Change in Albuminuria Measured by Urine Albumin-to-Creatinine Ratio and Associated Clinical Outcomes in Patients with Chronic Kidney Disease and Type 2 Diabetes

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Introduction

- Chronic kidney disease (CKD) impacts approximately 35 million adults in the United States, with diabetes as one of its leading risk factors.[1]
- Albuminuria, defined by an elevated level of albumin-to-creatinine ratio (UACR), is strongly associated with higher risks of cardiovascular (CV) outcomes, kidney failure, and mortality.[2, 3]
- Recent clinical guidelines recommend UACR reduction as one of the treatment targets for kidney-heart risk management.[4, 5] For example, the American Diabetes Association recommends targeting a ≥30% reduction in UACR for individuals with CKD and UACR levels ≥300 mg/g.[5]
- However, there is a scarcity of data on the effect of UACR reduction on clinical outcomes, especially CV events and all-cause mortality, in patients with CKD and type 2 diabetes (T2D).
- This study aimed to assess the association between patterns of UACR change and clinical outcomes in patients with CKD and T2D with albuminuria in real-world clinical practice.

Methods

- Adult patients with CKD (defined based on the 2020 KDIGO clinical guidelines) and T2D (defined based on a modified EMERGE algorithm) were identified in the Optum electronic health records (EHR) database (January 2007–September 2021), which included information on patient characteristics, disease diagnoses, procedures, medications, and laboratory tests.[6, 7]
- Patients were required to have at least one elevated UACR test (≥30 mg/g; the initial UACR test) on or after CKD diagnosis following T2D, a follow-up UACR test (the last UACR test within 182 to 730 days after the initial UACR test), and continuous eligibility from 1 year before to 2 years after the initial UACR test, with continuous enrollment windows defined as periods of time with records indicating clinical activity with a gap time less than 6 months.
- UACR change was assessed as the percent change in UACR from the initial UACR test to the follow-up UACR test and was categorized into 3 categories: >30% increase, stable (30% decrease to 30% increase), or >30% decrease.
- Clinical outcomes, including all-cause mortality, a composite CV outcome (CV death, myocardial infarction, stroke, or heart failure hospitalization), and a composite kidney disease progression outcome (≥40% estimated glomerular filtration rate [eGFR] decline or kidney failure) were evaluated using Kaplan–Meier analysis.
- The association between UACR change patterns and clinical outcomes was further evaluated using a Cox proportional hazards model adjusting for key baseline demographic and clinical characteristics.

Results

- The study included 160,382 patients with CKD and T2D who met the sample selection criteria and had a follow-up UACR measurement within 182 to 730 days after the initial UACR test (**Figure 1**).

Step 1: Patients with T2D
Inclusion: Patients who met T2D criteria were included
Exclusion: Patients with records at any time indicating other types of diabetes were excluded
N = 4,487,562

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Step 2: Patients with incident CKD on or after T2D
Inclusion: Patients who met any of the following criteria were included
1) ≥2 outpatient CKD diagnoses on different dates or ≥1 inpatient diagnosis
2) ≥2 reduced eGFR (<60 mL/min/1.73 m²) measured 90 to 548 days apart
3) ≥1 elevated UACR (≥30 mg/g)
N = 1,826,223 (40.7%)

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Step 3: Patients with at least one elevated UACR test (≥ 30 mg/g) on or after CKD diagnosis
N = 773,534 (42.4%)

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Step 4: Patients with at least one valid UACR test (follow-up UACR) within 182 to 730 days after first elevated UACR (initial UACR)
N = 408,152 (52.8%)

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Step 5: Patients aged 18 years or older on the date of initial UACR test
N = 407,966 (100.0%)

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Step 6: Patients with continuous eligibility from 1 year before to 2 years after the initial UACR test
N = 174,259 (42.7%)

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Step 7: Patients without pre-existing conditions and ESKD
N = 160,382 (92.0%)

Figure 1. Study population flowchart

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.
Note: Pre-existing conditions include albuminuria/proteinuria, systemic lupus erythematosus, polycystic kidney disease, and kidney cancer diagnosed during the 1-year period before the initial UACR test.

