Title

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Journal

Journal of the American College of Cardiology, 61(15)

ISSN

0735-1097

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Publication Date

2013-04-01

DOI

10.1016/j.jacc.2012.11.071

Published in final edited form as:
J Am Coll Cardiol. 2013 April 16; 61(15): 1626–1633. doi:10.1016/j.jacc.2012.11.071.

OUTCOMES ASSOCIATED WITH MICROALBUMINURIA: EFFECT MODIFICATIN BY CHRONIC KIDNEY DISEASE

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Abstract

Objectives—To compare association of microalbuminuria with outcomes in patients with different comorbidities.

Background—The risk of adverse outcomes associated with proteinuria has been found to be linearly decreasing with even low-normal levels of microalbuminuria. It is unclear if 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 US veterans. Associations of UACR with all-cause mortality overall and in subgroups of patients with and without diabetes, hypertension, cardiovascular

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Disclosures

None of the other authors declared any relevant relationship with Industry.

Parts of this material were presented at the American Society of Nephrology Renal Week 2011, November 8–13, 2011, Philadelphia, PA.

disease, congestive heart failure and advanced 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%CI) associated with UACR ≥200, compared to <5 mcg/mg were 1.53 (1.38–1.69, p<0.001) and −1.59 (−1.83, −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 10–19 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.

Keywords

microalbuminuria; chronic kidney disease; mortality

INTRODUCTION

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 CKD.(8–13) An important question about microalbuminuria is the level that should be applied as a cutoff both towards identifying increased risk, and ultimately to use as a therapeutic target. The most commonly used classification for the levels of UACR (the test most readily available in clinical practice) defines a level of 10 mcg/mg as the upper limit of normal (<15 mcg/mg for females, to account for the higher urine creatinine of males).(14) Nevertheless, studies in the general population have suggested that even UACR levels below 10 mcg/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 ESRD,(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 US veterans. We studied UACR ranges that included even those below the currently accepted normal level of 10 mcg/mg, and explored if the associations differed in patients with and without diabetes, CVD, 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 eGFR from the time period between October 1, 2004–September 30, 2006 from the VA Decision Support System National Data Extracts

Laboratory Results file (a VA-wide database containing select laboratory results obtained in the clinical setting).(17) GFR was estimated from serum creatinine measurements and demographic characteristics by the CKD-EPI equation.(18) Out 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.

Socio-demographic characteristics and comorbidities

Data on patient age, gender, race, geographic location (Veteran Integrated Service Network number), blood pressure and administration of ACEI or 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 the October 1, 2004–September 30, 2006 time period 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–September 30, 2009 time period. Data on comorbidities was collected from the VA Inpatient and Outpatient Medical SAS Datasets(20, 21) using *International Classification of Diseases, Ninth Revision* diagnostic and procedure codes and C*urrent Procedural Terminology* codes recorded during the October 1, 2004–September 30, 2006 time 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 was collected from the October 1, 2004–September 30, 2009 time 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 date recorded.

Statistical analyses

Data was 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%), WBC (12.5%) and alkaline phosphatase (10.3%). There were a total of 225,238 patients (75% of the total study population) with 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 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 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 vs. 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–Q3: 5–13) and a baseline eGFR >15 ml/min/1.73m^2 by ordinary least squares regression of eGFR vs. time in each individual patient. Progressive CKD was defined as a slope of <−4 ml/min/1.73m^2/year for logistic regression analyses.

Variables were included in multivariable models if they could be considered confounders(26) based on theoretical considerations and after examination of baseline associations with UACR. Associations were examined sequentially in models with incremental multivariable adjustments: unadjusted (Model 1), age, gender 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 WBC-adjusted (Model 4). Variables which 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. Non-liner associations were examined by categorizing UACR according to established cutoff points for male patients (<10, 10–19, 20–199 and ≥200 mcg/mg),(14) and by subdividing the <10 mcg/mg category into two groups (<5 and 5–9 mcg/mg) in order to examine if UACR levels below the currently accepted upper limit of normal (10 mcg/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 blood pressure level (<120 vs. ≥120 mmHg), CVD, CHF and eGFR level at baseline (<30 vs. ≥30 ml/min/1.73m^2). To better delineate the role of kidney function we also categorized eGFR according to pre-specified cutoffs of 15–29, 30–44, 45–60, 60–89 and ≥90 ml/min/1.73m^2.(27)

Sensitivity analyses were performed by using imputed values of independent variables. Statistical analyses were performed using STATA MP version 11 (STATA Corporation, College Station, TX). The study protocol was approved by the Institutional Review Boards at the Salem VAMC and the Memphis VAMC.

