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Changes in Albuminuria and Subsequent Risk of Incident Kidney Disease

Keiichi Sumida,*‡ Miklos Z. Molnar,*§ Praveen K. Potukuchi,* Koshy George,* Fridtjof Thomas,§ Jun Ling Lu,* Kunihiro Yamagata,† Kamyar Kalantar-Zadeh,* and Csaba P. Kovesdy***

Abstract
Background and objectives Albuminuria is a robust predictor of CKD progression. However, little is known about the associations of changes in albuminuria with the risk of kidney events outside the settings of clinical trials.

Design, setting, participants, & measurements In a nationwide cohort of 56,946 United States veterans with an eGFR ≥ 60 ml/min per 1.73 m², we examined the associations of 1-year fold changes in albuminuria with subsequent incident CKD (>25% decrease in eGFR reaching < 60 ml/min per 1.73 m²) and rapid eGFR decline (eGFR slope < -5 ml/min per 1.73 m² per year) assessed using Cox models and logistic regression, respectively, with adjustment for confounders.

Results The mean age was 64 (SD, 10) years old; 97% were men, and 91% were diabetic. There was a nearly linear association between 1-year fold changes in albuminuria and incident CKD. The multivariable-adjusted hazard ratios (95% confidence intervals) of incident CKD associated with more than twofold decrease, 1.25- to twofold decrease, 1.25- to twofold increase, and more than twofold increase (versus <1.25-fold decrease to <1.25-fold increase) in albuminuria were 0.82 (95% confidence interval, 0.77 to 0.89), 0.93 (95% confidence interval, 0.86 to 1.00), 1.12 (95% confidence interval, 1.05 to 1.20), and 1.29 (95% confidence interval, 1.21 to 1.38), respectively. Qualitatively similar associations were present for rapid eGFR decline (adjusted odds ratios; 95% confidence intervals) of incident CKD associated with more than twofold decrease, 1.25-fold increase, and more than twofold increase (versus <1.25-fold decrease to <1.25-fold increase) in albuminuria were 0.82 (95% confidence interval, 0.78 to 0.94; adjusted odds ratio, 0.86; 95% confidence interval, 0.78 to 0.94; adjusted odds ratio, 0.98; 95% confidence interval, 0.89 to 1.07; adjusted odds ratio, 1.18; 95% confidence interval, 1.08 to 1.29; and adjusted odds ratio, 1.67; 95% confidence interval, 1.54 and 1.81, respectively).

Conclusions Relative changes in albuminuria over a 1-year interval were linearly associated with subsequent risk of kidney outcomes. Additional studies are warranted to elucidate the underlying mechanisms of the observed associations and test whether active interventions to lower elevated albuminuria can improve kidney outcomes.


Introduction
Albuminuria is an established and strong prognostic factor for various adverse clinical outcomes, such as mortality, ESRD, and cardiovascular events, in the general population (1–5) and patients with diabetes, hypertension, vascular disease, and CKD (6–11). Existing clinical practice guidelines have emphasized the use of current level of albuminuria as well as eGFR for CKD definition and staging (12,13).

In recent years, there has been a growing interest in changing albuminuria as a potential surrogate measure of CKD progression. A recent meta-analysis of clinical trials has shown that short-term treatment-induced changes in albuminuria correlate well with long-term treatment effects on ESRD, suggesting that albuminuria could be considered a therapeutic target in clinical practice and also, a surrogate end point for ESRD in clinical trials (14). However, relatively short evaluation periods (a median of 6 months) for changes in albuminuria and highly selected patients with diabetes or hypertension treated mainly with renin-angiotensin system inhibitors in previous trials limit the generalizability of these findings, and the controversy as to whether changes in albuminuria can be used as an acceptable surrogate for ESRD continues to be debated (15–18). Outside the setting of clinical trials, few observational studies have examined the associations of changes in albuminuria with kidney outcomes (19–21). Furthermore, the changes in urinary albumin-to-creatinine ratio (UACR) in previous studies were generally defined using a single first measurement and a single last measurement, which may be subject to potentially substantial intraindividual variability of albuminuria over time (22,23), and thus, may be less precise than alternative analytic approaches using multiple albuminuria measurements.

