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ORIGINAL ARTICLE

Chronic kidney disease progression among patients with type 2 diabetes identified in US administrative claims: a population cohort study

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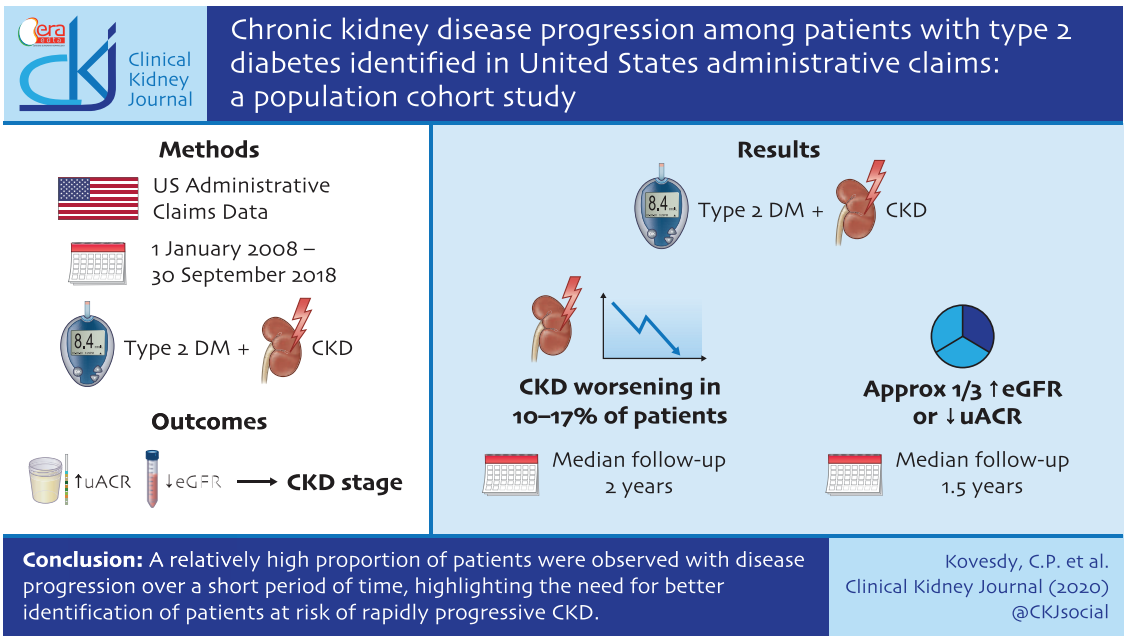
GRAPHICAL ABSTRACT



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ABSTRACT

Background. Chronic kidney disease (CKD), one of the most common complications of type 2 diabetes (T2D), is associated with poor health outcomes and high healthcare expenditures. As the CKD population increases, a better understanding of the prevalence and progression of CKD is critical. However, few contemporary studies have explored the progression of CKD relative to its onset in T2D patients using established markers derived from real-world care settings.

Methods. This retrospective, population-based cohort study assessed CKD progression among adults with T2D and with newly recognized CKD identified from US administrative claims data between 1 January 2008 and 30 September 2018. Included were patients with T2D and laboratory evidence of CKD as indicated by the established estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (UACR) criteria. Disease progression was described as transitions across the eGFR- and UACR-based stages.

Results. A total of 65 731 and 23 035 patients with T2D contributed to the analysis of eGFR- and UACR-based CKD stage progression, respectively. CKD worsening was observed in approximately 10–17% of patients over a median follow-up of 2 years. Approximately one-third of patients experienced an increase in eGFR values or a decrease in UACR values during follow-up.

Conclusions. A relatively high proportion of patients were observed with disease progression over a short period of time, highlighting the need for better identification of patients at risk of rapidly progressive CKD. Future studies are needed to determine the clinical characteristics of these patients to inform earlier diagnostic and therapeutic interventions aimed at slowing disease progression.

Keywords: chronic kidney disease, disease progression, eGFR, real-world data, type 2 diabetes, UACR

INTRODUCTION

Chronic kidney disease (CKD), a serious complication of type 2 diabetes (T2D), impacts 25–40% of the diabetic population [1, 2]. Progression of CKD is associated with poor health outcomes and can culminate in potentially fatal end-stage renal disease (ESRD) [1–3]. Dialysis, renal transplantation and the intensive care afforded to ESRD patients represent a severe strain on the healthcare system, reaching costs of nearly $34 billion in the US alone in 2015 [4]. With the diabetic population projected to grow, a substantial increase in the CKD population is expected [5]. Better understanding of the prevalence and timing of CKD progression in diabetes is needed to inform prevention and treatment strategies.

