionnaire by the patient’s physician. Autopsy reports were also obtained. All CHD events were validated by a committee of physicians using standardized criteria (17,24,25).

Statistical Analyses

ANOVA for continuous variables and χ² for categorical variables were used to compare baseline data according to Scr categories. Crude incidence density rates for CHD outcomes were calculated for each level of Scr, in the whole sample and according to presence or absence of anemia. Cox proportional-hazards regression was used to derive adjusted estimates for the association between renal function and CHD after controlling for all of the baseline covariates. Time to first CHD event was the dependent variable and the dichotomous Scr variable, the dichotomous Hgb variable, and all of the baseline covariates were the independent variables. The interaction between renal function and anemia status was tested by introducing a cross-product of the two dichotomous variables in the model. Because this interaction was statistically significant, we performed separate Cox proportional-hazards regression for the “anemia” and “normal Hgb” subgroups to examine the association between renal function and CHD after adjusting for the baseline covariates within each Hgb status subgroup. All of the tests were two-sided, and P < 0.05 was considered significant. Data were analyzed using the Statistical Analysis System version 8.2 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Because in women, a Scr of 1.2 mg/dl corresponds to both the 90th and 95th percentiles in this population, renal insufficiency (Scr ≥1.2 mg/dl for women and ≥1.5 mg/dl for men) was present in 9.5% of the sample population (Table 1). The mean age of the cohort was 54 yr; 43.3% of the subjects were men, 25.4% were black, and 26.0% were smokers. The prevalence of anemia was 9.3%. Because of the large sample size, most of the differences between strata of Scr for each covariate were significant (Table 1). Compared with subjects with normal Scr, people in the highest Scr category were older, less likely to be men (33.7% versus 44.3%), more likely to be black (43.0% versus 23.6%), more likely to have lower education (28.9% versus 21.9%), more likely to have diabetes (15.6% versus 9.7%), more likely to have high BP (50.8% versus 30.7%), more likely to have high LDL cholesterol (29.1% versus 25.0%), and more likely to be anemic (15.1% versus 8.7%). The mean and median Scr values were 1.09 and 1.10 mg/dl, respectively, within the normal Hgb group and 1.17 and 8.7%) the normal Hgb group was 2.8 mg/dl, with 5% of the subjects having Scr between 1.4 and 2.8 mg/dl.

Among the participants who were excluded because of missing values (n = 1,295), 47.3% were black, 43.4% were male, and 30.5% had <12 yr of education. These participants also tended to be sicker than the ones included in our final cohort; 12.1% had high Scr and 10.9% had anemia, 49.8% had hypertension, 23.4% had diabetes, and 47.3% had low HDL.

Outcomes

Mean and median follow-up times were 7.1 and 7.2 yr, respectively. There were 405 CHD events, with 44 occurring among subjects with anemia and 361 in subjects without anemia (Table 2). People with high Scr had a higher rate of events whether they were anemic or not (Table 2, Figure 1). However, the rate ratio comparing the rate of events between the high and normal Scr groups was much higher in patients with anemia.
Table 1. Baseline characteristics of the study population stratified by levels of serum creatinine

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All (n = 13,329)</th>
<th>Serum creatinine&lt;sup&gt;b&lt;/sup&gt;</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal (n = 12,060)</td>
<td>90.5%</td>
<td>High (n = 1269)</td>
</tr>
<tr>
<td>mean age (yr)</td>
<td>54.0</td>
<td>53.9</td>
<td>55.4</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>43.3</td>
<td>44.3</td>
<td>33.7</td>
<td></td>
</tr>
<tr>
<td>black</td>
<td>25.4</td>
<td>23.6</td>
<td>43.0</td>
<td></td>
</tr>
<tr>
<td>education (% &lt;12 yr education)</td>
<td>22.6</td>
<td>21.9</td>
<td>28.9</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Number of CHD events, person-years of follow-up, and rate of events according to serum creatinine categories, in the entire sample and stratified by anemia status<sup>a</sup>

<table>
<thead>
<tr>
<th>Serum creatinine&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Total sample</th>
<th>Normal Hgb</th>
<th>Anemia&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td>Person-years</td>
<td>Rate&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No. of events</td>
</tr>
<tr>
<td>Normal</td>
<td>342</td>
<td>85,851.8</td>
<td>3.98</td>
</tr>
<tr>
<td>High</td>
<td>63</td>
<td>8674.7</td>
<td>7.26</td>
</tr>
<tr>
<td>Total</td>
<td>405</td>
<td>94,526.5</td>
<td>4.28</td>
</tr>
</tbody>
</table>

a CHD, coronary heart disease; Hgb, hemoglobin.
b Anemia is defined as Hgb <12 g/dl for women and <13 g/dl for men.
c Rate per 1000 person-years.
d Serum creatinine is categorized into two levels: normal (<1.2 mg/dl for women or <1.5 mg/dl for men) and high (≥1.2 mg/dl for women or ≥1.5 mg/dl for men).

