

Outcomes Associated With Microalbuminuria

Effect Modification by Chronic Kidney Disease

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Objectives

This study sought to compare the association of microalbuminuria with outcomes in patients with different comorbidities.

Background

The risk of adverse outcomes associated with lower levels proteinuria has been found to be linearly decreasing with even low-normal levels of microalbuminuria. It is unclear whether comorbid conditions change these associations.

Methods

We examined the association of urine microalbumin-creatinine ratio (UACR) with mortality and the slopes of estimated glomerular filtration rate (eGFR) in a nationally representative cohort of 298,875 U.S. veterans. Associations of UACR with all-cause mortality overall and in subgroups of patients with and without diabetes mellitus, hypertension, cardiovascular disease, congestive heart failure, and advanced chronic kidney disease (CKD) were examined in Cox models, and with the slopes of eGFR in linear and logistic regression models.

Results

Very low levels of UACR were linearly associated with decreased mortality and less progression of CKD overall: adjusted mortality hazard ratio and estimated glomerular filtration rate slope (95% confidence interval [CI]) associated with UACR ≥ 200 $\mu\text{g}/\text{mg}$, compared to < 5 $\mu\text{g}/\text{mg}$ were 1.53 (95% CI: 1.38 to 1.69, $p < 0.001$) and -1.59 (95% CI: -1.83 to -1.35 , $p < 0.001$). Similar linearity was present in all examined subgroups, except in patients with CKD in whom a U-shaped association was present and in whom a UACR of 10 to 19 was associated with the best outcomes.

Conclusions

The association of UACR with mortality and with progressive CKD is modified in patients with CKD, who experience higher mortality and worse progression of CKD with the lowest levels of UACR. Proteinuria-lowering interventions in patients with advanced CKD should be implemented cautiously, considering the potential for adverse outcomes. (J Am Coll Cardiol 2013;61:1626–33) © 2013 by the American College of Cardiology Foundation

The high burden of cardiovascular disease in the general population (1) has prompted enhanced efforts to identify early disease markers and therapeutic targets. Microalbuminuria has shown associations with morbidity and mortality in the general population (2–7), and in patients with various comorbid conditions such as those at risk for or with established chronic kidney disease (CKD) (8–13). An important question about microalbuminuria is the level that should be applied as a cutoff both toward identifying increased

risk and, ultimately, to use as a therapeutic target. The most commonly used classification for the levels of urine microalbumin-creatinine ratio (UACR [the test most readily available in clinical practice]) defines a level of 10 $\mu\text{g}/\text{mg}$ as the

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upper limit of normal (< 15 $\mu\text{g}/\text{mg}$ for females, to account for the higher urine creatinine of males) (14). Neverthe-

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less, studies in the general population have suggested that even UACR levels $<10 \mu\text{g}/\text{mg}$ are associated with a linear decrement in event risks (3,6,15) questioning the idea of an “ideal” or “normal” range for this marker, and implying that a “the lower, the better” approach is warranted for risk stratification, and potentially for therapeutic interventions.

It is unclear to what extent these findings, and hence this concept, can be applied to patients with a high burden of comorbidities, whose risk of adverse outcomes such as mortality, cardiovascular events, and progressive kidney disease is substantially higher. Studies that examined patients with established CKD have, in general, found that lower UACR was associated with decreased incidence of mortality and end-stage renal disease (8–13), but neither the individual studies nor the meta-analyses pooling their results (8,10) performed a detailed analysis of UACR cutoffs below what is currently considered “normal” in this patient population. We examined the association of UACR with mortality and with progressive CKD in a large cohort of U.S. veterans. We studied UACR ranges that included even those below the currently accepted normal level of $10 \mu\text{g}/\text{mg}$, and explored whether the associations differed in patients with and without diabetes mellitus, cardiovascular disease (CVD), congestive heart failure (CHF), CKD, and in those with higher and lower levels of blood pressure.