CKD prevalence is defined and classified based on the presence of persistently low kidney function and/or the presence of kidney damage for a period of at least 3 months [6, 7]. CKD is observed on average 10–20 years after the onset of T2D [8]. Established markers of CKD include persistently low estimated glomerular filtration rate (eGFR) and elevated urine albumin:creatinine ratio (UACR) [9]. eGFR and UACR values are also used to determine CKD staging, according to the Kidney Disease: Improving Clinical Outcomes (KDIGO) recommendations [6]. Guidelines recommend two or more kidney function test results at least 3 months apart to confirm a CKD diagnosis [6]. eGFR values <60 mL/min/1.73 m^2 and UACR values ≥ 30 mg/g are indicative of CKD [6]. CKD progression is operationalized as a decrease in eGFR, an increase in UACR or a combination of both over time in an individual.

Prior studies on the timing of CKD progression in real-world data are limited due to the highly variable nature of CKD, the complexity of defining the exact time of diabetes onset and the rarity of T2D cohorts with long-term observability and availability of laboratory measurements [8, 10, 11]. A US-based cohort study of 3682 participants with progressive CKD reported that patients spent a median of 7.9 years in Stage 3a, 5 years in Stage 3b, 5.2 years in Stage 4 and <1 year in Stage 5 CKD; diabetes substantially shortened these times [12]. To our knowledge, few studies have explored the feasibility of assessing CKD progression relative to its onset in T2D patients or using established markers derived from real-world administrative claims data, which provide a unique opportunity to generate evidence that is generalizable to larger populations as observed in clinical practice. We sought to assess the prevalence of newly recognized CKD and subsequent disease progression using laboratory-based markers in a large administrative claims data source.

MATERIALS AND METHODS

Data source

This was a retrospective cohort study using Optum Clinformatics Data Mart (CDM) data, a US claims database comprised of deidentified health plan data captured during the billing of routine healthcare encounters. Comprehensive longitudinal information on demographics, coded inpatient and outpatient diagnoses and procedures, outpatient prescription dispensing and laboratory results is recorded in the database. This database captures ~63 million unique members (2007–18) and is considered to be representative of the commercially insured US population [13].

Study population

The study population consisted of health plan enrollees ≥ 18 years of age with T2D and laboratory evidence of CKD enrolled in a health plan between 1 January 2007 and 30 September 2018. Patients must have had evidence of compromised kidney function as indicated by at least two laboratory results indicating reduced eGFR (<60 mL/min/1.73 m^2) or at least two laboratory results indicating elevated UACR (≥ 30 mg/g) 90–365 days apart. The date of the second laboratory result confirming CKD defined the index date. Patients were required to have continuous health plan enrollment for 365 days prior to the index date (baseline period). T2D was defined as one or more inpatient International Classification of Diseases, Ninth Revision/Tenth Revision (ICD-9/10) diagnosis code for T2D, two or more outpatient ICD-9/10 diagnosis codes for T2D at least 30–

365 days apart or one or more prescription claim for second-line therapy for T2D during the baseline period. The following patients were excluded: prevalent CKD as defined by two or more laboratory results indicating a CKD diagnosis, at least one ICD-9/10 diagnosis code for kidney disease, any ICD-9/10 diagnosis code indicating kidney disease from causes other than T2D during the baseline period and patients without at least one additional eGFR or UACR laboratory result post-index, allowing for the evaluation of CKD progression in follow-up. Patients with eGFR values on both the index date and in follow-up were evaluated with regards to eGFR-based CKD progression, while those with multiple UACR values were evaluated with regards to UACR-based CKD progression. A full list of definitions is in the Supplementary data.

Patient characteristics

A priori patient characteristics were identified based on published literature and expert insight. Patient characteristics included demographic information, KDIGO-based eGFR and UACR stage at index [6], clinical characteristics (select cardiovascular conditions and CKD- and T2D-related diagnoses) and comedications (cardiovascular and antiglycemic agents). Patient demographic data were assessed on the index date. KDIGO-based eGFR and UACR stages were assessed on the index date among patients who entered the cohort on an eGFR and/or UACR laboratory result, respectively. Then we assessed the nearest laboratory value available for the other laboratory test within 30 days. Clinical characteristics and comedications were assessed during the 365-day baseline period. The presence of one or more medical or pharmacy claim indicated the presence of a diagnosis or treatment, respectively.

Outcomes

The primary outcome was the last observed CKD stage in follow-up based on an eGFR and/or UACR laboratory result. Follow-up began on the index date and ended at the earliest occurrence of the outcome, death, end of enrollment or end of data.

Statistical analyses

Kidney function was categorized according to KDIGO guidelines for CKD staging defined by eGFR and UACR values (Supplementary data, Table S1). Only eGFR and UACR results $\geq$0–<200 mL/min/1.73 m^2 and 3250 mg/g, respectively, were used in this study. Outliers outside of these thresholds, calculated as 3 times the standard deviation (SD), were not considered. To capture eGFR based on serum creatinine values, we used the Chronic Kidney Disease Epidemiology Collaboration equation, applying a formula specific to the documented race of the patient. This equation has shown accuracy across diverse populations in prior research [14]. Lastly, any patients with two or more nonidentical test results on the same day (<1% of the population) were excluded from the analysis.