- The majority of patients (91.6%) had initial UACR between 30 to 300 mg/g and less than 10% of patients had initial UACR ≥300 mg/g (**Table 1a**).
- There were 89,562 patients (55.8%) with elevated UACR who experienced a >30% decrease in UACR level, whereas 35,703 (22.3%) patients had a >30% increase in UACR level; these proportions were similar across initial UACR categories (**Table 1a**).
- Among 146,890 patients with microalbuminuria at initial UACR test, 72,807 (49.6%) had a reversal to normoalbuminuria. In contrast, among 13,492 patients with macroalbuminuria at initial UACR test, only 1,788 (13.3%) had a reversal to normoalbuminuria (**Table 1b**).

Table 1a. UACR change patterns by initial UACR level

	Total N = 160,382	Initial UACR category		
		30 – <300 mg/g N = 146,890	300 – <1000 mg/g N = 9,928	≥1000 mg/g N = 3,564
UACR change category				
>30% decrease	89,562 (55.8%)	82,016 (55.8%)	5,678 (57.2%)	1,868 (52.4%)
30% decrease to 30% increase	35,117 (21.9%)	32,183 (21.9%)	1,937 (19.5%)	997 (28.0%)
>30% increase	35,703 (22.3%)	32,691 (22.3%)	2,313 (23.3%)	699 (19.6%)

Abbreviations: UACR, urine albumin-to-creatinine ratio.

Table 1b. Change in UACR clinical category from initial to follow-up UACR test

	Total N = 160,382	Initial UACR clinical category	
		Microalbuminuria N = 146,890	Macroalbuminuria N = 13,492
Follow-up UACR clinical category[1]			
Normoalbuminuria (<30 mg/g)	74,595 (46.5%)	72,807 (49.6%)	1,788 (13.3%)
Microalbuminuria (≥30 and <300 mg/g)	71,314 (44.5%)	67,026 (45.6%)	4,288 (31.8%)
Macroalbuminuria (≥300 mg/g)	14,473 (9.0%)	7,057 (4.8%)	7,416 (55.0%)

Abbreviations: UACR, urine albumin-to-creatinine ratio.

- The mean age of the study population was 66.5 years old; 51.6% of patients were female and 82.0% were Caucasian (**Table 2**).
- Over two-thirds of patients (68.9%) had an eGFR level of G1 (≥90 ml/min/1.73 m²) or G2 (between 60 and <90 ml/min/1.73 m²). Compared with patients with a >30% decrease in UACR, those with stable or a >30% increase in UACR were more likely to have lower eGFR level.
- Compared with patients with a >30% decrease in UACR, those with stable or a >30% increase in UACR had higher prevalence of baseline

Table 2. Patient baseline demographic and clinical characteristics by UACR change category