The objective of our study was to investigate the associations of relative changes in albuminuria over a 1-year interval as well as annual changes (slopes) in albuminuria with various kidney outcomes in individuals with normal eGFR.
Materials and Methods

Cohort Definition
Our study used data from a retrospective cohort study (the Racial and Cardiovascular Risk Anomalies in CKD Study), which included 3,582,478 United States veterans with eGFR $\geq 60$ ml/min per 1.73 m$^2$ between October 1, 2004 and September 30, 2006 (baseline period) (24,25). The algorithm for cohort definition is shown in Supplemental Figure 1. In this study, we used at least two UACR measurements that were 1 year apart; therefore, patients without any UACR measurements ($n=3,374,292$) or those without two UACR measurements that were 1 year apart ($n=150,985$) during the baseline period were excluded. After further exclusion of patients with erroneous data ($n=255$), 56,946 patients were included in our final cohort.

Exposure Variable
The primary exposure of interest was a 1-year fold change in UACR during the 2-year baseline period. A margin of 6 months before and after the date of the last UACR measurement was allowed for determining the last available UACR to calculate the change (e.g., UACR between 0.5 and 1.5 years after the first UACR measurement could be used for the 1-year fold change) (26). We stratified 1-year fold UACR changes into five a priori categories before analyses started: more than twofold decrease, 1.25- to twofold decrease, 1.25-fold decrease to 1.25-fold increase, 1.25- to twofold increase, and more than twofold increase (20). The group with 1-year fold UACR changes of 1.25-fold decrease to 1.25-fold increase (i.e., stable UACR) was used as a reference in all categorical analyses. One-year fold UACR change was also treated as a continuous variable to examine nonlinear associations.

Covariates
Baseline variables were determined at the date of the first UACR measurement. Sociodemographic characteristics, comorbid conditions, laboratory characteristics, and medication use were obtained as previously described (27,28). Briefly, data on patients’ age, sex, race, marital status, body mass index, systolic BP, diastolic BP, comorbid conditions, medication use, mean per capita income, and service connectedness were collected from various national Veterans Affairs (VA) research data files (29). Prevalent comorbidities were defined as the presence of relevant International Classification of Diseases, Ninth Revision, Clinical Modification Diagnostic and Procedure Codes and Current Procedure Terminology codes recorded from October 1, 2004 to September 30, 2006 (Supplemental Table 1) (27,28). Intrindividual slopes of systolic BP and eGFR were estimated from linear mixed effects models using all of their available values from the UACR change evaluation period. The treatment status of renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors) was defined on the basis of their use at the dates of the first and last UACR measurements and categorized into four patterns (i.e., use at both, either, or neither dates). Renin-angiotensin system inhibitors adherence was also defined as the proportion of days covered by the drug during the evaluation period for UACR change (30). In addition to the information derived from VA sources, we included select socioeconomic indicators using 2004 county typology codes (housing stress, low education, low employment, and persistent poverty) (Supplemental Table 2).

Outcome Assessment
The coprimary outcomes were incident CKD and rapid eGFR decline. Incident CKD was defined as two eGFR levels $< 60$ ml/min per 1.73 m$^2$ separated by $\geq$90 days and a $>25\%$ decrease from baseline eGFR (31). The start of follow-up was the date of the last UACR measurement, and patients were censored at the time of death, the last encounter, or the last date of available kidney event (October 13, 2012 and September 13, 2011 for incident CKD and ESRD, respectively) (32). Rapid eGFR decline was defined as an eGFR slope $<-5$ ml/min per 1.73 m$^2$ per year calculated from an ordinary least squares regression model using all outpatient eGFR measurements available from the cohort entry date to October 13, 2012 (a median [interquartile interval (IQI)] of ten [5 to 17] measurements). Information about all-cause mortality was obtained from the VA Vital Status Files (33).