Frequency distributions for categorical variables and descriptive statistics for continuous variables among patients with nonmissing values were used. For claims-based variables, a lack of claims was assumed to indicate lack of the condition (e.g. comorbidities). No imputations on missing data were performed.

To identify a transition to a higher or lower CKD stage, we first identified the initial eGFR- and/or UACR-based stage on the index date. Next we identified the last observed corresponding laboratory result during the follow-up period. The number and percentage of patients transitioning from one CKD stage on the index date to another CKD stage in follow-up were cross-tabulated. The median [interquartile range (IQR)] time from the index date until the last observed laboratory result was reported in days.

Sensitivity analyses

In a sensitivity analysis, we assessed disease progression based on two eGFR test results in follow-up at least 90 days apart. Both test results in follow-up had to fall within the same CKD stage, different from the initial stage, to be considered a transition.

All statistical analysis was performed using the Aetion Evidence Platform version 3.7 (Aetion, New York, NY, USA) [15].

RESULTS

Participants and patient characteristics

Among 61 199 398 patients in the database, a total of 65 731 T2D patients with newly recognized CKD had sufficient data to assess eGFR progression. A total of 23 035 patients had sufficient data to assess UACR progression (Figure 1).

Patients described according to eGFR values were on average 71.3 (9.3) years of age, with 60.6% female and 61.9% White. Patients described according to UACR values were on average 65.8 (12.2) years of age, with 45.1% female and 45.2% White. At least half of all patients in the study population lived in the southern region of the USA (Table 1).

The majority (>78%) of patients who contributed to the eGFR-based disease progression analysis were at eGFR Stage 3a on the index date and most (>85%) patients with available UACR values were at UACR Stage A2 on the index date. The most common baseline comorbidities were hypertension ($\geq$85%), hyperlipidemia (>80%) and pain disorders ($\geq$65%). Other T2D-related comorbidities were also common (Table 2).

Among all patients, the most commonly prescribed cardiovascular medications at baseline were angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs, $\geq$69%), followed by statins (>65%), diuretics and β-blockers ($\geq$39%) and calcium channel blockers (>31%). More than half of all patients were prescribed metformin at baseline. More than 20% were prescribed at least two antiglycemic agents (Table 3).

Patients with eGFR values had a higher prevalence of most comorbidities, greater use of cardiovascular medications and lower use of glucose-lowering agents compared to those with UACR values.

Outcomes

Of the 65 731 patients with CKD in T2D who had sufficient data to assess eGFR progression, no change in eGFR stage was observed in ~50% of the population over a median of 1.1–1.5 years. Disease progression from Stages 3a, 3b and 4 to the next closest stage was observed in 16.9, 11.8 and 10.2% of patients, respectively, over a median of 1.8–2.3 years. Improved eGFR levels were observed in ~31% of patients over a median of 1.3–1.8 years. Disease progression over two eGFR stages was captured in 2.0% of patients over a median of 3.5 years. Of patients at eGFR Stage 5 on the index date, regression to eGFR Stage 4 was observed in 13.4% of patients over a median of 0.8 years (Table 4).