RESULTS

Baseline characteristics in patients categorized by their UACR level are shown in Table 1. Patients with higher UACR were older, more likely to be diabetic, to use ACEI/ARB and to have CVD and CHF, 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: 35.3/1000 patient-years, 95%CI: 35.0–35.7) during a median follow-up of 5.0 years. Patients with higher UACR experienced significantly higher mortality rates in a linearly incremental fashion above a UACR of 10 mcg/mg in all models (Figure 1). When analyzed as a continuous variable a one natural log-unit higher UACR was associated with hazard ratios and 95%CI of 1.31 (1.28–1.34) and 1.11 (1.09–1.13) 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 (Figure 2). UACR levels of 10–19, 20–199 and ≥200 mcg/mg (compared to <5 mcg/mg) were associated with mortality hazard ratios (95%CI) of 1.05 (0.98–1.13), 1.20 (1.12–1.29), 1.43 (1.33–1.54) and 1.57 (1.41–1.54) in patients with eGFR ≥30 ml/min/1.73m^2, and 0.94 (0.80–1.10), 0.81 (0.67–0.98), 0.96 (0.83–1.11) and 1.05 (0.88–1.25) in patients with eGFR

<30 ml/min/1.73m^2 (Figure 2). A more granular assessment of eGFR categories indicated that UACR developed a U-shaped association with mortality below an eGFR of <45 ml/min/1.73m^2: the adjusted mortality hazard ratios (95%CI) associated with UACR 10–19 compared to <5 mcg/mg in patients with eGFR levels ≥90, 60–89, 45–59, 30–44 and 15–29 were 1.19 (1.08–1.31), 1.32 (1.21–1.45), 1.11 (1.01–1.22), 1.00 (0.86–1.15) and 0.81 (0.67–0.98) (Supplemental Figure 1). Furthermore, the magnitude with which UACR was associated with mortality was highest in patients with eGFR 60–89, and gradually diminished in patients with eGFR levels <60 ml/min/1.73m^2 (Supplemental Figure 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 one natural log-unit higher UACR was associated with −0.38 ml/min/1.73m^2/year (95%CI: −0.37, −0.39, p<0.001) and − 0.27 ml/min/1.73m^2/year (−0.35, −0.19, p<0.001) steeper slopes, and with odds ratios (95%CI) of progressive CKD of 1.18 (1.15–1.21, p<0.001) and 1.12 (1.09–1.15, p<0.001) in unadjusted and in fully adjusted linear and logistic regression models, respectively. This association appeared to be linearly incremental at UACR levels ≥10 mcg/mg (Figure 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 (Figure 4). The U-shaped association between UACR and progressive CKD also became apparent in patients with eGFR <45 ml/min/1.73m^2: the adjusted odds ratios (95%CI) of progressive CKD associated with UACR 10–19 compared to <5 mcg/mg in patients with eGFR levels ≥90, 60–89, 45–59, 30–44 and 15–29 were 1.09 (0.98–1.22), 1.19 (1.09–1.21), 1.07 (0.98–1.16), 0.77 (0.63–0.93) and 0.38 (0.26–0.56) (Supplemental Figure 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 US veterans. Higher UACR showed incremental associations with both of these outcomes which were consistent in patients with and without diabetes, CVD, 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. While in patients with eGFR 60–89 ml/min/1.73m^2 UACR levels of <5 mcg/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/1.73m^2 (CKD stages 3B and 4); in the latter groups UACR levels below 10–19 mcg/mg were associated with a significant increase in adverse outcomes compared to patients with UACR 10–19 mcg/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 mcg/mg (<15 mcg/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 <10–15 mcg/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, since it could not only