Methods

Cohort definition. The establishment of our cohort was described previously (16). Briefly, we extracted all the available measurements of UACR and stable estimated glomerular filtration rate (eGFR) from the period between October 1, 2004, and September 30, 2006, from the Veterans Administration (VA) Decision Support System National Data Extracts Laboratory Results file (a VA-wide database containing select laboratory results obtained in the clinical setting) (17). The GFR was estimated from serum creatinine measurements and demographic characteristics by the Chronic Kidney Disease Epidemiology Collaboration equation (18). Of a total of 4,381,049 patients with any serum creatinine and 438,503 patients with any UACR measured between October 1, 2004 and September 30, 2006, we identified 298,875 patients with both stable kidney function and available UACR.

Sociodemographic characteristics and comorbidities. Data on patient age, sex, race, geographic location (Veteran Integrated Service Network number), blood pressure, and administration of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) was obtained through the VA Corporate Data Warehouse. Information on race was complemented with data obtained from Medicare through the VA-Medicare data merge project (19). All blood pressure values available from October 1, 2004, to September 30, 2006, were recorded and grouped by calendar quarters, and their quarterly averaged values were used for analyses. Administration of ACEI or ARB was

defined as the outpatient dispensation by a VA pharmacy of any agent belonging to these medication classes, and was assessed longitudinally in each calendar quarter for the October 1, 2004 to September 30, 2009 period. Data on comorbidities were collected from the VA Inpatient and Outpatient Medical SAS Datasets (20,21) using International Classification of Diseases-Ninth Revision diagnostic and procedure codes and Current Procedural Terminology codes recorded during the October 1, 2004, to September 30, 2006 period. Prevalent cardiovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina, or myocardial infarction, or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting. We calculated the Charlson comorbidity index using the Deyo modification for administrative datasets (22).

Laboratory characteristics. Data on laboratory variables were collected from the October 1, 2004, to September 30, 2009 period by using the National Data Extracts Laboratory Results file (17). To minimize random variability, all available laboratory values were grouped by calendar quarters, and their quarterly averaged values were used in analyses, except for eGFR values used to examine progression of CKD, which were examined with their actual recorded date.

Statistical analyses. Data were characterized using means, medians, and proportions as appropriate. Skewed variables were natural log-transformed. Data points were missing for race (4.5%), blood pressure (5.9%), serum albumin (17.4%), hemoglobin (11.9%), white blood cell count (12.5%), and alkaline phosphatase (10.3%). A total of 225,238 patients (75% of the total study population) had complete data available for the fully adjusted multivariable analyses. Missing values were not imputed in the primary analyses but were substituted by using multiple imputation procedures (23,24) in sensitivity analyses.

The start of the follow-up period was the date of the stable eGFR used to establish CKD. Patients were followed up until death or until the date of the last health-care or administrative encounter, as documented in the VA Vital Status Files. The VA Vital Status Files are a registry containing dates of death or last medical/administrative encounter from all available sources in the VA system. The sensitivity and specificity of the Vital Status Files using the National Death Index as gold standard were shown to be 98.3% and 99.8%, respectively (25). The association of

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin-receptor blocker
CHF = congestive heart failure
CI = confidence interval
CKD = chronic kidney disease
CVD = cardiovascular disease
ESRD = end-stage renal disease
eGFR = estimated glomerular filtration rate
UACR = urine microalbumin-creatinine ratio
VA = Veterans Administration

UACR with all-cause mortality was examined in time-dependent Cox models, with adjustment for potential confounders and clustered by geographic region. The association between UACR and progression of CKD was examined in linear and logistic regression analyses using the slopes of eGFR versus time as the dependent variable. The slopes of eGFR were calculated in 277,244 patients who had at least 3 eGFR values (median 8, Q1 to Q3: 5 to 13) and a baseline eGFR >15 ml/min/1.73 m² by ordinary least squares regression of eGFR versus time in each individual patient. Progressive CKD was defined as a slope of <−4 ml/min/1.73 m² per year for logistic regression analyses.