	Total N = 160,382	UACR change category		
		>30% decrease N = 89,562	30% decrease to 30% increase N = 35,117	>30% increase N = 35,703
Demographics				
Age at follow-up UACR test, mean (SD)	65.9 (11.9)	65.0 (12.0)	66.7 (11.8)	67.3 (11.7)
Sex				
Female	82,753 (51.6%)	49,586 (55.4%)	16,777 (47.8%)	16,390 (45.9%)
Male	77,586 (48.4%)	39,946 (44.6%)	18,334 (52.2%)	19,306 (54.1%)
Unknown	43 (0.0%)	30 (0.0%)	6 (0.0%)	7 (0.0%)
Race				
African American	18,306 (11.4%)	9,953 (11.1%)	3,968 (11.3%)	4,385 (12.3%)
Asian	3,337 (2.1%)	1,865 (2.1%)	732 (2.1%)	740 (2.1%)
Caucasian	131,479 (82.0%)	73,679 (82.3%)	28,830 (82.1%)	28,970 (81.1%)
Other/unknown	7,260 (4.5%)	4,065 (4.5%)	1,587 (4.5%)	1,608 (4.5%)
Durations				
Time from initial to follow-up UACR test (months), mean (SD)	16.9 (4.6)	16.8 (4.5)	16.6 (4.6)	17.2 (4.6)
Follow-up time after follow-up UACR test (years), mean (SD)	3.4 (2.2)	3.4 (2.2)	3.4 (2.1)	3.3 (2.1)
Laboratory measures4				
eGFR (ml/min/1.73 m2), mean (SD)	76.2 (23.5)	77.8 (22.9)	75.8 (23.6)	72.7 (24.4)
G1/G2: ≥ 60 ml/min/1.73 m2	110,536 (68.9%)	63,930 (71.4%)	23,978 (68.3%)	22,628 (63.4%)
G3: ≥ 30 and < 45 ml/min/1.73 m2	35,825 (22.3)	18,192 (20.3%)	7,950 (22.6%)	9,683 (27.1%)
G4: ≥ 15 and < 30 ml/min/1.73 m2	3,461 (2.2%)	1,518 (1.7%)	783 (2.2%)	1,160 (3.2%)
G5: < 15 ml/min/1.73 m2	400 (0.2%)	145 (0.2%)	98 (0.3%)	157 (0.4%)
Unknown	10,160 (6.3%)	5,777 (6.5%)	2,308 (6.6%)	2,075 (5.8%)
Initial UACR (mg/g), mean (SD)	146.1 (445.5)	148.3 (481.5)	153.1 (461.5)	133.8 (316.8)
Follow-up UACR (mg/g), mean (SD)	162.3 (715.4)	54.5 (424.8)	166.4 (632.2)	428.7 (1,163.3)
Comorbidities				
Hypertension	119,844 (74.7%)	65,967 (73.7%)	26,317 (74.9%)	27,560 (77.2%)
Ischemic heart diseases	27,744 (17.3%)	14,538 (16.2%)	6,201 (17.7%)	7,005 (19.6%)
Heart failure	11,382 (7.1%)	5,945 (6.6%)	2,358 (6.7%)	3,079 (8.6%)
Diabetes-related microvascular complications	26,058 (16.2%)	14,326 (16.0%)	5,340 (15.2%)	6,392 (17.9%)
Hyperlipidemia	114,473 (71.4%)	64,310 (71.8%)	25,022 (71.3%)	25,141 (70.4%)
Anemia	18,327 (11.4%)	9,781 (10.9%)	3,915 (11.1%)	4,631 (13.0%)

Abbreviations: CKD, chronic kidney disease; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

- Patients with a >30% decrease in UACR had the highest overall survival (median time to death, 10.3 years), followed by patients with a stable UACR (9.1 years) and a >30% increase in UACR (7.8 years).
- Compared to patients with a stable UACR, those with a >30% decrease in UACR had significantly lower risk of all-cause mortality, with adjusted hazard ratio (HR) of 0.93 (95% CI: 0.90, 0.96; P < 0.001); while patients with a >30% increase in UACR had significantly higher risk of all-cause mortality, with adjusted HR of 1.24 (95% CI: 1.19, 1.28; P < 0.001).