Statistical Analyses
Baseline characteristics were summarized according to categories of UACR change and presented as a number (percentage) for categorical variables and mean $\pm$SD for continuous variables with normal distribution or median (IQI) for those with skewed distribution. Differences across categories were assessed using ANOVA and chi-squared tests for continuous and categorical variables, respectively. The associations of UACR changes with kidney outcomes were assessed using Cox proportional hazards models (for incident CKD) and logistic regression models (for rapid eGFR decline). For the Cox models, the proportionality assumption was tested by plotting log ($-\log$ [survival rate]) against log (survival time) and by scaled Schoenfeld residuals, which showed no violations. Models were incrementally adjusted for the following confounders on the basis of theoretical considerations: model 1 unadjusted; model 2 adjusted for age, sex, race, baseline eGFR, and log-transformed UACR; model 3 additionally accounted for prevalent comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and HIV/AIDS); and model 4 additionally included baseline body mass index, systolic and diastolic BP, slopes of systolic BP and eGFR calculated during the 1-year UACR change estimation period, baseline use of statins and nonopioid analgesics, renin-angiotensin system inhibitor treatment status, and renin-angiotensin system inhibitor adherence. Because we took a clinical trial approach, in which we assume that future change in UACR is a surrogate end point of incident CKD, we adjusted for baseline covariates measured at the first UACR measurement and started the follow-up at the last UACR measurement. Nonlinear associations were tested by adding the quadratic term of UACR change to the models. We further explored nonlinearity by using restricted cubic splines.

We performed several sensitivity analyses to evaluate the robustness of our main findings. The associations of
UACR change with outcomes were examined in subgroups of patients stratified by baseline UACR levels and the number of UACR measurements available during the 2-year baseline period as well as various other characteristics. Potential interactions were tested by including interaction terms. Because death and incident CKD are competing events, competing risk regression models were performed. We also investigated whether accounting for socioeconomic parameters and baseline serum albumin and total cholesterol further attenuates the associations of UACR change with kidney outcomes as an additional model (model 5). Additionally, the associations were examined using UACR slopes calculated by both ordinary least squares regression models and linear mixed effects models using all intraindividual UACR values (34).

Of the variables included in multivariable-adjusted models, data points were missing for race (8%), body mass index (3%), systolic and diastolic BP (<1%), and eGFR slope (<1%). Missing values were not imputed in primary analyses but were substituted by multiple imputation procedures using the STATA mi set of command in sensitivity analyses. The reported P values are two sided and reported as significant at <0.05 for all analyses. All of the analyses were conducted using Stata/MP, version 14 (Stata Corporation, College Station, TX). The study was approved by the institutional review boards at the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

Results

Patients’ baseline characteristics overall and in patients stratified by 1-year fold UACR change categories are shown in Table 1. Among 56,946 patients, 9412 (17%), 8536 (15%), 16,368 (29%), 10,972 (19%), and 11,658 (20%) experienced more than twofold decrease, 1.25- to twofold decrease, stable, 1.25- to twofold increase, and more than twofold increase in UACR, respectively. Overall, the mean age at baseline was 64 (SD, 10) years old; 97% were men, and 15% were black. Also, 91% were diabetic, and 84% had a history of hypertension. The mean eGFR was 79 (SD, 16) ml/min per 1.73 m², and the median (IQR) of UACR was 13 (6–29) mg/g at baseline. Compared with patients with stable UACR (29% of the cohort), both those with decreases in UACR (31% of the cohort) and those with increases in UACR (40% of the cohort) tended to have a poorer risk profile.

Incident CKD

During a median follow-up of 6.3 years, there was a total of 8194 events of incident CKD (Supplemental Table 3A). The adjusted association between 1-year fold UACR change and incident CKD was nearly linear (P=0.003 for the quadratic term), with better outcome observed with decreases in 1-year fold UACR (Supplemental Figure 2).

