Prognostic Implications of the Urinary Albumin to Creatinine Ratio in Veterans of Different Ages With Diabetes

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**Background:** Albuminuria is associated with an increased risk of death independent of level of renal function. Whether this association is similar for adults of all ages is not known.

**Methods:** We examined the association between the albumin to creatinine ratio (ACR) and all-cause mortality after stratification by estimated glomerular filtration rate (eGFR) and age group in 94,934 veterans with diabetes mellitus. Cohort members had at least 1 ACR recorded in the Veterans Affairs Health Care System between October 1, 2002, and September 30, 2003, and were followed up for death through October 15, 2009.

**Results:** From the youngest to the oldest age group, the prevalence of an eGFR less than 60 mL/min/1.73 m² ranged from 11% to 41%; microalbuminuria (ACR 30-299 mg/g) ranged from 19% to 28%; and macroalbuminuria (ACR ≥300 mg/g) ranged from 3.2% to 3.7%. Of patients with an eGFR less than 60 mL/min/1.73 m², 72% of those younger than 65 years, 74% of those 65 to 74 years old, and 59% of those 75 years and older had an eGFR of ≥45 to 59 mL/min/1.73 m². In all age groups, less than 35% of these patients had albuminuria (ie, ACR ≥30 mg/g). In patients 75 years and older, the ACR was independently associated with an increased risk of death at all levels of eGFR after adjusting for potential confounders. In younger age groups, this association was present at higher levels of eGFRs but seemed to be attenuated at lower levels.

**Conclusion:** The ACR is independently associated with mortality at all levels of eGFR in older adults with diabetes and may be particularly helpful for risk stratification in the large group with moderate reductions in eGFR.

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**Methods**

**Patients and Data Sources**

We identified patients with an albumin to creatinine ratio (ACR) and a serum creatinine level recorded in national Veterans Affairs Health Care System (VA) data sources between October 1, 2002, and September 30, 2003, with follow-up through October 15, 2009, for the primary outcome of all-cause mortality. We used several data sources to assemble the analytic data set for this study. The VA Decision Support System Laboratory Results file (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) was used to obtain ACR and serum creatinine test results. We used VA inpatient and outpatient administrative
data to characterize demographic characteristics and diagnosed comorbid conditions of cohort patients based on International Classification of Diseases, Ninth Revision (ICD-9) diagnostic and procedure codes and Current Procedural Terminology codes. We used the VA Corporate Data Warehouse (which includes vital signs measurements entered into the VA electronic medical record) to obtain each patient’s most recent outpatient measurements of blood pressure, height, and weight at or within 1 year before cohort entry. Because many VA patients also use Medicare, we used linked Medicare inpatient and outpatient claims to supplement comorbidity and race information for these patients. Information on medication prescriptions at the time of cohort entry was obtained from the VA Decision Support System Pharmacy (which includes information on all medications prescribed through the VA). We used data from the US Renal Data System (national end-stage renal disease registry) to exclude patients with prevalent end-stage renal disease.

There were 117,188 veterans aged 20 to 100 years with at least 1 urinary ACR recorded in the VA Decision Support System Laboratory Results file between October 1, 2002, and September 30, 2003 (Figure 1). Of these, 110,104 had a serum creatinine measurement on the same day or during the 180 days preceding cohort entry. We excluded 399 of these patients because they had already reached end-stage renal disease at the time of cohort entry or because their most recent eGFR at the time of cohort entry was less than 15 mL/min/1.73 m². We excluded 3 patients because sex was unavailable. From the remaining 109,702 patients, we identified a subset of 94,934 patients with a diagnostic code for diabetes (ICD-9 code 250.xx) during the year before cohort entry in either VA or Medicare administrative files. Because some patients with diabetes might not have been captured by diagnostic codes, we also considered patients to have diabetes if they had been prescribed insulin or an oral hypoglycemic agent in the VA during the year before cohort entry. Patients entered the cohort at the time of their first ACR measurement during the ascertainment period.

