

# Patients With Diabetes and Chronic Kidney Disease: ACE Inhibitor or ARB Treatment, Medical Costs for Disease Management, and the FINE-CKD Model to Evaluate Economic Value of Finerenone

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## HIGHLIGHTS

- › ACE Inhibitor or ARB Treatment Among Patients With Diabetes and Chronic Kidney Disease
- › Medical Costs for Managing Chronic Kidney Disease and Related Complications in Patients With Chronic Kidney Disease and Type 2 Diabetes
- › FINE-CKD Model to Evaluate Economic Value of Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes

# Patients With Diabetes and Chronic Kidney Disease: ACE Inhibitor or ARB Treatment, Medical Costs for Disease Management, and the FINE-CKD Model to Evaluate Economic Value of Finerenone

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## Patients With Diabetes and Chronic Kidney Disease: ACE Inhibitor or ARB Treatment, Medical Costs for Disease Management, and the FINE-CKD Model to Evaluate Economic Value of Finerenone

### OVERVIEW

This supplement to *The American Journal of Managed Care*<sup>®</sup> explores the treatment patterns and treatment initiation after initial chronic kidney disease (CKD) diagnosis; provides cost estimates for CKD management; and describes the approach and structure of a cost-effectiveness model for finerenone for patients with CKD and type 2 diabetes (T2D) and compares it with existing economic models in CKD.

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# ACE Inhibitor or ARB Treatment Among Patients With Diabetes and Chronic Kidney Disease

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## Introduction

Type 2 diabetes (T2D) is a highly prevalent disease, with approximately 23.1 million individuals receiving a diagnosis in the United States in 2017.<sup>1</sup> Chronic kidney disease (CKD), a serious complication of T2D that affects between 25% and 40% of all patients with T2D, is characterized by compromised renal function or renal injury, as evidenced by the presence of albuminuria, due to persistent uncontrolled hyperglycemia and hypertension.<sup>2</sup> CKD in T2D is associated with elevated rates of cardiovascular disease and is partially responsible for the elevated mortality risk in these patients.<sup>3,4</sup> Prolonged, unmanaged CKD often leads to end-stage kidney disease, requiring dialysis or renal transplantation.<sup>5</sup> In 2015, the costs associated with kidney disease in the United States were nearly \$34 billion.<sup>6</sup>

No current therapy has been shown to reverse CKD damage in patients with T2D, but existing treatments aim to slow CKD progression. Current American Diabetes Association treatment guidelines recommend controlling blood pressure with antihypertensive drugs to slow or halt CKD progression,<sup>7</sup> including angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs).<sup>8,9</sup> Recent studies report that mineralocorticoid receptor antagonists (MRAs) may also have a role in reducing albuminuria in patients with diabetes and CKD.<sup>10</sup> These antihypertensive therapies also target the renin-angiotensin-aldosterone system to lower blood pressure and preserve kidney function.<sup>11-14</sup> Antidiabetic treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2is) has also been shown to exhibit renoprotective effects, in addition to controlling blood glucose levels.<sup>15</sup>

Despite established clinical practice guidelines, data on timing of initiation of antihypertensive treatment for CKD in T2D and adherence to guideline recommendations in real-world clinical practice are limited.<sup>16</sup> This study aimed to describe ACEi or ARB utilization rates and identify factors associated with treatment initiation among patients with T2D and newly identified CKD in a US-based administrative claims database representative of the commercially insured US population.

## ABSTRACT

**OBJECTIVES:** Many patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) experience a delay in treatment or fail to initiate treatment with guideline-recommended angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) after CKD diagnosis. This study aimed to describe treatment patterns and treatment initiation after initial CKD diagnosis among patients with T2D.

**STUDY DESIGN:** Retrospective analysis using data from the Optum Clinformatics Data Mart administrative claims database (January 2014-September 2018).

**METHODS:** Adult patients with T2D entered the cohort if they met the criteria for CKD, defined as 2 laboratory test results 90 to 365 days apart (January 2014-September 2017) indicating CKD. Included were patients with no prior use of ACEis or ARBs or evidence of kidney disease in the 365 days prior to cohort entry (baseline). Patients were followed for a maximum of 365 days and were censored on death, disenrollment, or end of data. Patient demographics, comorbidities, and medication use were assessed at baseline, and treatments were assessed over a 1-year follow-up period. Multivariate logistic regression was used to identify factors associated with ACEi or ARB initiation.

**RESULTS:** Among 15,400 eligible patients without prior ACEi or ARB treatment, only 17% initiated such therapy within a year after meeting CKD criteria. Patients who were White, resided in the northeastern United States, had more comorbidities, had less advanced albuminuria, or used sodium-glucose cotransporter 2 inhibitors were less likely to initiate treatment.

**CONCLUSIONS:** A large proportion of patients with T2D meeting criteria for CKD do not initiate the recommended therapy within 1 year of CKD diagnosis, highlighting a need for new therapies that can slow the progression of CKD.

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For author information and disclosures, see end of text.

## TAKEAWAY POINTS

- This observational cohort study of US administrative claims described ACEi or ARB utilization rates and identified factors associated with treatment initiation among patients with T2D and CKD. The findings highlight a need for new therapies that can slow the progression of CKD.
- Treatment guidelines for CKD recommend controlling blood pressure with antihypertensive drugs, such as ACEis and ARBs, to slow or halt CKD progression; however, the timing and factors associated with treatment initiation within the first year after diagnosis have not been well described.
- This study demonstrated that a large proportion of patients with T2D meeting criteria for CKD did not initiate the recommended ACEi or ARB therapy within 1 year of diagnosis, and that certain demographic and clinical characteristics were predictors of not receiving ACEi or ARB therapy.
- Further investigation is needed to identify ways to optimize care and reduce CKD progression in this population.