define the number of individuals 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 to our findings in CKD is that UACR is also a marker of intraglomerular pressure, and the 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 auto-regulate 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) This could lead to adverse outcomes under conditions of end-organ ischemia, as has been suggested by numerous earlier observational studies in ESRD (33–37) and in non-dialysis dependent CKD patients (38, 39) showing a U-shaped association between systolic blood pressure and mortality. It is possible thus 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 towards increased, not decreased risk of mortality and progressive CKD in patients with 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 in 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 towards 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. Based on 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. 10–19 mcg/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. Our study also has a number of limitations. We examined mostly male patients; hence it is unclear if the same results can be extrapolated to females. 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 diabetics 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 or absence of diabetes mellitus, CVD, CHF and of blood pressure level. In patients with normal kidney function and in those with mild decreases in eGFR the lowest UACR is also associated with the best outcomes, with the lowest event rates seen in those with UACR <10, and in some cases even <5 mcg/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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Relevant relationships with Industry:

Csaba P Kovesdy received a research grant without salary support from Abbott. Kamyar Kalantar-Zadeh received honoraria and research grants from Abbott.

This study was supported by grant 1R01DK078106-01 to CPK and KKZ and by the Department of Veterans Affairs. CPK, EHL and SMM are employees of the Department of Veterans Affairs.

Opinions expressed in this paper are those of the authors’ and do not necessarily represent the opinion of the Department of Veterans Affairs.

Abbreviations list

ACEI	angiotensin converting enzyme inhibitor
ARB	angiotensin receptor blockers
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVD	cardiovascular disease
ESRD	end stage renal disease
eGFR	estimated glomerular filtration rate
UACR	urine microalbumin-creatinine ratio
VA	Veterans Administration
WBC	white blood cell count

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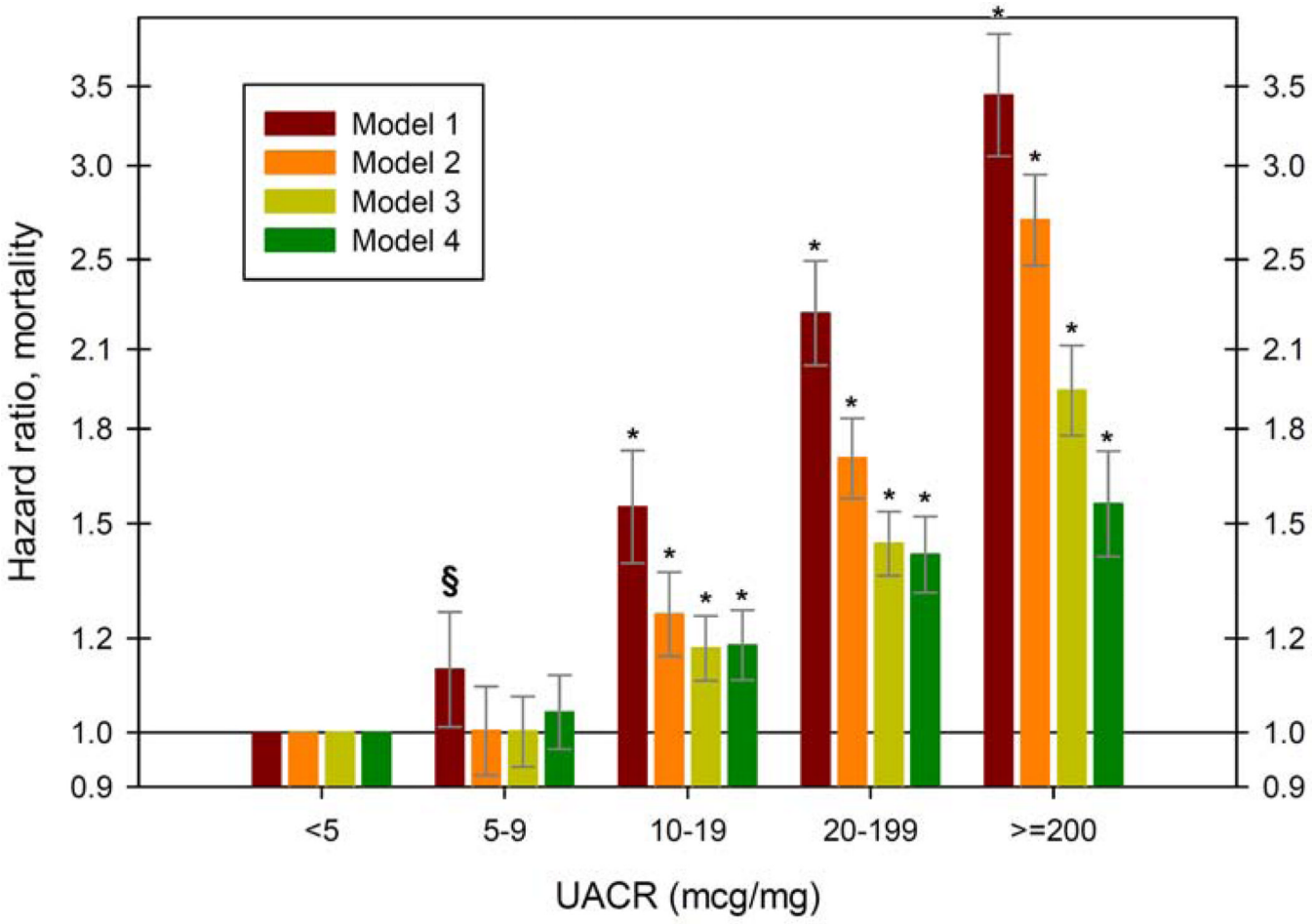