PREDICTOR VARIABLE

The primary predictor variable was ACR category at cohort entry. When patients had more than 1 measurement, we used only the first ACR measure during the ascertainment period. Patients were grouped into the following ACR categories: less than 30 mg/g (normoalbuminuria), 30 to 299 mg/g (microalbuminuria), and 300 mg/g or greater (macroalbuminuria).

OUTCOME

Patients were followed up from the date of cohort entry to either the date of death or October 15, 2009, whichever came first. Mortality data were obtained from the VA Vital Status file and were available through October 15, 2009.22 Date of death in this file is ascertained from a variety of sources, including the Social Security Administration, the VA Beneficiary Identification and Records Locator Subsystem, and Medicare and VA utilization data.

COVARIATES

The eGFR was calculated using the most recent outpatient serum creatinine measurement determined at or within 180 days of cohort entry. We used the 4-variable Modification of Diet in Renal Disease formula to estimate GFR based on sex, race, and age at the time of creatinine measurement.23 Whenever available, we used Medicare race data instead of VA race data because of its superior accuracy and completeness.23,24 Patient race was characterized as black, nonblack, or missing (race data were not available for 5% of patients). In estimating the GFR, we assumed that patients who were missing information on race were non-black. We also conducted a sensitivity analysis limited to patients with complete race data. The eGFR was categorized as follows: 90 mL/min/1.73 m² or greater, 60 to 89 mL/min/1.73 m², 45 to 59 mL/min/1.73 m², 30 to 44 mL/min/1.73 m², and 15 to 29 mL/min/1.73 m². A history of coronary artery disease was defined using ICD-9 diagnostic codes for this condition or a procedure code for angioplasty or bypass during the year before cohort entry. Peripheral arterial disease was defined using diagnostic codes for either of these conditions during the year before cohort entry. We also included each patient’s most recent body mass index (calculated as weight in kilograms divided by height in meters squared) (categorized for multivariate analysis as <18.5, 18.5-24, 25-29, 30-34, 35-39, and ≥40), systolic blood pressure (categorized for multivariate analyses as 110, 110-119, 120-139, 140-159, and ≥160 mm Hg), and diastolic blood pressure (categorized for multivariate analyses as <80, 80-89, 90-99, and ≥100 mm Hg) based on outpatient measurements within a year before cohort entry. Patients were also classified according to whether the following medications were prescribed at the time of cohort entry or during the preceding year: insulin, oral hypoglycemic agents, and medications known to affect level of proteinuria (angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, non–dihydropyridine calcium channel blockers [diltiazem and verapamil], and statins).