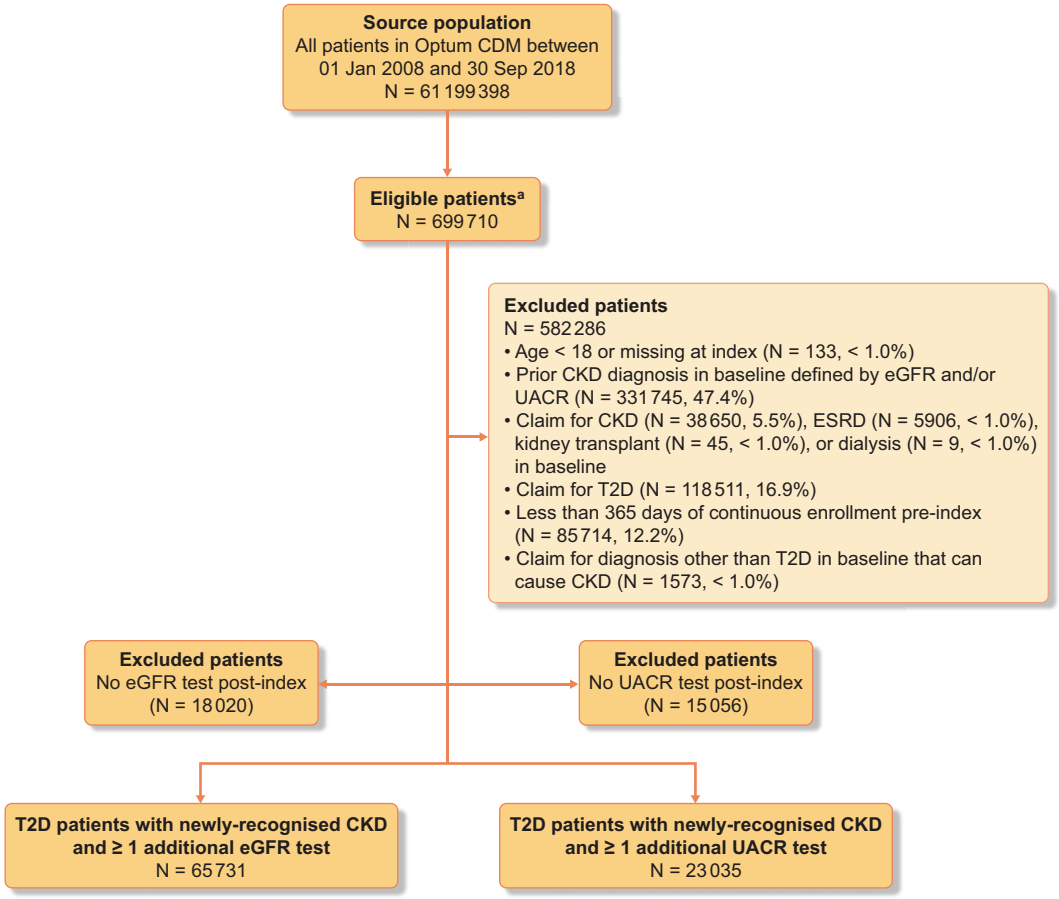

FIGURE 1: Selection of patients with T2D and newly recognized CKD identified in Optum CDM (1 January 2008–30 September 2018). [a]Eligible patients are defined as patients with two abnormal eGFR test results or two abnormal UACR test results 30–365 days apart from 1 January 2014 to 30 September 2018.

Among the 23 035 T2D patients with CKD who had sufficient data to assess UACR progression, ∼64% of patients had no change in UACR stage over a median follow-up of 1.3 years. Among patients at UACR Stage A2 on the index date, disease progression to the next stage was observed in 10.4% of patients over a median of ∼2 years. Increased UACR values were observed in ∼28% of patients over a median follow-up of 1.5 years and <5% of patients regressed from Stage A3 to A1 during all available follow-ups (Table 5).

Sensitivity analysis

A total of 47 938 patients had two eGFR test results during the follow-up, allowing assessment of eGFR-based disease progression using two test results. No change in eGFR stage was observed for 58–72% of patients. Disease progression from Stages 3a, 3b and 4 to the next closest stage was observed in 8.4, 5.9 and 4.7% of patients, respectively, over a median of 3 years. Improved eGFR levels were observed in ∼18% of patients over a median of 2 years. Disease progression over two eGFR stages was captured in 2.0% of patients over a median of 4 years. Of patients at eGFR Stage 5 on the index date, regression to eGFR Stage 4 was observed in 8% of patients over a median of 2.3 years (Supplementary data, Table S5).

DISCUSSION

In the published literature, few studies report stage-based progression relative to a newly recognized CKD diagnosis [8]. In the years after CKD onset, the rate of eGFR decline and UACR incline is variable and can be influenced by managed therapy for hyperglycemia, hypertension and hyperlipidemia [16]. In this study, we found that 50–64% of patients with CKD and T2D showed no disease progression over a median follow-up of ∼1.3 years. Approximately 10–17% of patients experienced CKD stage progression over a median of 2 years. Few (<2%) patients progressed more than one stage after a median follow-up of 3.4 years.

Results of the sensitivity analysis showed a lower rate of progression over a longer follow-up time, with approximately 5–8.4% showing a progression over a period of 3 years. This finding suggests the selection of healthier individuals with longer follow-up time needed to observe two test results or the variability of test results over time, in which fewer patients had a sustained decline as indicated by two test results in the same stage range. The presence of acute kidney injury among some patients who are classified as disease progression based on one test result is also possible.

Our findings are comparable to those reported in the existing literature [17]. For example, a study by Ruzafa *et al.* [17] using data from the UK primary care setting reported that roughly 10–19% of patients progressed one stage over 1.7–1.9 years of

Table 1. Demographic characteristics among patients with DKD

Characteristics	eGFR cohort ($n = 65\,731$)	UACR cohort ($n = 23\,035$)
Demographics		
Age (years)		
Mean (SD)	71.28 (9.42)	65.84 (12.15)
Median (IQR)	72.00 (66.00–79.00)	68.00 (58.00–74.00)
Gender, *n* (%)		
Male	25 838 (39.3)	12 636 (54.9)
Female	39 845 (60.6)	10 390 (45.1)
Unknown	48 (0.1)	9 (0.0)
Race, *n* (%)		
White	40 694 (61.9)	10 409 (45.2)
Asian	1688 (2.6)	1510 (6.6)
Black	7036 (10.7)	2463 (10.7)
Hispanic	6981 (10.6)	5237 (22.7)
Missing	9332 (14.2)	3416 (14.8)
Region, *n* (%)		
Northeast	5507 (8.4)	2986 (13.0)
Midwest	6253 (9.5)	1542 (6.7)
South	38 854 (59.1)	12 001 (52.1)
West	14 819 (22.5)	6428 (27.9)
Missing	298 (0.5)	78 (0.3)
Provider specialty, *n* (%)		
Endocrinologist	1298 (2.0)	821 (3.6)
Nephrologist	248 (0.4)	73 (0.3)
Cardiologist	1689 (2.6)	253 (1.1)
General practitioner/ internist	33 391 (50.8)	9206 (40.0)
Urologist	208 (0.3)	38 (0.2)
Inpatient facility	1546 (2.4)	267 (1.2)
Outpatient facility	941 (1.4)	304 (1.3)
Missing	37 205 (56.6)	10 417 (45.2)

DKD, diabetic kidney disease.