Figure 1 shows the unadjusted and multivariable-adjusted hazard ratios (HRs) associated with 1-year fold UACR change categories. In the crude model, both increases and decreases in UACR were incrementally associated with higher risk of incident CKD. The associations were substantially modified, particularly for decreases in UACR, after further adjustment for potential confounders and showed a nearly linear relationship (adjusted HRs; 95% confidence intervals [95% CIs] for more than twofold decrease, 1.25- to twofold decrease, 1.25- to twofold increase, and more than twofold increase [versus stable] in UACR; adjusted HR, 0.82; 95% CI, 0.77 to 0.89; adjusted HR, 0.93; 95% CI, 0.86 to 1.00; adjusted HR, 1.12; 95% CI, 1.05 to 1.20; and adjusted HR, 1.29; 95% CI, 1.21 to 1.38, respectively, in model 4) (Figure 1).

In subgroup analyses, a similar trend of association was observed in patients with different baseline UACR levels (P for interaction =0.05) (Figure 2) and different numbers of UACR measurements during the baseline period (Supplemental Figure 3A) as well as in other examined subgroups with statistically significant interactions with age and coronary heart disease (Figure 3). Results were largely consistent after accounting for death as a competing risk, imputing missing data, or further adjusting for additional covariates (Supplemental Tables 4–6). A similar near-linear association was observed for UACR changes estimated by ordinary least squares regression (Supplemental Figure 4A), whereas the association with decreasing UACR was null for UACR changes estimated by linear mixed effects models (Supplemental Figure 5A).

Rapid eGFR Decline

A total of 6512 (12%) patients had rapid eGFR decline during the follow-up period (Supplemental Table 3B). Similar to the associations with incident CKD, the multivariable-adjusted risk associated with rapid eGFR decline was also nearly linear (adjusted odds ratios [ORs]; 95% CI for more than twofold decrease, 1.25- to twofold decrease, 1.25- to twofold increase, and more than twofold increase [versus stable] in UACR; adjusted OR, 0.86; 95% CI, 0.78 to 0.94; adjusted OR, 0.98; 95% CI, 0.89 to 1.07; adjusted OR, 1.18; 95% CI, 1.08 to 1.29; and adjusted OR, 1.67; 95% CI, 1.54 to 1.81, respectively, in model 4) (Figure 4). In subgroup analyses, the associations of 1-year fold UACR change with rapid eGFR decline were generally consistent across subgroups (Supplemental Figures 3B, 6, and 7). Baseline UACR qualitatively modified the association of 1-year fold UACR change with rapid eGFR decline, with slightly better outcomes associated with UACR decline among patients with baseline UACR >30 mg/g (Supplemental Figure 6). Findings were robust to several sensitivity analyses (Supplemental Tables 5B and 6B). Analyses with two different indices of UACR change yielded essentially similar associations, except for the associations with decreasing UACR (<–30 mg/g per year), which were null and greater for UACR changes estimated by ordinary least squares regression models and linear mixed effects models, respectively (Supplemental Figures 4B and 5B).