Variables were included in multivariable models if they could be considered confounders (26) on the basis of theoretical considerations and after examination of baseline associations with UACR. Associations were examined sequentially in models with incremental multivariable adjustments: unadjusted (model 1); age, sex, and race adjusted (model 2); model 2 plus diabetes, CVD, CHF, and Charlson comorbidity index adjusted (model 3); and model 3 plus blood pressure, administration of ACEI or ARB, eGFR (except for analyses of slopes), serum albumin, alkaline phosphatase, hemoglobin, and white blood cell count adjusted (model 4). Variables that were measured repeatedly during follow-up (blood pressure, ACEI/ARB use, and

laboratory covariates) were handled as time-dependent variables in Cox models and as time-averaged values in regression analyses. Nonlinear associations were examined by categorizing UACR according to established cutoff points for male patients (<10, 10 to 19, 20 to 199, and ≥200 μg/mg) (14), and by subdividing the <10 μg/mg category into 2 groups (<5 and 5 to 9 μg/mg) to examine whether UACR levels below the currently accepted upper limit of normal (10 μg/mg) (14) are still associated with clinical outcomes, as suggested by some studies (3,6,15). Analyses were also performed separately in patients categorized according to diabetic status, baseline systolic blood pressure level (<120 mm Hg vs. ≥120 mm Hg), CVD, CHF, and eGFR level at baseline (<30 ml/min/1.73 m² vs. ≥30 ml/min/1.73 m²). To better delineate the role of kidney function, we also categorized eGFR according to pre-specified cutoffs of 15 to 29, 30 to 44, 45 to 59, 60 to 89, and ≥90 ml/min/1.73 m² (27).

Sensitivity analyses were performed by using imputed values of independent variables. Statistical analyses were performed using STATA MP Version 11 (Stata Corp., College Station, Texas). The study protocol was approved by the institutional review boards at the Salem VAMC and the Memphis VAMC.

Table 1 Baseline Characteristics of Patients Stratified by Level of Baseline Urine Microalbumin-Creatinine Ratio

Characteristics	Urine Microalbumin/Creatinine, μg/mg				
	<5 (n = 72,448)	5 to 9 (n = 64,053)	10 to 19 (n = 55,664)	20 to 199 (n = 90,828)	≥200 (n = 15,882)
Age, yrs	62.4 ± 11.8	64.6 ± 11.1	66.2 ± 11.2	67.6 ± 11.2	67.4 ± 10.9
Race					
White	52,635 (77)	49,988 (82)	44,410 (83)	72,383 (83)	12,339 (80)
Black	12,983 (19)	8,586 (14)	6,833 (13)	11,437 (13)	2,266 (15)
Hispanic	1,041 (1.5)	871 (1.4)	827 (1.6)	1,638 (1.9)	320 (2.1)
Other	1,658 (2.4)	1,345 (2.2)	1,136 (2.1)	1,990 (2.3)	511 (3.3)
Male	69,836 (96)	61,792 (96)	53,906 (97)	88,691 (98)	15,723 (98)
DM	51,363 (71)	50,810 (79)	46,673 (84)	79,811 (88)	14,593 (91)
ASCVD	19,283 (27)	19,728 (31)	19,441 (35)	35,925 (40)	6,888 (43)
CHF	4,405 (6)	4,188 (7)	4,964 (9)	11,940 (14)	3,288 (21)
Comorbidity index	2 (1–3)	2 (1–3)	2 (1–4)	3 (1–4)	4 (2–5)
SBP, mm Hg	132 ± 16	133 ± 16	134 ± 17	137 ± 18	141 ± 19
DBP, mm Hg	75 ± 10	74 ± 11	74 ± 11	73 ± 11	74 ± 12
ACEI/ARB use	19,283 (27)	18,962 (30)	17,911 (32)	32,189 (35)	6,230 (39)
eGFR, ml/min/1.73 m ²	78.3 ± 20.3	77.2 ± 19.7	74.9 ± 20.9	70.6 ± 20.4	61.5 ± 24.8
Serum albumin, g/dl	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	4.0 ± 0.4	3.8 ± 0.5
Total cholesterol, mg/dl	175 ± 40	172 ± 40	171 ± 41	170 ± 42	172 ± 46
Serum calcium, mg/dl	9.3 ± 0.4	9.3 ± 0.4	9.3 ± 0.4	9.3 ± 0.5	9.2 ± 0.5
Serum ALP, U/l	75 ± 31	76 ± 30	77 ± 32	79 ± 35	86 ± 44
Serum bicarbonate, mEq/l	27.7 ± 2.7	27.6 ± 2.7	27.6 ± 2.8	27.3 ± 3.0	26.9 ± 3.2
Blood Hgb, g/dl	14.5 ± 1.5	14.4 ± 1.5	14.3 ± 1.6	14.1 ± 1.7	13.7 ± 1.9
Blood WBC, 1,000/mm ³	7.1 ± 3.2	7.3 ± 3.3	7.4 ± 2.9	7.6 ± 3.5	7.8 ± 3.8
UACR, μg/mg	3.0 (2.7–4.0)	7.2 (6.0–8.5)	14.0 (11.9–16.7)	44.0 (28.7–78.0)	388.4 (266.3–716.8)