Table 2. Baseline comorbidities among patients with DKD

Comorbidities	eGFR cohort ($n = 65\,731$)	UACR cohort ($n = 23\,035$)
Comorbidity score		
Deyo comorbidity score		
Mean (SD)	2.22 (1.53)	2.00 (1.30)
Median (IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)
Index CKD stage[a]		
eGFR stage, *n* (%)		
1	0 (0.0)	3523 (15.3)
2	0 (0.0)	4953 (21.5)
3a	51 349 (78.1)	2041 (8.9)
3b	12 734 (19.4)	516 (2.2)
4	1474 (2.2)	82 (0.4)
5	174 (0.3)	8 (0.0)
Missing	0 (0.0)	11 912 (51.7)
UACR category, *n* (%)		
A1	4980 (7.6)	0 (0.0)
A2	2507 (3.8)	19 460 (84.5)
A3	648 (1.0)	3575 (15.5)
Missing	57 596 (87.6)	0 (0.0)
Comorbidities, *n* (%)		
Anemia	13 290 (20.2)	3112 (13.5)
Angina pectoris	16 867 (25.7)	4573 (19.9)
Atrial fibrillation	7289 (11.1)	1796 (7.8)
Chronic lung/pulmonary disease	13 217 (20.1)	3839 (16.7)
Coronary artery disease	8488 (12.9)	2988 (13.0)
Diabetic retinopathy	11 474 (17.5)	4191 (18.2)
Edema	7458 (11.3)	1711 (7.4)
Fatigue and sleep-related disorders	17 066 (26.0)	4225 (18.3)
Heart failure	7995 (12.2)	1713 (7.4)
Hyperlipidemia	54 923 (83.6)	18 534 (80.5)
Hypertension	58 893 (89.6)	19 530 (84.8)
Microvascular complications disease	20 361 (31.0)	8336 (36.2)
Obesity	10 690 (16.3)	5454 (23.7)
Pain disorders	46 098 (70.1)	14 899 (64.7)
Peripheral vascular disease	10 423 (15.9)	3555 (15.4)
Resistant hypertension	11 372 (17.3)	3164 (13.7)
Sleep apnea	6841 (10.4	2572 (11.2)

[a]Stage 1: eGFR $\geq$90 mL/min/1.73 m^2 and UACR $\geq$30 mg/g; Stage 2: eGFR 60–89 mL/min/1.73 m^2 and UACR $\geq$30 mg/g; Stage 3a: eGFR 45–59 mL/min/1.73 m^2; Stage 3b: eGFR 30–44 mL/min/1.73 m^2; Stage 4: eGFR 15–29 mL/min/1.73 m^2; Stage 5: eGFR $<$15 mL/min/1.73 m^2; A1: UACR $<$30 mg/g and eGFR $<$60 mL/min/1.73 m^2; A2: UACR 30–299 mg/g; A3: UACR $\geq$300 mg/g.

follow-up. Authors also reported that $<$4% of patients progressed two stages during the study period, with a median follow-up time of 5 years.

We report that ∼30% of all patients experienced improvement in eGFR or UACR values over an average follow-up of 1.5 years. While prior studies have established a strong relationship between eGFR decline and worsening CKD, the opposite may also be true. Some evidence suggests that positive eGFR slopes are associated significantly with a higher risk of ESRD and mortality [18]. Thus regression among these patients may not be actual improvement in kidney function, but rather a well-documented phenomenon of artificially improved eGFR due to underlying and irreversible kidney injury or temporary fluctuations in test results. Recent literature points to a number of reasons for this phenomenon, including the overestimation of eGFR levels due to decreases in muscle mass that are reflected in serum creatinine levels. Weight loss among these patients usually indicates worsening of health or frailty and more advanced disease stage. Other potential reasons for observed artificial improvements in eGFR include volume overload or recovery from previous acute kidney injury [19]. In our study we observed slight differences among patients experiencing eGFR regression compared with patients with worsening disease, such as lower baseline albuminuria levels and lower prevalence of cardiovascular and diabetes-related comorbidities (Supplementary data, Tables S6–S9). While baseline medication between patients showing regression and progression did not differ notably, the role of changes in renin–angiotensin system blockade treatment on increasing eGFR levels requires further investigation.