Discussion

In this large cohort of United States veterans with eGFR ≥60 ml/min per 1.73 m², we found that relative changes in UACR over a 1-year interval were linearly associated with subsequent risk of incident CKD and rapid eGFR decline independent of known kidney disease risk factors. Our findings are generally consistent with previous observational studies that investigated the associations of changes in UACR (defined by single first and last measurements) with the risk of kidney outcomes (19,20,35). Among
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total, N = 56,946</th>
<th>More than Twofold Decrease, n = 9412</th>
<th>1.25- to Twofold Decrease, n = 8536</th>
<th>Stable, n = 16,368</th>
<th>1.25- to Twofold Increase, n = 10,972</th>
<th>More than Twofold Increase, n = 11,658</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>64 ± 10</td>
<td>63 ± 11</td>
<td>64 ± 10</td>
<td>64 ± 10</td>
<td>65 ± 10</td>
<td>64 ± 10</td>
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<td>Men, n (%)</td>
<td>55,441 (97)</td>
<td>9109 (97)</td>
<td>8315 (97)</td>
<td>15,963 (98)</td>
<td>10,703 (98)</td>
<td>11,351 (97)</td>
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<td>Black, n (%)</td>
<td>7624 (15)</td>
<td>1465 (17)</td>
<td>1194 (15)</td>
<td>1970 (13)</td>
<td>1369 (14)</td>
<td>1,626 (15)</td>
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<td>Diabetes mellitus, n (%)</td>
<td>51,690 (91)</td>
<td>8632 (92)</td>
<td>7721 (91)</td>
<td>14,713 (90)</td>
<td>9943 (91)</td>
<td>10,681 (92)</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>47,813 (84)</td>
<td>8210 (86)</td>
<td>7180 (84)</td>
<td>13,486 (82)</td>
<td>9153 (83)</td>
<td>9874 (85)</td>
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<tr>
<td>CHD, n (%)</td>
<td>10,192 (18)</td>
<td>1802 (19)</td>
<td>1465 (17)</td>
<td>2801 (17)</td>
<td>1877 (17)</td>
<td>2247 (19)</td>
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<td>CHF, n (%)</td>
<td>3981 (7)</td>
<td>828 (9)</td>
<td>511 (6)</td>
<td>986 (6)</td>
<td>651 (6)</td>
<td>1005 (9)</td>
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<tr>
<td>CVD, n (%)</td>
<td>4617 (8)</td>
<td>828 (9)</td>
<td>689 (8)</td>
<td>1235 (8)</td>
<td>857 (8)</td>
<td>1008 (9)</td>
</tr>
<tr>
<td>PAD, n (%)</td>
<td>5682 (10)</td>
<td>1034 (11)</td>
<td>841 (10)</td>
<td>1533 (9)</td>
<td>1010 (9)</td>
<td>1264 (11)</td>
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<tr>
<td>Chronic lung disease, n (%)</td>
<td>10,401 (18)</td>
<td>1805 (19)</td>
<td>1562 (18)</td>
<td>2843 (17)</td>
<td>1926 (18)</td>
<td>2265 (19)</td>
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<td>Liver disease, n (%)</td>
<td>236 (1)</td>
<td>40 (1)</td>
<td>39 (1)</td>
<td>64 (1)</td>
<td>41 (1)</td>
<td>52 (1)</td>
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<td>Dementia, n (%)</td>
<td>350 (1)</td>
<td>59 (1)</td>
<td>46 (1)</td>
<td>86 (1)</td>
<td>66 (1)</td>
<td>93 (1)</td>
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<td>Rheumatologic disease, n (%)</td>
<td>707 (1)</td>
<td>134 (1)</td>
<td>103 (1)</td>
<td>189 (1)</td>
<td>133 (1)</td>
<td>148 (1)</td>
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<td>Malignancies, n (%)</td>
<td>5887 (10)</td>
<td>984 (11)</td>
<td>878 (10)</td>
<td>1607 (10)</td>
<td>1111 (10)</td>
<td>1307 (11)</td>
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<td>Depression, n (%)</td>
<td>5386 (10)</td>
<td>1020 (11)</td>
<td>811 (10)</td>
<td>1411 (9)</td>
<td>976 (9)</td>
<td>1168 (10)</td>
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<td>HIV/AIDS, n (%)</td>
<td>123 (1)</td>
<td>24 (1)</td>
<td>18 (1)</td>
<td>27 (1)</td>
<td>26 (2)</td>
<td>28 (1)</td>
</tr>
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<td>BMI, kg/m²</td>
<td>31.9 ± 6.1</td>
<td>32.2 ± 6.5</td>
<td>31.8 ± 6.0</td>
<td>31.7 ± 6.0</td>
<td>31.8 ± 6.0</td>
<td>31.9 ± 6.2</td>
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<tr>
<td>Systolic BP, mm Hg</td>
<td>133 ± 17</td>
<td>136 ± 18</td>
<td>134 ± 17</td>
<td>133 ± 16</td>
<td>132 ± 16</td>
<td>132 ± 17</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>74 ± 11</td>
<td>76 ± 11</td>
<td>75 ± 11</td>
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<td>74 ± 10</td>
<td>73 ± 11</td>
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<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>79 ± 16</td>
<td>80 ± 16</td>
<td>79 ± 16</td>
<td>80 ± 15</td>
<td>79 ± 16</td>
<td>78 ± 16</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>4.1 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>4.1 ± 0.4</td>
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<tr>
<td>UACR categories, mg/g</td>
<td>13 (6, 29)</td>
<td>28 (14–78)</td>
<td>14 (7–31)</td>
<td>11 (6–21)</td>
<td>9 (5–22)</td>
<td>9 (4–20)</td>
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<td>UACR categories, mg/g</td>
<td>&lt;30</td>
<td>43,098 (76)</td>
<td>4856 (52)</td>
<td>6308 (74)</td>
<td>13,349 (82)</td>
<td>8895 (81)</td>
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<td>30 to &lt;300</td>
<td>12,244 (22)</td>
<td>3929 (42)</td>
<td>1995 (23)</td>
<td>2681 (16)</td>
<td>1828 (17)</td>
<td>1811 (16)</td>
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<td>≥300</td>
<td>1604 (3)</td>
<td>627 (7)</td>
<td>233 (3)</td>
<td>338 (2)</td>
<td>249 (2)</td>
<td>157 (1)</td>
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<td>Statin use, n (%)</td>
<td>16,637 (29)</td>
<td>2754 (29)</td>
<td>2572 (30)</td>
<td>4702 (28)</td>
<td>3205 (29)</td>
<td>3404 (29)</td>
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<td>Nonopioid analgesics use, n (%)</td>
<td>17,537 (31)</td>
<td>3134 (33)</td>
<td>2671 (31)</td>
<td>4819 (29)</td>
<td>3169 (29)</td>
<td>3744 (32)</td>
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<td>RASt use, n (%)</td>
<td>10,614 (19)</td>
<td>1936 (21)</td>
<td>1525 (18)</td>
<td>2926 (18)</td>
<td>1991 (18)</td>
<td>2236 (19)</td>
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<td>RASt adherence (&gt;80%), n (%)</td>
<td>29,340 (52)</td>
<td>5182 (55)</td>
<td>4330 (51)</td>
<td>8203 (50)</td>
<td>5564 (51)</td>
<td>6061 (52)</td>
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<td>Married, n (%)</td>
<td>32,854 (60)</td>
<td>5169 (57)</td>
<td>4926 (60)</td>
<td>9671 (61)</td>
<td>6501 (61)</td>
<td>6587 (58)</td>
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<td>Service connected, n (%)</td>
<td>23,793 (42)</td>
<td>3972 (42)</td>
<td>3557 (42)</td>
<td>6754 (41)</td>
<td>4552 (42)</td>
<td>4958 (43)</td>
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Table 1. (Continued)