Figure 1. Unadjusted and multivariable adjusted hazard ratios (95% confidence intervals) of all-cause mortality associated with various levels of urine microalbumin-creatinine ratio in 298,875 patients (time-dependent Cox models)

The groups with urine microalbumin-creatinine ratio <5 mcg/mg served as referent. Models represent unadjusted association (Model 1) and associations after adjustment for age, gender and race (Model 2), Model 2 variables + diabetes mellitus, cardiovascular disease, congestive heart failure and the Charlson comorbidity index (Model 3) and Model 3 variables + blood pressure, ACEI/ARB use, estimated glomerular filtration rate, serum albumin, blood hemoglobin, white blood cell count and serum alkaline phosphatase (Model 4). *$p<0.001$, $^{\#}p<0.01$, $^{\S}p<0.05$

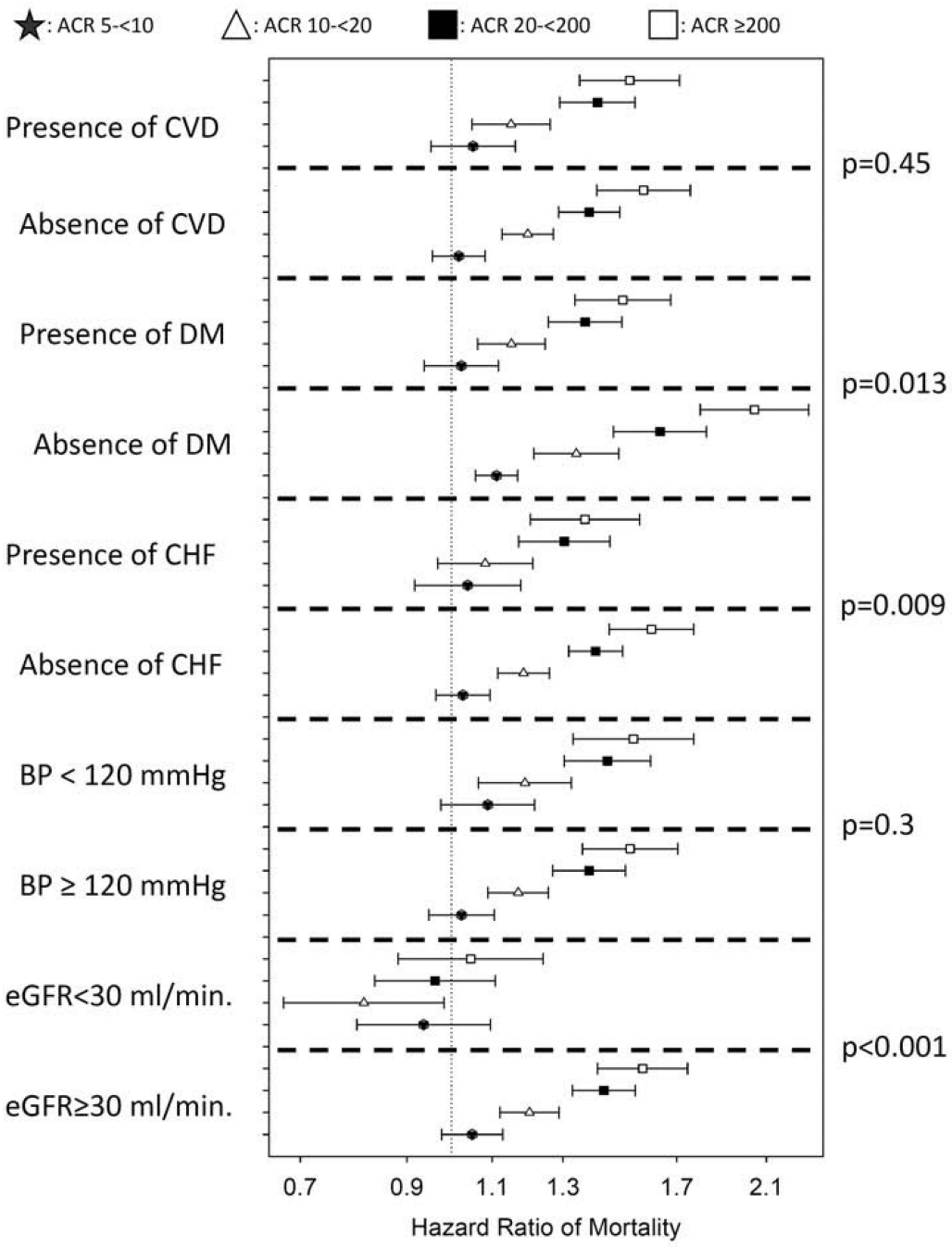

Figure 2. Hazard ratios (95%CI) of mortality associated with urine microalbumin-creatinine ratio categories of 5–9, 10–19, 20–199 and ≥200 mcg/mg, compared to <5 mcg/mg in different subgroups of patients

Results were obtained from Cox models adjusted for age, gender, race, diabetes mellitus, cardiovascular disease, congestive heart failure, the Charlson comorbidity index, blood pressure, ACEI/ARB use, estimated glomerular filtration rate, serum albumin, blood hemoglobin, white blood cell count and serum alkaline phosphatase. P values represent significance levels for interaction terms.