In contrast to changing eGFR values, previous research indicates that declining and increasing UACR over time results in better and worse health outcomes, respectively [20]. In a large cohort study using Swedish Population Registry data, Carrero *et al.* [21] reported lower risks of ESRD among patients with greater reductions in UACR measured over 1- to 3-year intervals; significantly higher ESRD risk was observed with increases in UACR over these times. A study of diabetic patients by Jun *et al.* [22] that analyzed ADVANCE-ON trial data additionally reported a positive, linear association between changes in UACR over 2 years and the risk of

Table 3. Baseline medication use among patients with DKD

Medications	eGFR cohort ($n = 65\,731$)	UACR cohort ($n = 23\,035$)
Antiglycemic agents, *n* (%)		
Metformin	33 825 (51.5)	15 503 (67.3)
Any second-line therapy	33 885 (51.6)	14 066 (61.1)
Sulfonylurea	20 877 (31.8)	8176 (35.5)
Thiazolidinedione	6536 (9.9)	2089 (9.1)
DPP4i	7373 (11.2)	3555 (15.4)
SGLT2i	996 (1.5)	967 (4.2)
GLP1ra	2231 (3.4)	1352 (5.9)
Basal insulin	10 084 (15.3)	5444 (23.6)
Any two second-line therapies[a]	12 875 (19.6)	6342 (27.5)
Sulfonylurea + thiazolidinedione	2877 (4.4)	991 (4.3)
Sulfonylurea + DPP4i	3009 (4.6)	1518 (6.6)
Sulfonylurea + SGLT2i	333 (0.5)	288 (1.3)
Sulfonylurea + GLP1ra	655 (1.0)	410 (1.8)
Sulfonylurea + basal insulin	2352 (3.6)	1325 (5.8)
Thiazolidinedione + DPP4i	891 (1.4)	369 (1.6)
Thiazolidinedione + SGLT2i	85 (0.1)	72 (0.3)
Thiazolidinedione + GLP1ra	304 (0.5)	151 (0.7)
Thiazolidinedione + basal insulin	679 (1.0)	302 (1.3)
DPP4i + SGLT2i	275 (0.4)	233 (1.0)
DPP4i + basal insulin	979 (1.5)	617 (2.7)
SGLT2i + GLP1ra	138 (0.2)	148 (0.6)
SGLT2i + basal insulin	244 (0.4)	227 (1.0)
GLP1ra + basal insulin	530 (0.8)	413 (1.8)
Combination injectable therapy[b]	4430 (6.7)	2191 (9.5)
Cardiovascular agents, *n* (%)		
ACEi/ARB	45 263 (68.9)	17 075 (74.1)
α-blocking agent	2293 (3.5)	621 (2.7)
α-glucosidase inhibitor	182 (0.3)	108 (0.5)
Aspirin	527 (0.8)	242 (1.1)
β-blocker	28 921 (44.0)	8878 (38.5)
Calcium channel blocker	20 964 (31.9)	8147 (35.4)
Centrally acting antihypertensive	2765 (4.2)	797 (3.5)
Diuretic	37 135 (56.5)	9085 (39.4)
Loop diuretic	13 310 (20.2)	2631 (11.4)
Thiazide diuretic	27 538 (41.9)	7120 (30.9)
Potassium-sparing diuretic	7201 (11.0)	1015 (4.4)
MRA	3460 (5.3)	529 (2.3)
Epithelial sodium channel blocker	3992 (6.1)	537 (2.3)
Direct renin inhibitor	326 (0.5)	110 (0.5)
HMG-CoA reductase inhibitor (statin)	43 093 (65.6)	15 861 (68.9)
Meglitinide	663 (1.0)	262 (1.1)
Oral anticoagulant	5917 (9.0)	1515 (6.6)
Potassium binding agent	139 (0.2)	22 (0.1)

[a]Dual second-line therapy included drugs used concurrently for ≥30 days.
[b]Combination injectable therapy included the concurrent use of basal and mealtime insulin for ≥30 days.
DPP4i: dipeptidyl peptidase-4 inhibitor; GLP1ra: glucagon-like peptide-1 receptor agonist; HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium–glucose co-transporter-2 inhibitor.

cardiorenal outcomes and all-cause mortality. Published literature suggests this relationship could plausibly be explained by underlying pathophysiologic processes including dysfunction of the vascular endothelium and chronic, low-grade inflammation [20–22]. The reported risks of major clinical outcomes and mortality associated with CKD progression support the prognostic utility of actively monitoring eGFR and UACR values over time.

Overall, this study adds to the existing body of literature on CKD and T2D by examining CKD disease progression and timing among T2D patients from the onset of newly recognized CKD. We observed CKD progression by eGFR- and UACR-based stages among 10–17% of patients in this study over a relatively short period of 2 years. This finding highlights a nonnegligible proportion of patients with T2D and newly recognized CKD who are expected to experience rapid disease progression and worsening health outcomes. The prompt identification of these patients is crucial to informing a vulnerable population with potential unmet therapeutic need. Future studies are needed to determine the clinical characteristics of these patients at risk of rapidly progressive CKD to inform earlier diagnostic and therapeutic interventions that slow disease progression and the need to develop better therapeutic interventions for patients at risk of rapid progression.