<table>
<thead>
<tr>
<th>1-yr Fold Changes in UACR</th>
<th>Total, (n = 56,946)</th>
<th>More than Twofold Decrease, (n = 8,536)</th>
<th>1.25- to Twofold Decrease, (n = 9,412)</th>
<th>Stable, (n = 16,368)</th>
<th>1.25- to Twofold Increase, (n = 10,972)</th>
<th>More than Twofold Increase, (n = 11,658)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living in area with high housing stress, (n(%))</td>
<td>22,732 (40)</td>
<td>3783 (41)</td>
<td>1162 (14)</td>
<td>7065 (13)</td>
<td>1238 (12)</td>
<td>716 (9)</td>
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<td>Living in area with low education, (n(%))</td>
<td>4648 (8)</td>
<td>732 (8)</td>
<td>716 (9)</td>
<td>7065 (13)</td>
<td>1238 (12)</td>
<td>716 (9)</td>
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<tr>
<td>Living in area of persistent poverty, (n(%))</td>
<td>1677 (3)</td>
<td>260 (3)</td>
<td>250 (3)</td>
<td>1238 (12)</td>
<td>1907 (12)</td>
<td>1487 (9)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage), mean ± SD, or median (interquartile range). All \(P\) values except variables indicated for comparing differences across categories were statistically significant. UACR, urinary albumin-to-creatinine ratio; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cerebrovascular disease; PAD, peripheral arterial disease; BMI, body mass index; RASi, renin-angiotensin system inhibitor.