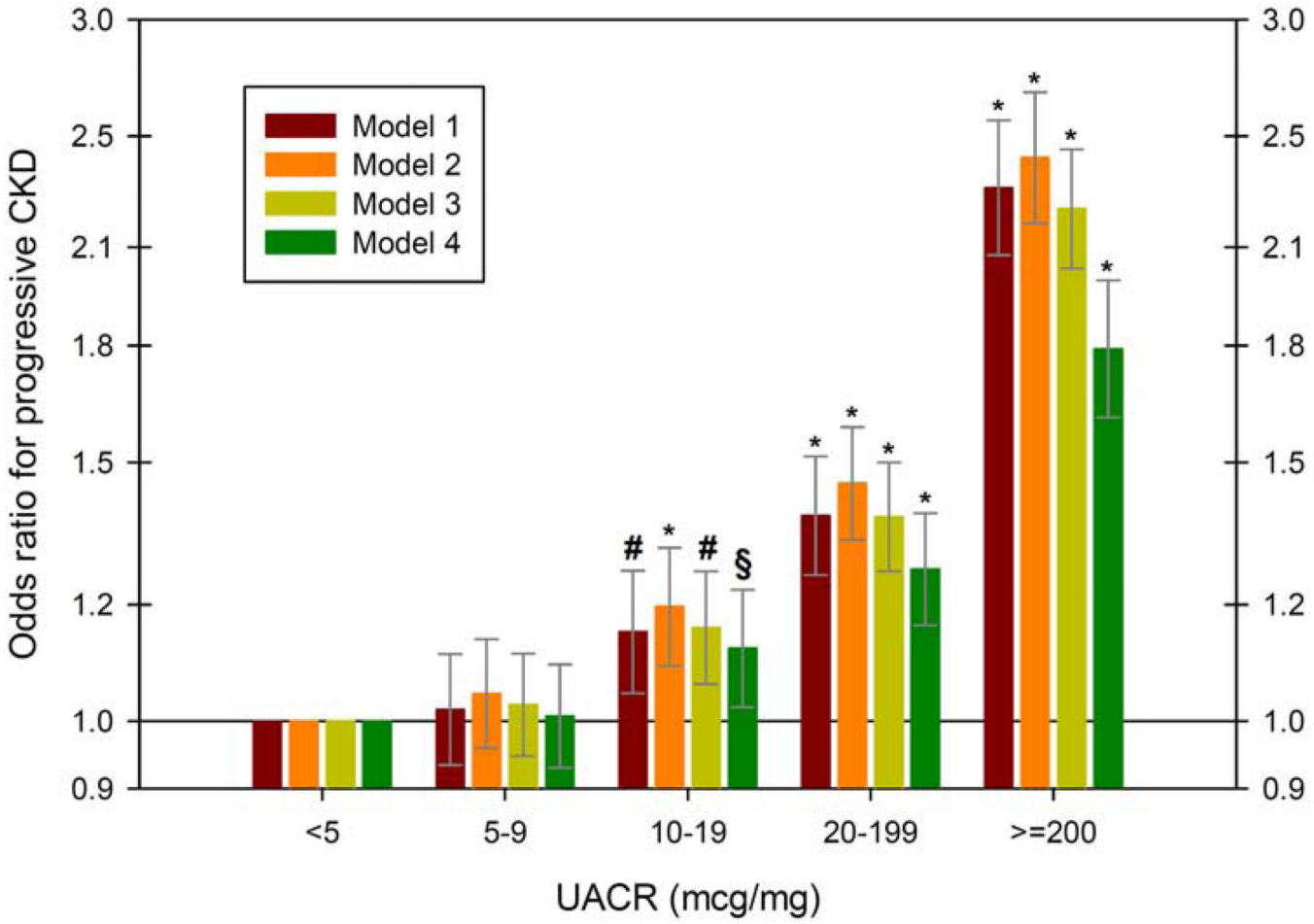

Figure 3. Unadjusted and multivariable adjusted odds ratios (95% confidence intervals) of progressive CKD associated with various levels of urine microalbumin-creatinine ratio in logistic regression models

The groups with urine microalbumin-creatinine ratio <5 mcg/mg served as referent. Models represent unadjusted association (Model 1) and associations after adjustment for age, gender and race (Model 2), Model 2 variables + diabetes mellitus, cardiovascular disease, congestive heart failure and the Charlson comorbidity index (Model 3) and Model 3 variables + blood pressure, ACEI/ARB use, serum albumin, blood hemoglobin, white blood cell count and serum alkaline phosphatase (Model 4). *p<0.001, #p<0.01, §p<0.05