Several limitations common to administrative claims data existed. First, laboratory results were available for ∼30% of patients in the database; only a small fraction of individuals available in the Optum database qualified for inclusion in this analysis, partly due to the necessary stringent definitions used for T2D and especially CKD and CKD progression. This reduced our sample size and may have resulted in selection bias [23]. To explore the presence of any selection bias due to the additional test result requirement in follow-up, we compared baseline patient characteristics of newly recognized CKD patients (defined by the laboratory test results criteria) and no additional test results in follow-up ($n = 117\,424$) to patients with one additional test result included in the main analysis for eGFR progression ($n = 65\,731$) and UACR progression ($n = 23\,035$), as well as to those with two additional tests for eGFR included in the sensitivity analysis ($n = 47\,938$) (Supplementary data, Table S10). We observed that patients with one and two additional tests in follow-up did not differ from patients with no test results in follow-up in terms of demographic characteristics, CKD stage at the index date, comorbidities and medication use; however, patients with two additional tests in follow-up were observed for a longer time period (median of 3 versus 1.7 years). Second, we refer to eGFR and UACR laboratory results as the gold standard for identification of renal disease [14, 24, 25]. However, there are circumstances in which any creatinine-based estimate of kidney function, including eGFR, should not be used. For example, creatinine-based estimates should be avoided in patients with changing serum creatinine values; people with acute kidney injury; people with extremes in muscle mass, body size or altered diets; and people taking medications that affect excretion of creatinine. To address this limitation, we required patients to have at least two laboratory results confirming CKD before they were classified as having the disease. We also performed sensitivity analyses to evaluate disease progression based on two test results for eGFR [6, 14, 15]. Third, the Optum CDM is considered to be representative of the commercially insured US population but may not be representative of non-US-based populations or non-commercially insured US populations. Finally, because of the limited follow-up time available in the claims data, full progression from newly recognized CKD to ESRD is unlikely to be captured. This limitation may have also impacted our ability to observe more patients with disease progression. While the maximum allowable follow-up time was ∼10 years, the typical transition from Stage 1 to 5 CKD based on eGFR measurements is closer to 20 years [8].

Table 4. Proportion and median (IQR) time to CKD progression according to eGFR values during follow-up among patients with DKD

Patients with available eGFR results ($N = 65\,731$)						
	Last observed eGFR stage in follow-up					
eGFR stage on index[a]	1	2	3a	3b	4	5
From 3a, *n* (%)	306 (0.6)	14 540 (28.3)	26 393 (51.4)	8694 (16.9)	1197 (2.3)	179 (0.3)
3b, *n* (%)	34 (0.3)	1071 (8.4)	3984 (31.3)	5914 (46.4)	1504 (11.8)	213 (1.7)
4, *n* (%)	11 (0.7)	74 (5.0)	189 (12.8)	478 (32.4)	572 (38.8)	150 (10.2)
5, *n* (%)	1 (0.6)	8 (4.6)	21 (12.1)	14 (8.0)	23 (13.2)	107 (61.5)
Time to transition (days)	1	2	3a	3b	4	5
From 3a, median (IQR)	932 (487–1505)	641 (285–1151)	533 (235–1010)	846 (402–1528)	1243 (667–2088)	1705 (938, 2407)
3b, median (IQR)	744 (143–1319)	615 (265–1163)	526 (223–1026)	572 (236–1094)	850 (410–1530)	1232 (661, 2004)
4, median (IQR)	570 (310–1603)	478 (102–950)	628 (193–1043)	490 (177–960)	413 (184–812)	632 (334, 1215)
5, median (IQR)	680 (680–680)	639 (243–1030)	394 (202–755)	291 (118–948)	293 (33–825)	477 (189, 854)

[a]Stage 1: eGFR ≥90 mL/min/1.73 m^2 and UACR ≥30 mg/g; Stage 2: eGFR 60–89 mL/min/1.73 m^2 and UACR ≥30 mg/g; Stage 3a: eGFR 45–59 mL/min/1.73 m^2; Stage 3b: eGFR 30–44 mL/min/1.73 m^2; Stage 4: eGFR 15–29 mL/min/1.73 m^2; Stage 5: <15 mL/min/1.73 m^2.

Table 5. Proportion and median (IQR) time to CKD progression according to UACR values during follow-up, among patients with DKD

Patients with available UACR results ($n = 23\,035$)			
	Last observed eGFR stage in follow-up		
UACR category at index[a]	A1	A2	A3
From A2, *n* (%)	5027 (25.8)	12 387 (63.7)	2033 (10.4)
A3, *n* (%)	138 (3.9)	1106 (30.9)	2326 (65.1)
Time to transition (days)	A1	A2	A3
From A2, median (IQR)	541 (272–935)	487 (245–909)	739 (381–1227)
A3, median (IQR)	690 (259–1283)	477 (241–959)	461 (229–883)

[a]A1: UACR <30 mg/g and eGFR <60 mL/min/1.73 m^2; A2: UACR 30–299 mg/g; A3: UACR ≥300 mg/g.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

D.I., N.P., and P.V. were employees of Aetion and owned stock options at the time this work was conducted. C.P.K. received honoraria for consultant work from Amgen, AstraZeneca, Bayer, Takeda, Reata, Tricida and Cara Therapeutics. L.F. received honoraria from Bayer and Novo Nordisk. M.B., A.G. and K.F. are employees of Bayer AG.