In contrast with the association of increase in UACR with poorer kidney outcomes, Carrero et al. (20) found that relative changes in UACR over a 1-, 2-, or 3-year interval were consistently and linearly associated with subsequent risk of ESRD, with significantly higher and lower risks seen in those with greater increases and reductions in UACR, respectively. In contrast, another study offered seemingly conflicting evidence on the kidney risk associated with decreases in UACR, showing no association between remission of UACR and the risk of subsequent kidney events (21). These conflicting results may be partly explained by the different populations across studies (e.g., patients with higher [versus lower] baseline UACR showed stronger associations in our study) and/or different analytic methods to express changes in UACR. Indeed, slightly discrepant associations of decreasing UACR with incident CKD were also observed in our study when using different approaches to estimate changes in UACR (i.e., absolute versus relative changes). The two-measurement approach used in our primary analyses is simple and easy to implement in real world settings, but it may be subject to potential intra-individual variability of UACR over time. More sophisticated modeling techniques, such as generalized estimating equations and linear mixed effects models, might thus be preferable for the assessment of UACR changes if multiple measurements were available, just as proposed for the assessment of eGFR trajectories (34), but may be less applicable in daily clinical practice. In this context, our study is, to our knowledge, the first to investigate the associations of UACR changes with subsequent incident CKD by expressing the exposure as absolute changes in UACR (i.e., UACR slope) as well as relative changes in UACR (i.e., 1-year fold UACR changes).

There are several plausible explanations for the underlying mechanisms of the observed near-linear association between UACR changes and adverse kidney outcomes. In line with previous findings on the possible biologic link between albuminuria and cardiovascular events, it is likely that an increase in UACR is a manifestation of worsened generalized vascular dysfunction, particularly endothelial dysfunction, as proposed in the Steno hypothesis (36). Increasing UACR might also reflect increased single-nephron hyperfiltration accompanied by the decrease in the number of functional nephrons (i.e., compensatory hyperfiltration of the remaining nephrons) as well as glycocalyx dysfunction in the glomerular endothelium, both of which are risk factors for subsequent glomerulosclerosis (37–39).

Recent evidence also suggests that increased glomerular albumin leakage increases the exposure and uptake of excessive albumin in proximal tubular cells, which in turn, trigger the activation of intracellular signaling pathways that induces the release of inflammatory, vasoactive, and fibrotic substances (40–43). These pathophysiologic processes collectively lead to tubulointerstitial damage and could ultimately result in irreversible kidney damage.

In contrast with the association of increase in UACR with poorer kidney outcomes, we did not find similar associations for decreases in UACR when we expressed UACR changes as slopes, particularly for the slopes estimated by linear mixed effects models, but observed null or slightly worse kidney outcomes in patients who
experienced larger absolute decreases in UACR over time. This seemingly counterintuitive finding may be due to the imperfect nature of modeling techniques for UACR slopes (e.g., single outliers causing misclassification of slope categories) as well as residual confounding from baseline albuminuria, which has substantial biologic variability. However, decreases in UACR may not always be the result of improving or resolving kidney pathology. In addition to being a manifestation of endothelial dysfunction, UACR is also a marker of intraglomerular pressure, which is maintained by glomerular autoregulation under normal circumstances. In patients with diabetes and persistent albuminuria (i.e., with nephropathy) accompanied by impaired glomerular autoregulation, for example, decreases in UACR may represent their decreased ability to adapt to lower kidney perfusion pressures (46), which could cause ischemic kidney injury. Therefore, it is possible that large decreases in UACR could identify some vulnerable patients at high risk for ischemic kidney damage, which may overwhelm the physiologic benefits of reduced UACR when reaching a certain threshold. It is also important to note that similar associations have been reported between decreases in UACR and cardiovascular events or mortality in different patient populations (21,47), and very low UACR levels have been associated with higher mortality and poorer kidney outcomes in patients with advanced CKD (48).