Values are mean ± SD, n (% of total), or median (interquartile range). To convert glomerular filtration rate (GFR) in ml/min/1.73 m² to ml/s/1.73 m², multiply by 0.01667; serum albumin in g/dl to g/l, multiply by 10; serum total cholesterol in mg/dl to mmol/l, multiply by 0.02586; serum calcium in mg/dl to mmol/l, multiply by 0.2495; and hemoglobin in g/dl to g/l, multiply by 10.

ALP = alkaline phosphatase; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; Hgb = hemoglobin; SBP = systolic blood pressure; UACR = urine microalbumin-creatinine ratio; WBC = white blood cell count.

Results

Baseline characteristics in patients categorized by their UACR level are shown in Table 1. Patients with higher UACR were older, and more likely to be diabetic, to use ACEI/ARB and to have CVD and CHF, and had a higher comorbidity index, systolic blood pressure, serum alkaline phosphatase, and white blood cell count, and lower eGFR, serum albumin, and hemoglobin.

Mortality. A total of 49,586 patients died (mortality rate 35.3/1,000 patient-years, 95% confidence interval [CI]: 35.0 to 35.7) during a median follow-up of 5 years. Patients with higher UACR experienced significantly higher mortality rates in a linearly incremental fashion above a UACR of 10 $\mu\text{g}/\text{mg}$ in all models (Fig. 1). When analyzed as a continuous variable, a 1 natural log-unit higher UACR was associated with hazard ratios 1.31 (95% CI: 1.28 to 1.34) and 1.11 (95% CI: 1.09 to 1.13) in unadjusted and in fully adjusted models, respectively ($p < 0.001$ for both).

The association of UACR with mortality was similarly linear (albeit quantitatively different) in patients with and without diabetes, CVD, and CHF and in patients with higher or lower blood pressure levels, but was qualitatively different in patients with advanced CKD (Fig. 2). UACR levels of 5 to 9, 10 to 19, 20 to 199, and ≥ 200 $\mu\text{g}/\text{mg}$ (compared to < 5 $\mu\text{g}/\text{mg}$) were associated with mortality hazard ratios 1.05 (95% CI: 0.98 to 1.13), 1.20 (95% CI: 1.12 to 1.29), 1.43 (95% CI: 1.33 to 1.54), and 1.57 (95% CI: 1.41 to

1.54) in patients with $\text{eGFR} \geq 30$ $\text{ml}/\text{min}/1.73$ m^2 ; and 0.94 (95% CI: 0.80 to 1.10), 0.81 (95% CI: 0.67 to 0.98), 0.96 (95% CI: 0.83 to 1.11), and 1.05 (95% CI: 0.88 to 1.25) in patients with $\text{eGFR} < 30$ $\text{ml}/\text{min}/1.73$ m^2 (Fig. 2). A more granular assessment of eGFR categories indicated that UACR developed a U-shaped association with mortality below an eGFR of 45 $\text{ml}/\text{min}/1.73$ m^2 : the adjusted mortality hazard ratios associated with UACR 10 to 19 compared to < 5 $\mu\text{g}/\text{mg}$ in patients with eGFR levels ≥ 90 , 60 to 89, 45 to 59, 30 to 44, and 15 to 29 $\text{ml}/\text{min}/1.73$ m^2 were 1.19 (95% CI: 1.08 to 1.31), 1.32 (95% CI: 1.21 to 1.45), 1.11 (95% CI: 1.01 to 1.22), 1.00 (95% CI: 0.86 to 1.15), and 0.81 (95% CI: 0.67 to 0.98) (Online Fig. 1). Furthermore, the magnitude with which UACR was associated with mortality was highest in patients with eGFR 60 to 89 $\text{ml}/\text{min}/1.73$ m^2 , and gradually diminished in patients with eGFR levels < 60 $\text{ml}/\text{min}/1.73$ m^2 (Online Fig. 1). Results of analyses using imputed values for missing variables yielded similar results (data not shown).