(18.45/3.05 = 6.05) than in patients without anemia (5.48/4.07 = 1.35). Because the high rate of CHD events among people with high Scr and anemia may be carried only by the people with the highest Scr levels, we examined more closely the distribution of events in the anemic group and found that only four CHD events were experienced by the 18 subjects who had a Scr ≥2.8 mg/dl. The value of 2.8 was chosen because it is the highest Scr level in the non-anemic group. The highest Scr level for which there was an event in the anemic group was 7.8 mg/dl (Figure 2).
value of 2.8 to obtain a similar Scr distribution between the

Figure 1. Incidence of coronary heart disease (CHD) events according to serum creatinine (Scr) categories in the entire sample and stratified by hemoglobin (Hgb) levels status. Anemia is defined as Hgb <12 g/dl for women and <13 g/dl for men. Scr is categorized into two levels: normal (<1.2 mg/dl for women or <1.5 mg/dl for men) and high (≥1.2 mg/dl for women or ≥1.5 mg/dl for men).

In subjects with normal Hgb, multivariate proportional hazards regression analysis confirmed the lack of significant association between renal insufficiency and CHD (relative risk [RR], 1.20; 95% confidence interval [CI], 0.86 to 1.67). In contrast, in anemic subjects, high Scr was associated with an increased risk of CHD events 174% higher than in participants with normal Scr (RR, 2.74; 95% CI, 1.42 to 5.28; Table 3). The interaction between Hgb concentration and Scr level was significant (P = 0.02).

Because the interaction may not be a true interaction but may only be due to the high rate of events in the patients with very high creatinine levels, we limited the data set, in further analysis, to patients with Scr ≤2.8 mg/dl. We chose a cutoff value of 2.8 to obtain a similar Scr distribution between the anemic and non-anemic groups. As expected, the adjusted risk associated with high Scr did not change in the non-anemic group (RR, 1.20; 95% CI, 0.86 to 1.67). Although the number of events decreased from 44 to 40 in the anemic group, the results of the multivariate regression analysis were very similar to the results obtained using the full data set. The adjusted risk associated with high Scr was still significant (RR, 2.66; 95% CI, 1.34 to 5.30) as was the interaction between Hgb and Scr (P = 0.04).

Because anemia is frequent in diseases characterized by a high inflammation status and because more and more evidence suggests that inflammation is related to CHD (26,27), we added fibrinogen in the model to control for inflammation and found that the interaction between Scr and Hgb remained significant (P = 0.04) as did the RR associated with high Scr in the anemic group (RR, 2.42; 95% CI, 1.25 to 4.70).

Finally, we examined the interaction between Scr and Hgb separately in men and women. It remained significant in women (P = 0.03) but not in men. In women, the RR associated with high Scr were 3.47 (95% CI, 1.39 to 8.67) in the anemic group and 1.10 (95% CI, 0.64 to 1.88) in the normal-Hgb group. In men, they were 1.43 (95% CI, 0.47 to 4.37) and 1.23 (95% CI, 0.80 to 1.89), respectively.

### Table 3. Adjusted riska of coronary heart disease according to serum creatinine and Hgb levels

<table>
<thead>
<tr>
<th>Serum creatinineb</th>
<th>Normal Hgb (n = 12,089)</th>
<th>Anemiaa (n = 1240)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Normal</td>
<td>1.00</td>
<td>Ref</td>
</tr>
<tr>
<td>High</td>
<td>1.20</td>
<td>0.86–1.67</td>
</tr>
</tbody>
</table>

a Cox proportional-hazards regression adjusted for the continuous variables age, body mass index, systolic and diastolic BP, LDL and HDL cholesterol, insulin, carotid IMT, and the dichotomous variables (race, gender, education level (<12 years of education, ≥12 years), hypertension, diabetes, current smoking.

b Serum creatinine is categorized into two levels: normal (<1.2 mg/dl for women or <1.5 mg/dl for men) and high (≥1.2 mg/dl for women or ≥1.5 mg/dl for men).

c Anemia is defined as Hgb <12 g/dl for women and <13 g/dl for men.