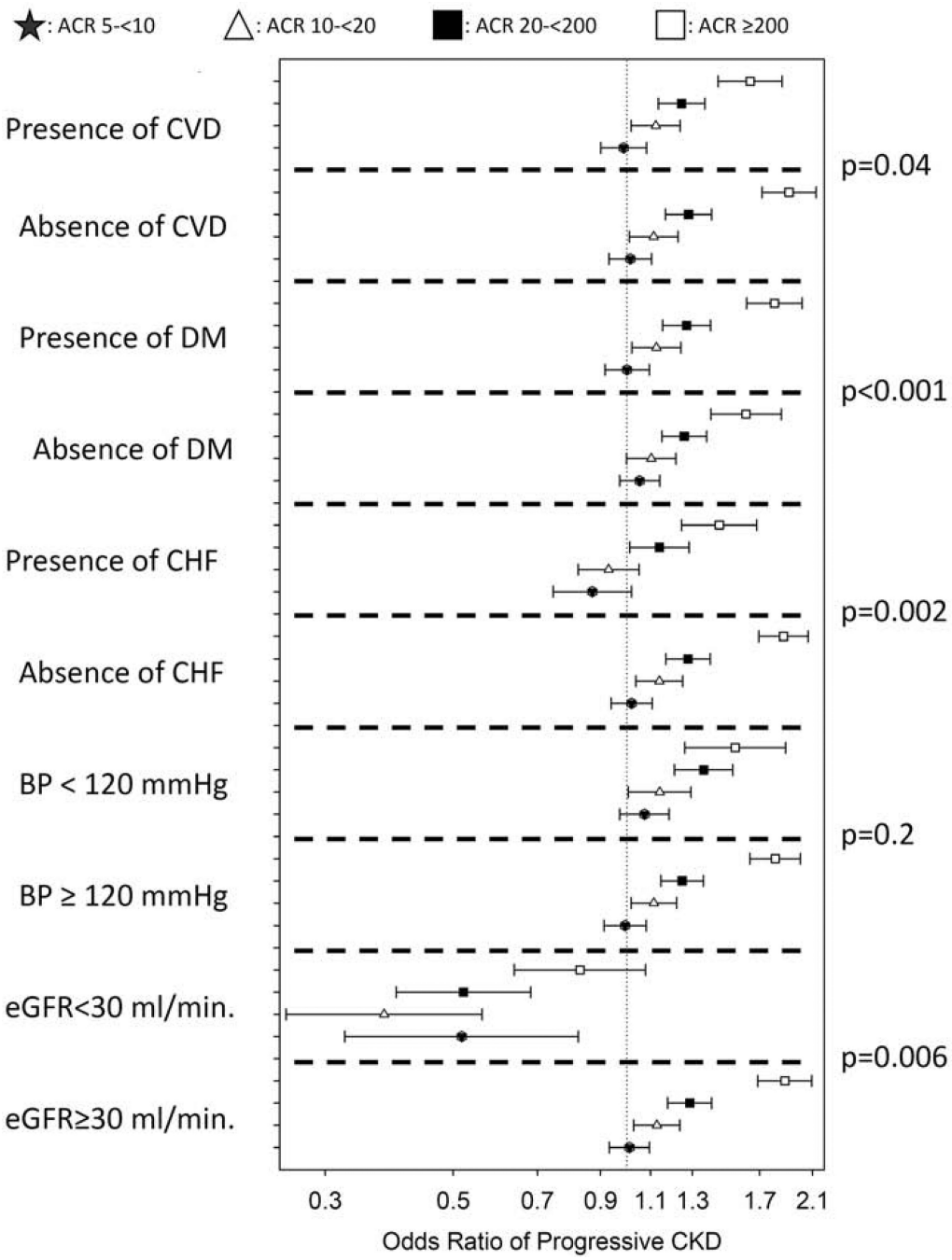

Figure 4. Odds ratios (95% confidence intervals) of progressive CKD associated with urine microalbumin-creatinine ratio categories of 5–9, 10–19, 20–199 and ≥200 mcg/mg, compared to <5 mcg/mg in different subgroups of patients

Results were obtained from logistic regression models adjusted for age, gender, race, diabetes mellitus, cardiovascular disease, congestive heart failure, the Charlson comorbidity index, blood pressure, ACEI/ARB use, serum albumin, blood hemoglobin, white blood cell count and serum alkaline phosphatase. P values represent significance levels for interaction terms.

J Am Coll Cardiol. Author manuscript; available in PMC 2014 April 16.

Table 1

Baseline characteristics of individuals stratified by level of baseline urine microalbumin-creatinine ratio

		Urine microalbumin/creatinine (mcg/mg)				
		<5	**5–9**	**10–19**	**20–199**	**≥ 200**
		(N= 72,448)	**(N= 64,053)**	**(N= 55,664)**	**(N= 90,828)**	**(N= 15,882)**
Age (years)		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)
Gender (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 (mmHg)		132 ± 16	133 ± 16	134 ± 17	137 ± 18	141 ± 19
DBP (mmHg)		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/1.73m^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

	Urine microalbumin/creatinine (mcg/mg)				
	<5 (N= 72,448)	**5–9 (N= 64,053)**	**10–19 (N= 55,664)**	**20–199 (N= 90,828)**	**≥ 200 (N= 15,882)**
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 (1000/mm^3)	7.1 ± 3.2	7.3 ± 3.3	7.4 ± 2.9	7.6 ± 3.5	7.8 ± 3.8
UACR (mcg/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)

Data is presented as means ± SD, number (% of total) or median (interquartile range). DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; Hgb, hemoglobin; WBC, white blood cell count. To convert GFR in mL/min/1.73m^2 to mL/s/1.73m^2, 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; hemoglobin in g/dL to g/L, multiply by 10.

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