Progression of CKD. In the overall patient population, a 1 natural log-unit higher UACR was associated with -0.38 $\text{ml}/\text{min}/1.73$ m^2 per year (95% CI: -0.37 to -0.39 , $p < 0.001$) and -0.27 $\text{ml}/\text{min}/1.73$ m^2 per year (95% CI: -0.35 to -0.19 , $p < 0.001$) steeper slopes, and with odds ratios (95% CI) of progressive CKD of 1.18 (95% CI: 1.15 to 1.21, $p < 0.001$) and 1.12 (95% CI: 1.09 to 1.15, $p < 0.001$) in unadjusted and in fully adjusted linear and logistic

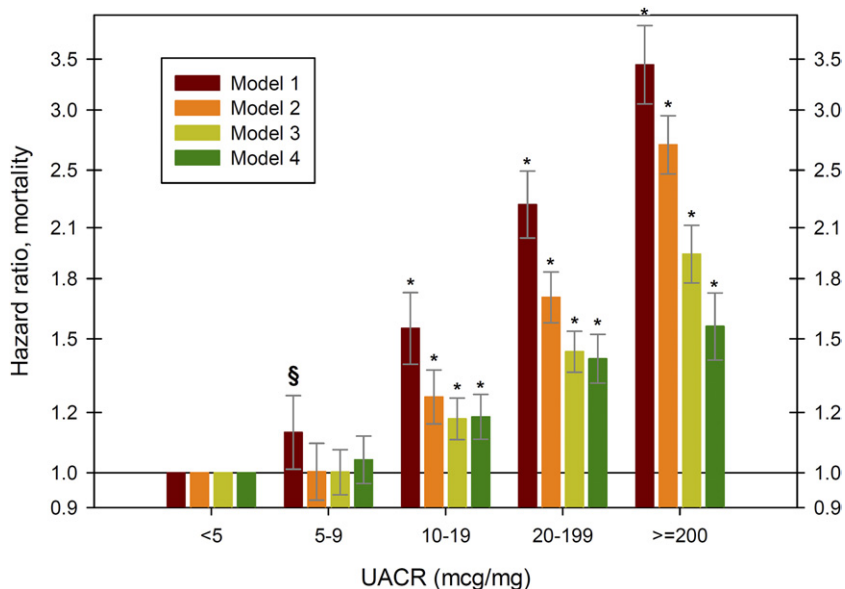


Figure 1 Unadjusted and Multivariable Adjusted HR (95% CI) of All-Cause Mortality Associated With Various Levels of UACR in 298,875 Patients

In time-dependent Cox models, the groups with urine microalbumin-creatinine ratio (UACR) < 5 $\mu\text{g}/\text{mg}$ served as referent. Models represent unadjusted association (model 1 [dark red bars]); associations after adjustment for age, sex, and race (model 2 [orange bars]); model 2 variables plus diabetes mellitus, cardiovascular disease, congestive heart failure, and Charlson comorbidity index (model 3 [yellow-green bars]); and model 3 variables plus systolic blood pressure, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use, estimated glomerular filtration rate, serum albumin, blood hemoglobin, white blood cell count, and serum alkaline phosphatase (model 4 [green bars]). * $p < 0.001$; § $p < 0.05$. CI = confidence interval; HR = hazard ratio.