STATISTICAL ANALYSIS

Demographic and clinical characteristics of the study population are presented according to ACR category as percentage and 95% confidence interval for categorical variables and as mean and 95% confidence interval for continuous variables. Crude death rates were calculated after stratification for ACR, eGFR, and age group (categorized as <65, 65-74, and ≥75 years). We used Cox proportional hazards regression models to estimate the adjusted hazard of death for each ACR category within age and eGFR.
Table 1. Cohort Characteristics by Category of Albumin to Creatinine Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;30 (n=70328)</th>
<th>30-299 (n=21311)</th>
<th>≥300 (n=3295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>66.0 (66.0-66.1)</td>
<td>68.3 (68.2-68.5)</td>
<td>67.6 (67.2-68.0)</td>
</tr>
<tr>
<td>Black race</td>
<td>13.6 (13.4-13.9)</td>
<td>11.1 (10.7-11.6)</td>
<td>11.6 (10.5-12.7)</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.1 (2.0-2.2)</td>
<td>1.6 (1.5-1.8)</td>
<td>1.4 (1.0-1.8)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>27.8 (27.5-28.1)</td>
<td>33.2 (32.6-33.9)</td>
<td>34.5 (32.8-36.1)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1.8 (1.7-1.9)</td>
<td>2.8 (2.5-3.0)</td>
<td>4.0 (3.3-4.7)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>9.8 (9.6-10.1)</td>
<td>15.2 (14.7-15.6)</td>
<td>20.8 (19.4-22.1)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>3.1 (2.9-3.2)</td>
<td>4.1 (3.9-4.4)</td>
<td>4.3 (3.6-4.9)</td>
</tr>
<tr>
<td>Blood pressure, mean (95% CI)</td>
<td>Systolic</td>
<td>137.2 (137.1-137.3)</td>
<td>141.9 (141.6-142.2)</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>74.2 (74.2-74.3)</td>
<td>74.3 (74.1-74.4)</td>
</tr>
<tr>
<td>Body mass index, mean (95% CI)</td>
<td>31.2 (31.2-31.3)</td>
<td>31.1 (31.1-31.2)</td>
<td>31.1 (30.9-31.4)</td>
</tr>
<tr>
<td>eGFR, mean (95% CI), mL/min/1.73 m²</td>
<td>77.1 (76.9-77.2)</td>
<td>71.8 (71.5-72.1)</td>
<td>61.6 (60.8-62.5)</td>
</tr>
<tr>
<td>Insulin, %</td>
<td>18.9 (18.6-19.2)</td>
<td>26.3 (25.7-26.9)</td>
<td>39.4 (37.7-41.0)</td>
</tr>
<tr>
<td>Oral hypoglycemic agent</td>
<td>69.0 (68.7-69.4)</td>
<td>71.6 (71.0-72.2)</td>
<td>67.3 (65.7-68.9)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>8.3 (8.1-8.5)</td>
<td>10.2 (9.8-10.6)</td>
<td>13.2 (12.1-14.4)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>58.8 (58.5-59.2)</td>
<td>65.8 (65.2-66.5)</td>
<td>69.1 (67.6-70.7)</td>
</tr>
<tr>
<td>ARB</td>
<td>7.1 (6.9-7.3)</td>
<td>8.7 (8.3-9.0)</td>
<td>10.9 (9.8-12.0)</td>
</tr>
<tr>
<td>Statin</td>
<td>53.4 (53.0-53.8)</td>
<td>55.1 (54.3-55.7)</td>
<td>58.4 (56.7-60.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor antagonist; CI, confidence interval; eGFR, estimated glomerular filtration rate.

(a) Data are given as percentage (95% confidence interval).

(b) Calculated as weight in kilograms divided by height in meters squared.

The mean (SD) age of the cohort was 66.6 (10.9) years, 98% of cohort members were male, and 13% were black. Seventy-four percent of patients had an ACR of less than 30 mg/g, 22.5% had an ACR of 30 to 299 mg/g, and 3.5% had an ACR of at least 300 mg/g (Table 1). The mean age was higher and the proportion of patients who were black was slightly lower for those with an ACR of 30 to 299 mg/g compared with the other groups. From the lowest to the highest ACR category, the proportion of women decreased slightly; the prevalence of all comorbidities increased; mean systolic and diastolic blood pressure increased; the use of insulin, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, statins, and non-dihydropyridine calcium channel blockers increased; and mean eGFR decreased. Mean body mass index was similar across ACR categories.
Forty-two percent of patients were younger than 65 years, 32% were 65 to 74 years old, and 26% were 75 years and older. Across age groups, the proportion of all patients who met the criteria for CKD (defined as an eGFR <60 mL/min/1.73 m^2 or an ACR ≥30 mg/g) increased from 26.5% in those younger than 60 years to 36.4% in those aged 75 years and older (Figure 2). The distribution of eGFR and ACR varied markedly with increasing age. Seventy-two percent of all patients younger than 65 years who met the criteria for CKD did so because they had albuminuria only (ie, their eGFR was ≥60 mL/min/1.73 m^2). This was true for only 27.9% of patients aged 75 years and older. On the other hand, 44.6% of patients 75 years or older who met the criteria for CKD had mild to moderate reductions in eGFR in the 45- to 59-mL/min/1.73 m^2 range.