Discussion

The principal finding of this study is that in people with anemia, elevated Scr confers a 2.7-fold risk of coronary events compared with people with normal Scr independent of gender, age, race, and other risk factors. In contrast, elevated Scr is not a risk factor in subjects with normal Hgb. To our knowledge, this study is the first population-based cohort study to examine the effect of anemia on the association between renal function and CHD events.

Studies in older patients (6), patients with hypertension (5), and patients with known CVD (4,7) revealed that mild renal insufficiency was an independent predictor of cardiovascular events. Population-based cohort studies from the National

Figure 2. Distribution of the absolute number of events according to Scr, stratified by Hgb levels status. In the anemia group (■), the highest concentrations of Scr (from 8.3 mg/dl to 17.6 mg/dl) are not included because of space limitation. However, the highest concentration for which there is an event is 7.8 mg/dl. In the normal Hgb group (□), the highest concentration of Scr is 2.8 mg/dl; the highest concentration for which there is an event is 2.1 mg/dl.
Health and Nutrition Examination Survey I and the Framingham cohort, however, have not found an association between cardiovascular mortality and mild renal insufficiency (9,10). It has been suggested that this discrepancy may reflect the co-occurrence of renal insufficiency with other traditional risk factors such as preexisting CVD, hypertension, and older age and that moderate renal insufficiency may be only a marker for the burden of exposure to those CVD risk factors (9).

Evidence suggests that low Hgb is a risk factor for CVD. A recent analysis of the ARIC data found a 40% increased risk of CVD in subjects with anemia compared with patients with normal Hgb (14). GFR was included in the model to control for renal function, but the interaction between renal function and anemia was not studied. Low Hgb increases also the risk of death in patients with heart failure independent of renal function (16,28). Other investigators have described a U-shaped relationship between hematocrit levels and risk of CVD (29–31). In the present analysis, we focused only on patients with anemia defined according to well-accepted criteria (22).

It is widely known that patients with a GFR <60 ml/min per 1.73 m² are much more likely to have anemia (32) and the prevalence and severity of anemia increase with declining renal function (32). Therefore, that anemia was more prevalent in the group of subjects with high Scr (15.1%) than in the group with normal Scr (8.7%) was an expected finding (Table 1). These results are not different from those of other studies (32–34).

Likewise, the prevalence of the other risk factors in the full sample (Table 1) is not different from the one reported by Manjunath et al. (35), who, like us, examined the ARIC database. Although our population was stratified by levels of Scr instead of levels of GFR, most of the risk factors follow a similar distribution pattern to the one described by Manjunath et al. Contrary to them, however, we found a higher proportion of blacks in the high Scr group than in the normal Scr group. This may be because blacks have higher levels of Scr on average (36) and that the Modification of Diet in Renal Disease (MDRD) equation used by Manjunath et al. (37) to estimate GFR is adjusted for race in its calculation.

The association between increased risk of CHD and high Scr in patients with anemia might be explained by an impairment in the physiologic mechanisms of adaptation to maintain the oxygen supply to the tissues in the presence of anemia. These mechanisms of adaptation are both nonhemodynamic and hemodynamic (13). Nonhemodynamic mechanisms include increased erythropoietin production to stimulate erythropoiesis and increased oxygen extraction. In normal resting conditions, the nonhemodynamic factors can almost entirely compensate for Hgb deficit (13). However, in the setting of kidney disease, erythropoietin production is impaired, and, therefore, the only nonhemodynamic mechanism of compensation is an increase in oxygen extraction, which has a limited effect (38).

When the Hgb concentration is <10 g/dl, nonhemodynamic factors become inadequate, and increased cardiac output and blood flow begin to compensate for tissue hypoxia. There are three major components in the hemodynamic compensation (13): (1) increase in cardiac output; (2) increase in preload as a result of higher venous return; and (3) decrease in systemic vascular resistance as a result of arterial dilation, formation of collaterals, arteriovenous shunts, de novo angiogenesis, and decrease in blood viscosity (13,39).

We suggest that the adaptive decrease in systemic vascular resistance may be impaired in chronic kidney disease as a result of endothelial dysfunction (40,41) and impairment of de novo angiogenesis (39,42). Endothelial dysfunction is a known consequence of renal insufficiency with impairment of vasodilation, which may interact with anemia to limit delivery of oxygen during hypoxia.