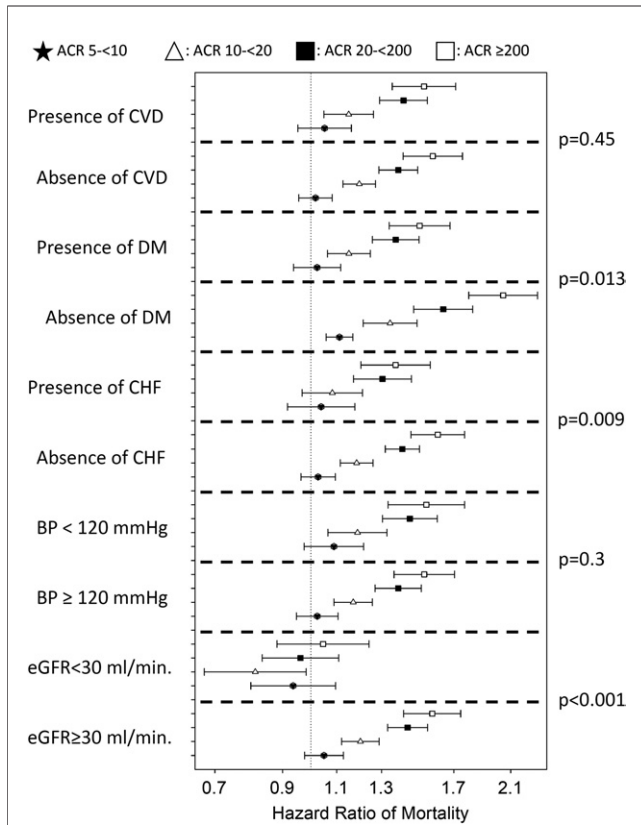


Figure 2

Mortality HR (95% CI) Associated with UACR Categories of 5 to 9, 10 to 19, 20 to 199, and ≥200 μg/mg, Compared to <5 μg/mg in Different Subgroups of Patients

Results were obtained from Cox models adjusted for age, sex, race, diabetes mellitus (DM), cardiovascular disease (CVD), congestive heart failure (CHF), Charlson comorbidity index, systolic blood pressure (BP), angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use, estimated glomerular filtration rate (eGFR), serum albumin, blood hemoglobin, white blood cell count, and serum alkaline phosphatase. The p values represent significance levels for interaction terms. ACR = albumin-creatinine ratio; CI = confidence interval; HR = hazard ratio; UACR = urine microalbumin-creatinine ratio.

regression models, respectively. This association appeared to be linearly incremental at UACR levels ≥10 μg/mg (Fig. 3).

Similar to associations with mortality, the associations of UACR with progressive CKD were also linearly incremental in all examined subgroups except in patients with advanced CKD, in whom there was a U-shaped association (Fig. 4). The U-shaped association between UACR and progressive CKD also became apparent in patients with eGFR <45 ml/min/1.73 m²: the adjusted odds ratios of progressive CKD associated with UACR 10 to 19 compared to <5 μg/mg in patients with eGFR levels ≥90, 60 to 89, 45 to 59, 30 to 44, and 15 to 29 ml/min/1.73 m² were 1.09 (95% CI: 0.98 to 1.22), 1.19 (95% CI: 1.09 to 1.21), 1.07 (95% CI: 0.98 to 1.16), 0.77 (95% CI: 0.63 to 0.93), and 0.38 (95% CI: 0.26 to 0.56) (Online Fig. 2). Results of analyses using imputed values for missing variables yielded similar results (data not shown).

Discussion

We describe associations of UACR with all-cause mortality and with the slopes of eGFR in a large cohort of U.S. veterans. Higher UACR showed incremental associations with both of these outcomes, which were consistent in patients with and without diabetes, CVD, and CHF and in patients with lower and higher blood pressure levels. A markedly different pattern of association was observed in patients with moderate and advanced CKD. Whereas in patients with eGFR 60 to 89 ml/min/1.73 m², UACR levels of <5 μg/mg were associated with the most favorable outcomes, these associations were U-shaped in patients with eGFR <45, and especially in those with levels <30 ml/min/1.73 m² (CKD stages 3B and 4); in the latter groups, UACR levels <10 to 19 μg/mg were associated with a significant increase in adverse outcomes compared to patients with UACR 10 to 19 μg/mg.