During median follow-up of 6.4 years (25th-75th percentile, 6.0-6.7 years), 25 481 patients (26.8%) died. In all age groups, crude mortality rates generally increased with progressively higher levels of ACR in patients with similar levels of eGFR (Figure 3). For any given ACR and eGFR category, crude mortality rates were higher in older than in younger patients. In Cox proportional hazards regression analysis, ACR was independently associated with death at all levels of eGFR in patients 75 years and older (Table 2). Although, in general, this association was of similar magnitude in older and younger cohort members, the association did differ across age groups in some eGFR categories. For younger compared with older patients, point estimates for the association of ACR with mortality were of slightly greater magnitude at eGFR levels of 60 to 89 mL/min/1.73 m^2 and were attenuated at lower levels of eGFR (Table 2).

Results of a parallel sensitivity analysis that excluded patients with missing race data did not differ substantially from the primary analysis (data not shown). Cohort patients were younger (mean [SD] age, 66.6 [10.9] vs 72.5 [8.3] years) and had a higher mean (SD) eGFR (75.3 [22.3] vs 66.4 [22.7] mL/min/1.73 m^2) compared with patients with diabetes who underwent serum creatinine but not ACR measurement in the VA during the cohort entry period (n=236 983).

In older members of this large cohort with diabetes, ACR was independently associated with an increased risk of death at all levels of eGFR. In younger cohort members, this association was present at higher levels but seemed to be attenuated at lower levels of eGFR.

Several previous studies in diabetic and nondiabetic cohorts have described an association between proteinuria and mortality that is independent of eGFR and that is present even in patients with a low eGFR. Most of these studies demonstrate that in persons with normal, mild, or moderate reductions in eGFR, the presence or absence of proteinuria is as (if not more) strongly associated with mortality compared with level of eGFR. However, the existing literature provides limited and conflicting information on the prognostic value of proteinuria at older ages. Roderick et al examined the association between dipstick proteinuria and mortality during a median of 7.3 years in 13 177 primary care patients 75 years and older in the United Kingdom. After accounting for eGFR, proteinuria was associated with a modest increase in risk of death, but this association was not present at all levels of eGFR. Conway et al did not find a statistically significant independent association between level of proteinuria and risk of death in an elderly referred population with advanced kidney disease after adjustment for eGFR and other potential confounders. de Boer et al examined the association of eGFR and albuminuria with mortality in 691 adults 65 years and older with diabetes observed for 10 years. In this study, an ACR of at least 30 mg/g and an eGFR less than 60 mL/min/1.73 m^2 were independently associated with mortality, each conferring an approximately 70% increase in mortality risk. In a com-
munity cohort of 9709 adults 20 years and older observed for 8.3 years, Hallan et al9 examined the association between cardiovascular mortality and microalbuminuria (defined as an ACR of 30-300 mg/g in men and 20-200 mg/g in women) and “high normal” albuminuria (defined as an ACR of 30-300 mg/g in men and 6-29 mg/g in women) by level of eGFR (Table 2). Point estimates are adjusted for age, sex, eGFR, comorbidity (diabetes mellitus, coronary artery disease, peripheral arterial disease, and stroke or transient ischemic attack), systolic and diastolic blood pressure, body mass index, and medication use (insulin, oral hypoglycemic agents, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, non-dihydropyridine calcium channel blockers, and statins).

In the clinical setting, the ACR may be particularly helpful for risk stratification in elderly patients who meet the current eGFR criteria for CKD. Mild to moderate reductions in eGFR are common in elderly patients but are of uncertain clinical significance and in many instances may represent part of the spectrum of renal senescence.28 Several studies17-19 have demonstrated that the relative risk of death associated with a given level of eGFR is attenuated with age and that older patients with mild to moderate reductions in eGFR seem to experience mortality rates that are comparable with those of their peers with higher levels of eGFR. In contrast, the association of ACR with mortality in this cohort was not attenuated with age and in patients 75 years and older was present at all levels of eGFR. Forty percent of patients in this oldest age group had a low eGFR, but most had moderate reductions in eGFR in the 45- to 59-mL/min/1.73 m² range, and most did not have either microalbuminuria or macroalbuminuria. Thus, at older ages, an ACR of less than 30 mg/g may serve to identify a large subgroup of patients with moderate reductions in eGFR who are at relatively lower risk for death.