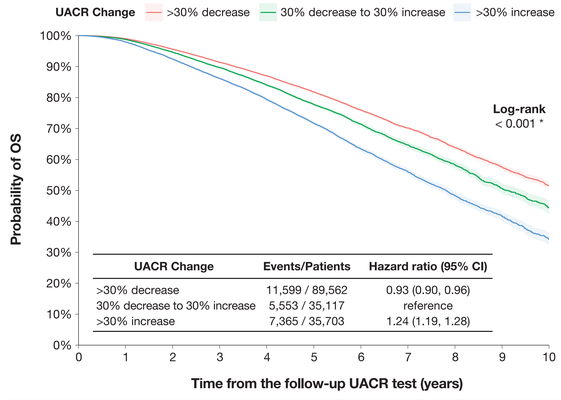

Figure 2. Overall survival by UACR change category

- The median time to the composite CV outcome was 11.1 years for patients with a >30% decrease in UACR, 9.9 years for patients with a stable UACR, and 8.1 years for patients with a >30% increase in UACR (**Figure 3**).
- Compared to patients with a stable UACR, those with a >30% decrease in UACR had significantly lower adjusted risk of the composite CV outcome, with an adjusted HR of 0.93 (95% CI: 0.90, 0.95; P < 0.001); while patients with a >30% increase in UACR had significantly higher adjusted risk of the composite CV outcome, with an adjusted HR of 1.24 (95% CI: 1.20, 1.28; P < 0.001).

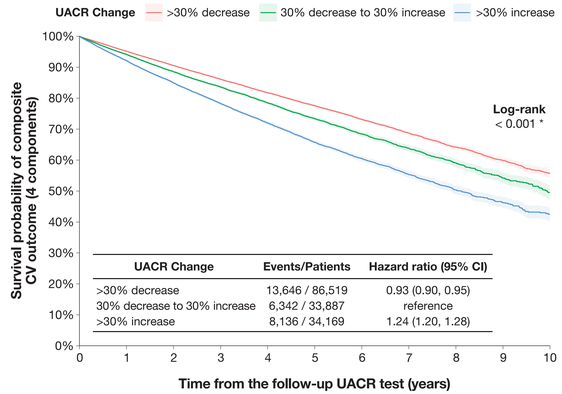

Figure 3. CV event-free survival by UACR change category

- The median time to the composite kidney outcome was 11.4 years for patients with a >30% decrease in UACR, 9.2 years for patients with a stable UACR, and 6.8 years for patients with a > 30% increase in UACR (**Figure 4**).
- Compared to patients with a stable UACR, those with a >30% decrease in UACR had significantly lower adjusted risk of kidney disease progression, with an adjusted HR of 0.84 (95% CI: 0.81, 0.86; P < 0.001); while patients with a >30% increase in UACR had a significantly higher adjusted risk of the kidney disease progression, with an adjusted HR of 1.41 (95% CI: 1.36, 1.46; P < 0.001).

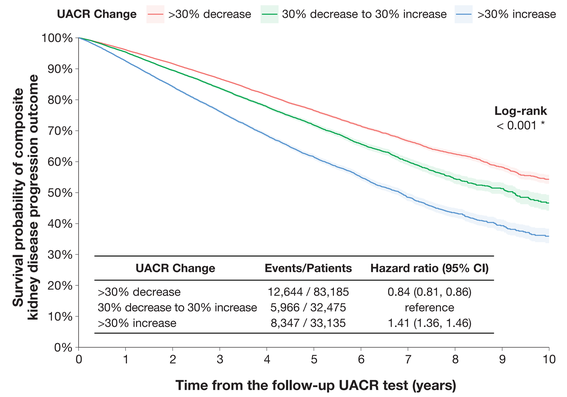

Figure 4. Kidney disease progression-free survival by UACR change category

Limitations

- UACR measurements were less frequently tested and recorded in the data, which have led to the use of single UACR test to define albuminuria and UACR change and a relatively long interval to identify the follow-up UACR test (i.e., 0.5 to 2 years after the initial UACR).
- As measures of UACR are highly variable, there may have been misclassification of UACR category and change status.
- Patients were required to have at least 2 years of continuous eligibility after the initial UACR test for follow-up UACR assessment. As a result, patients with fast disease progression after the initial UACR test that led to early death were not included in current study.

Conclusions

- In patients with CKD and T2D, there remain unmet needs in UACR management, as shown by over one fifth of patients having a >30% increase in UACR and less than half of patients having a reversal to normoalbuminuria.
- Achieving a UACR decrease and maintaining stable UACR level were associated with benefits in terms of overall mortality, CV outcomes, and progression of CKD.
- Early and sufficient UACR monitoring and management are important for patients with CKD and T2D.

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