Elevated UACR is considered a robust predictor of adverse clinical outcomes both in the general population (2–7) and in patients with CKD (8–13). It is less clear, however, what cutoff should be used to denote a “normal” UACR. The most commonly used classification considers UACR <10 μg/mg (<15 μg/mg for females) normal, and classifies patients with higher levels as having high-normal level, microalbuminuria and macroalbuminuria (14). Designating an upper limit of normal implies that UACR levels <10 to 15 μg/mg are physiologic and are unrelated to outcomes. This idea has been challenged by studies in the general population showing a decremental association of UACR levels below this “normal” cutoff with clinical outcomes (3,6,15), suggesting that any elevation in, and indeed, the mere presence of a measurable UACR can in fact be considered pathologic. The determination of a normal UACR is important from a public health perspective, because it could not only define the number of persons indentified as being at risk for outcomes or having a disease such as CKD, but it would also lead to different therapeutic targets.

To the best of our knowledge, our study is the first to describe in detail the association of low and very low UACR with clinical outcomes in patients with different comorbid conditions. Of these comorbidities, CKD appeared to represent an effect-modifier in the association of UACR with mortality and with progressive CKD. Explaining the different associations seen in advanced CKD necessitates the understanding of what the meaning of a high or a low UACR is. The most commonly accepted theory is that UACR represents both a cause and a consequence of vascular damage (28). Whichever may be the case, it is difficult to imagine why patients with CKD who have the lowest UACR levels (and would thus either be at the lowest risk or have the lowest severity of vascular disease) would have higher mortality and more rapid progression of CKD. A more likely explanation of our findings in CKD is that UACR is also a marker of intraglomerular pressure, and the

Figure 3 Unadjusted and Multivariable Adjusted OR (95% CI) of Progressive CKD Associated With Various Levels of UACR in Logistic Regression Models

The groups with urine microalbumin-creatinine ratio (UACR) $<5 \mu\text{g}/\text{mg}$ served as referent. Models represent unadjusted association (model 1 [dark red bars]); associations after adjustment for age, sex, and race (model 2 [orange bars]); model 2 variables plus diabetes mellitus, cardiovascular disease, congestive heart failure, and Charlson comorbidity index (model 3 [yellow-green bars]); and model 3 variables plus systolic blood pressure, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use, serum albumin, blood hemoglobin, white blood cell count, and serum alkaline phosphatase (model 4 [green bars]). * $p < 0.001$; # $p < 0.01$; § $p < 0.05$. CI = confidence interval; CKD = chronic kidney disease; OR = odds ratio.

different association patterns seen in some subgroups may represent their decreased ability to adapt to lower renal perfusion pressures. Patients with CKD have an inability to autoregulate end-organ perfusion pressure in the face of lower blood pressure (29) due to a combination of small vessel changes (30–32) incurred with the older age and many of the comorbid conditions present in this group (33). That could lead to adverse outcomes under conditions of end-organ ischemia, as has been suggested by numerous earlier observational studies in end-stage renal disease (33–37) and in non-dialysis-dependent CKD patients (38,39) showing a U-shaped association between systolic blood pressure and mortality. Therefore, it is possible that a low UACR identifies patients at high risk for ischemic end-organ damage among those with advanced CKD.