This study has the following limitations. First, we required that patients have at least 1 ACR measurement during the ascertainment period and at least 1 serum creatinine measurement during the preceding 180 days. Although most patients with an ACR had a serum creatinine measurement, the reverse was not true, and the study cohort seemed to be healthier and younger than their counterparts with diabetes, who had a serum creatinine measurement but did not undergo ACR measurement. Therefore, the results of this study may be generalizable only to persons with diabetes in whom the ACR tends to be requested in the clinical setting, and absolute and relative mortality rates associated with a given level of eGFR and ACR reported herein may differ from those of the overall population of VA patients with diabetes. Nevertheless, this limitation must be weighed against the ad-
vantages of the data source for supporting detailed analyses of the relationships among eGFR, ACR, and mortality. Second, to limit ascertainment bias as much as possible, these analyses were based on each patient’s first ACR measurement during the ascertainment period. However, in the clinical setting, more than 1 urinary albumin measurement is recommended. On the other hand, it is unclear whether sequential measurements of urinary albumin excretion have greater prognostic significance than does a single measurement. Third, serum creatinine measurements used in this study were not calibrated to the Cleveland Clinic laboratory. The absence of creatinine calibration may affect the accuracy of GFR estimates greater than 45 mL/min/1.73 m² but is unlikely to differentially affect the accuracy of GFR estimates by level of ACR or age. Fourth, these data sources had several inherent limitations: we had no information on cause of death and did not have reliable or complete information on other risk factors of mortality, such as physical activity, smoking, lipid levels, and duration of diabetes. Similar to other large cohort studies of this nature, comorbidity information was obtained from diagnostic codes rather than from medical record diagnosis or patient interview and, thus, may be inaccurate and sensitive to the specific search strategy used. Fifth, this population was predominantly male; thus, we could not examine differences in the association of eGFR and ACR with mortality by sex. The ACR was independently associated with mortality at all levels of eGFR in older members of this cohort with diabetes. More than half of all patients 75 years and older met the current criteria for CKD, in many cases because of an isolated moderate reduction in eGFR. At all levels of eGFR, ACR was independently associated with mortality in these older patients. Collectively, these findings suggest that the ACR may be a valuable tool for mortality risk stratification in the elderly, particularly in the large group a moderate reduction in eGFR.

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REFERENCES

13. So WY, Kong AP, Ma RC, et al. Glomerular filtration rate, carotid end points,


**Correction**

Age Error and Typographical Errors. In the Original Investigation titled “Prognostic Implications of the Urinary Albumin to Creatinine Ratio in Veterans of Different Ages With Diabetes” by O’Hare et al, published in the June 14th issue of the Archives (2010;170[11]:930-936) the age was misstated on page 933, left-hand column, first paragraph, in lines 6 and 17. The age should have been “younger than 65 years” in both places. The sentences should have read as follows: “Across age groups, the proportion of all patients who met the criteria for CKD (defined as an eGFR <60 mL/min/1.73 m² or an ACR ≥30 mg/g) increased from 26.5% in those younger than 65 years to 56.4% in those aged 75 years and older (Figure 2).” “On the other hand, 44.6% of patients 75 years or older who met the criteria for CKD did so because of an isolated low eGFR (ie, ACR <30 mg/g) compared with 23.6% of patients younger than 65 years.”

On page 930, right-hand column, “Results” section of the Abstract, the last sentence should have read as follows: “In younger age groups, this association was present at higher levels of eGFR but seemed to be attenuated at lower levels.” On page 933, left-hand column, the last sentence of the complete paragraph should have read as follows: “Collectively, these findings suggest that the ACR may be a valuable tool for mortality risk stratification in the elderly, particularly in the large group with a moderate reduction in eGFR.”