REFERENCES

1. Afkarian M, Zelnick LR, Hall YN *et al*. Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. *JAMA* 2016; 316: 602–610
2. Zhou Z, Chaudhari P, Yang H *et al*. Healthcare resource use, costs, and disease progression associated with diabetic nephropathy in adults with type 2 diabetes: a retrospective observational study. *Diabetes Ther* 2017; 8: 555–571
3. Evans M, Palaka E, Furuland H *et al*. The value of maintaining normokalaemia and enabling RAASi therapy in chronic kidney disease. *BMC Nephrol* 2019; 20: 31
4. Saran R, Robinson B, Abbott KC *et al*. US Renal Data System 2017 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2018; 71(3 Suppl 1): A7
5. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol* 2017; 12: 2032–2045
6. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150
7. Ozieh MN, Bishu KG, Dismuke CE *et al*. Trends in healthcare expenditure in United States adults with chronic kidney disease: 2002–2011. *BMC Health Serv Res* 2017; 17: 368

8. Gheith O, Farouk N, Nampoory N *et al*. Diabetic kidney disease: world-wide difference of prevalence and risk factors. *J Nephropharmacol* 2015; 5: 49–56
9. Levey AS, De Jong PE, Coresh J *et al*. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. *Kidney Int* 2011; 80: 17–28
10. Yee J, Krol GD, eds. Chronic Kidney Disease (CKD): Clinical Practice Recommendations or Primary Care Physicians and Healthcare Providers. Detroit, MI: Henry Ford Health Systems, 2011.
11. Go AS, Yang J, Tan TC *et al*. Contemporary rates and predictors of fast progression of chronic kidney disease in adults with and without diabetes mellitus. *BMC Nephrol* 2018; 19: 146
12. Ku E, Johansen KL, McCulloch CE. Time-centered approach to understanding risk factors for the progression of CKD. *Clin J Am Soc Nephrol* 2018; 13: 693–701
13. Optum. Retrospective Database Analysis. https://www.optum.com/content/dam/optum/resources/productSheets/Retrospective-Database-Analysis.pdf (25 May 2017, date last accessed)
14. Levey AS, Inker LA, Matsushita K *et al*. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the national kidney foundation and the US food and drug administration. *Am J Kidney Dis* 2014; 64: 821–835
15. Wang SV, Verpillat P, Rassen JA *et al*. Transparency and reproducibility of observational cohort studies using large healthcare databases. *Clin Pharmacol Ther* 2016; 99: 325–332
16. Seaquist ER, Ibrahim HN. Approach to the patient with type 2 diabetes and progressive kidney disease. *J Clin Endocrinol Metab* 2010; 95: 3103–3110
17. Ruzafa CJ, Paczkowski R, Boye KS *et al*. Estimated glomerular filtration rate progression in UK primary care patients with type 2 diabetes and diabetic kidney disease: a retrospective cohort study. *Int J Clin Pract* 2015; 69: 871–882
18. Kovesdy CP, Coresh J, Ballew SH *et al*. Past decline versus current eGFR and subsequent ESRD risk. *J Am Soc Nephrol* 2016; 27: 2447–2455
19. Sumida K, Kovesdy CP. Disease trajectories before ESRD: implications for clinical management. *Semin Nephrol* 2017; 37: 132–143
20. Sumida K, Molnar MZ, Potukuchi PK *et al*. Changes in albuminuria and subsequent risk of incident kidney disease. *Clin J Am Soc Nephrol* 2017; 12: 1941–1949
21. Carrero JJ, Grams ME, Sang Y *et al*. Albuminuria changes and subsequent risk of end-stage renal disease and mortality. *Kidney Int* 2017; 91: 244–251
22. Jun M, Ohkuma T, Zoungas S *et al*. Changes in albuminuria and the risk of major clinical outcomes in diabetes: results from ADVANCE-ON. *Diabetes Care* 2018; 41: 163–170
23. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veteran Affairs based on computerized patient data. *Diabetes Care* 2004; 27(Suppl 2): b10–b21
24. Menke A, Casagrande S, Geiss L *et al*. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. *JAMA* 2015; 314: 1021–1029
25. Lund JL, Horvath-Puho E, Szepligeti SK *et al*. Conditioning on future exposure to define study cohorts can induce bias: the case of low-dose acetylsalicylic acid and risk of major bleeding. *Clin Epidemiol* 2017; 9: 611–626