Our findings suggest that when used as a tool for risk stratification, UACR levels in the lowest range appear to point toward increased, not decreased, risk of mortality and progressive CKD in patients with moderate and advanced CKD. For patients with various other comorbid conditions and for patients with eGFR levels in the normal range and those with mild CKD, we confirm findings from studies involving the general population in that very low UACR levels can be used to identify patients at the lowest risk for adverse outcomes. It is less clear how our findings should be applied toward identifying therapeutic targets, as we cannot determine from our data what the clinical outcomes would be if UACR was decreased therapeutically to extremely low

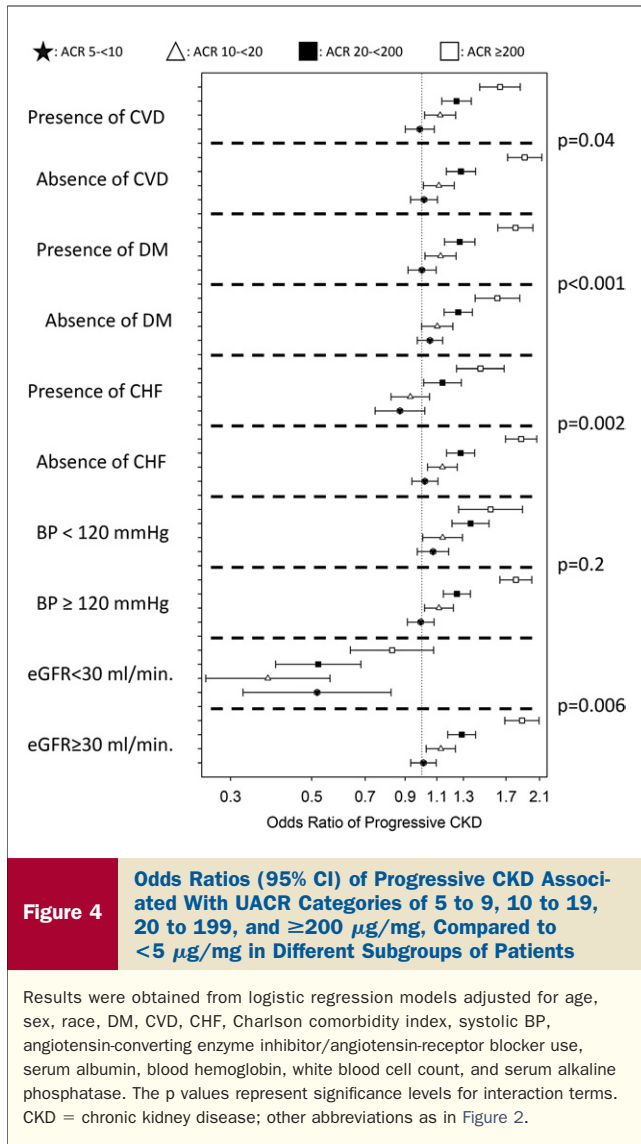
levels. On the basis of our observational data, it is possible that in most patients, lowering proteinuria to very low or undetectable levels could be beneficial. However, in patients with moderate and advanced CKD, we would consider it prudent to regard the UACR levels associated with the lowest risks in observational studies (e.g., 10 to 19 $\mu\text{g}/\text{mg}$) as the optimal therapeutic target worth exploring in clinical trials.

Our study is notable for its large sample size, which allowed us to include substantial numbers of patients with various comorbidities and with UACR levels spanning a wide range, and for it being representative of veterans from the entire geographic United States.

Study limitations. We examined mostly male patients; hence, it is unclear whether the same results can be extrapolated to female patients. We used data obtained during the course of clinical practice; hence, selection bias is likely. Our patients' UACR would have been measured based on clinical indications, as suggested by the high proportion of diabetic patients in our cohort, but the concordance of our findings in patients with normal eGFR with those of studies examining the general population support the validity and generalizability of our results.

Conclusions

Higher UACR, especially in the macroalbuminemic range, is associated with increased mortality and worse



progression of CKD in patients irrespective of the presence of diabetes mellitus, CVD, CHF, and blood pressure level. In patients with normal kidney function and in patients with mild decreases in eGFR, the lowest UACR is also associated with the best outcomes, with the lowest event rates seen among those with UACR <10 µg/mg, and in some cases, even <5 µg/mg. In patients with moderate and advanced CKD, UACR levels below what is currently considered normal are associated with worse clinical outcomes. Clinical trials will be needed to test the validity of the optimal UACR cutoffs established in our study as therapeutic targets.

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Key Words: chronic kidney disease ■ microalbuminuria ■ mortality.

 **APPENDIX**

For supplementary figures, please see the online version of this article.