Our results may have several clinical implications. Given its robust associations with kidney outcomes, a relative change in UACR over a 1-year interval could potentially be used as a surrogate for CKD progression. The slightly discrepant associations of decreasing UACR with kidney outcomes depending on different indices of changes in UACR raise the need to determine an optimal modeling technique to express changes in UACR over time. In addition, given that a decrease in UACR may be a multifactorial phenomenon potentially representing a beneficial evolution of kidney disease (e.g., as a result of therapy or spontaneous resolution), various pathophysiologic conditions affecting the glomeruli, or a combination of these, our findings suggest that caution is warranted when interpreting decreases in UACR in terms of prognostication of future risk of adverse clinical outcomes. A true association of changes in UACR, particularly decreases in UACR, with kidney events and the optimal intervention to lower elevated UACR toward improving kidney outcomes across different patient populations may deserve future prospective studies, including clinical trials.

Our study results must be interpreted in light of several limitations. First, most of our patients were United States veterans who were men; hence, the results may not apply to women or patients from other geographical areas. Second, because UACR is not universally available and is...
usually tested in patients with underlying glomerular diseases, such as diabetic nephropathy, hypertensive nephrosclerosis, or GN, our analytic cohort consisted mostly of older patients with diabetes and/or hypertension, which may also limit the generalizability of our findings. Also of note, only <2% (i.e., 56,946 subjects) of 3,582,478 patients in our original cohort had sufficient albuminuria data available, and thus, we cannot ignore the potential effect of selection bias, such that our analytic sample may reflect individuals whose treating physician thought it prudent to collect multiple urine samples for UACR assessment. Third, because this was an observational study, only associations, but no cause-effect relationships, can be inferred. Most importantly, we cannot conclude that the risk of kidney events associated with various changes in UACR, particularly with larger decreases in UACR, is equal to the risk imparted by the same UACR changes when they occur as a result of therapeutic interventions in clinical practice. Therefore, it must be emphasized that our findings on the inconsistent associations with decreasing UACR depending on different indices of UACR changes should not divert clinicians’ efforts from lowering elevated UACR to prevent CKD progression. Finally, as with all observational studies, we cannot eliminate the possibility of an effect from unmeasured confounders, such as smoking history.

In conclusion, in this large nationwide cohort of United States veterans, relative changes in UACR over a 1-year interval were associated with subsequent risk of incident CKD and rapid eGFR decline. Further studies are warranted to elucidate the underlying mechanisms of the observed associations and test whether active interventions aimed at lowering elevated albuminuria can improve kidney outcomes.

Figure 3. The associations of 1-year fold UACR changes with incident CKD were generally consistent across subgroups. Renin-angiotensin system inhibitor (RASi) indicates patients with any exposure to RASi between the first and last UACR measurement during the 2-year baseline period. Data are adjusted for age, sex, race, baseline eGFR, log-transformed UACR, comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and HIV/AIDS), baseline body mass index, systolic BP, diastolic BP, slopes of systolic BP and eGFR, use of statins and nonopioid analgesics at baseline, RASi treatment status (four categories on the basis of RASi use at the dates of the first and last UACR measurements during the baseline period [i.e., use at both, either, or neither dates]), and RASi adherence. CHD, coronary heart disease; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension.

Figure 4. The adjusted association between 1-year fold UACR changes and rapid eGFR decline was nearly linear. Models represent unadjusted association (model 1); associations after adjustment for age, sex, race, baseline eGFR, and log-transformed UACR (model 2); model 2 variables plus comorbidities (diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral arterial disease, chronic lung disease, liver disease, dementia, rheumatic disease, malignancy, depression, and HIV/AIDS; model 3); and model 3 plus baseline body mass index, systolic BP, diastolic BP, slopes of systolic BP and eGFR, use of statins and nonopioid analgesics at baseline, renin-angiotensin system inhibitor (RASI) treatment status (four categories on the basis of RASI use at the dates of the first and last UACR measurements during the baseline period [i.e., use at both, either, or neither dates]), and RASI adherence (model 4).
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Disclosures
None.

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