Anemia has also been identified as a risk factor for left ventricular growth in patients with mild to moderate renal insufficiency (15,43). Left ventricular hypertrophy predisposes to heart failure or ischemic heart disease and ultimately premature death (15,16,43).

### Study Limitations

We cannot rule out that anemia may be only a reflection of the duration of kidney disease. Patients who have long-standing impaired renal function with a slow progression for many years may be at higher risk for CHD because of a higher burden of exposure to “traditional” risk factors than patients with new onset of kidney disease, who are probably not anemic. However, we controlled for subclinical atherosclerosis by introducing IMT in our multivariate analysis. This suggests that anemia per se may play a role in the increased risk for CHD in patients with poor renal function.

Because the highest levels of Scr were 2.8 mg/dl in the non-anemic group and 17.6 mg/dl in the anemic group, one might argue that the higher rate of events in the anemic group is only due to the larger prevalence of high Scr levels. However, after reducing the sample population to the participants with Scr ≤2.8 mg/dl, we found again a significant interaction between Hgb and Scr levels. This result adds another piece of evidence in favor of a true interaction between Hgb and Scr.

Variability of serum creatinine measurements can cast doubts on the accuracy of the results (44). However, the interlaboratory variability is not of concern in the ARIC study because all of the samples were sent to the same laboratory. The within-person coefficient of variation was calculated at 4.3%, and the reliability coefficient was 0.68 (correlation coefficient of repeated measurements analyzed at multiple time points) (45). This low reliability coefficient indicates that the Scr values may not represent the true Scr values, which would bias the association with CHD toward the null. The lower the reliability coefficient, the stronger the true correlation must be for the observed correlation to be statistically significant (45). Had the creatinine measurements been more reliable, we would have found an even stronger association.

Estimating kidney function from Scr level has well-recognized limitations, including variation in creatinine production by age, gender, and race (46). However, direct measurements of GFR using inulin or iothalamate are not feasible in a large population-based study such as ARIC. Moreover, the use of the MDRD or the Cockroft-Gault equations to estimate GFR can result in misclassification of subjects according to their kidney function status as a result of differences in Scr calibration from
one laboratory to the other (44,47,48). Although some authors have suggested applying a calibration factor to Scr values when using the MDRD equation to reduce the misclassification bias (35,44,49), we decided to base our analysis only on the crude Scr levels for two reasons. The first is that our purpose was not to assess the prevalence of low kidney function in the ARIC population; therefore, estimating GFR seemed superfluous in view of the risk of misclassification. The second is that our estimate of the risk of CHD is adjusted for age, race, gender, and body mass index, all variables that are known to influence the levels of Scr independently of any disease such as hypertension or diabetes.

That the interaction in men was nonsignificant may be due to insufficient power because of repeated stratification. However, the direction of the effect modification by anemia on the association between Scr and coronary events is consistent with the results of the overall analysis.

Finally, our analysis is based on observational data; therefore, we cannot rule out confounding from unmeasured factors to explain our results. Those could be related, for example, to other causes of kidney disease and anemia, such as sickle cell disease or systemic lupus erythematosus. Moreover, we also cannot rule out a false-positive result because of the low number of events (n = 44) in the anemia group. Our model, however, is very stable as demonstrated by the fact that restricting the subjects to only those with Scr ≤ 2.8 mg/dl did not modify the results.

Overall, our study indicates that Scr levels as low as 1.2 mg/dl in women and 1.5 mg/dl in men are associated with a 2.7-fold risk of MI or death from CHD among middle-aged people with anemia and that this association is not seen in people with normal Hgb. Although true biologic interaction is rare and the duration of kidney disease, which could explain the observed association, is unknown, the magnitude of the effect may warrant, if these results are confirmed, aggressive prevention strategies of progression of kidney disease and early treatment of anemia. Clinical trials studying the effect of early treatment of anemia in patients with kidney disease are necessary, however, before suggesting a change in guidelines.

Acknowledgments

The Atherosclerosis Risk in Communities Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the Atherosclerosis Risk in Communities Study Investigators. This manuscript has been reviewed by NHLBI for scientific content and consistency of data interpretation with previous Atherosclerosis Risk in Communities Study publications, and significant comments were incorporated before submission for publication.

The results described in this manuscript were partly presented in an abstract at the American Society of Nephrology Conference, Philadelphia, October 2002 (J Am Soc Nephrol 13[Suppl]: 434A, 2002).

References