## Methods

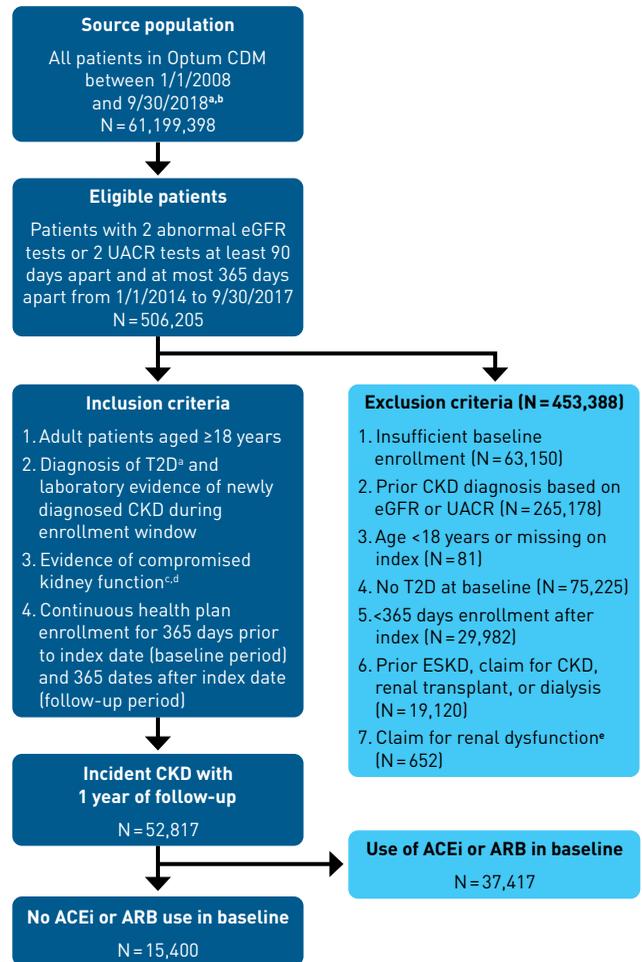
## Data Source

This observational cohort study used deidentified administrative claims data from Optum Clinformatics Data Mart (January 2014-September 2018), which contains longitudinal outpatient and inpatient diagnoses and procedures, outpatient prescription dispensing data, and laboratory data for patients enrolled in commercial health plans and Medicare Advantage.<sup>17</sup> This research was exempt from Health and Human Services requirements for institutional review board approval and informed consent (45CFR46.104[d]).

## Study Population and Design

Adult patients with T2D were included upon meeting criteria for CKD, defined as at least 2 clinical laboratory results 90 to 365 days apart (January 2014-September 2017) indicating a reduced estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73 m<sup>2</sup>) or least 2 test results 90 to 365 days apart demonstrating an elevated urinary albumin to creatinine ratio (UACR) (≥30 mg/g). Index date was defined as the second clinical laboratory test result indicating CKD 90 to 365 days after the first. Patients were required to have no evidence of ACEi or ARB use or renal disease in the baseline period, defined as the 365 days prior to the index date. Patient demographics, comorbidities, and medication use were assessed during the baseline period. Treatment was recorded over the 1-year follow-up period, beginning on the index date and ending on the earliest occurrence of death, disenrollment, or end of data. **Figure 1**

FIGURE 1. Patient Flow Diagram



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CDM, Clinformatics Data Mart; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ICD-9/10, *International Classification of Diseases, 9th/10th Revision*; T2D, type 2 diabetes; UACR, urinary albumin to creatinine ratio.

<sup>a</sup>T2D diagnosis defined as ≥1 ICD-9/10 diagnosis code for T2D, ≥2 outpatient ICD-9/10 diagnosis codes for T2D at least 30 to 365 days apart, or ≥1 prescription claim for second-line therapy for T2D during the baseline period. This algorithm was chosen for its high sensitivity (73.7%) and specificity (98.1%) compared with patient self-reporting.<sup>18</sup>

<sup>b</sup>Data were available from January 2008 to September 2018.

<sup>c</sup>Evidenced by at least 2 laboratory results indicating reduced eGFR (<60 mL/min/1.73 m<sup>2</sup>) or at least 2 laboratory results indicating elevated UACR (≥30 mg/g) 90 to 365 days apart.

<sup>d</sup>The date of the second laboratory result confirming CKD defined the index date.

<sup>e</sup>Renal dysfunction conditions include glomerulonephritis, focal glomerulosclerosis/focal sclerosing glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis type 1/diffuse membranoproliferative glomerulosclerosis, postinfectious glomerulonephritis, immunoglobulin A nephropathy/Berger disease, rapidly progressive systemic lupus erythematosus nephritis, glomerulonephritis, other proliferative glomerulonephritis, Wegener granulomatosis, other vasculitis with kidney involvement, interstitial nephritis/pyelonephritis from analgesic abuse, gouty nephropathy, acquired obstructive uropathy, chronic pyelonephritis/reflux nephropathy, chronic interstitial nephritis, acute interstitial nephritis, urolithiasis, renal artery stenosis, renal artery occlusion, polycystic kidneys (adult type), renal tumor [malignant], multiple myeloma, AIDS nephropathy, tubular necrosis, renal agenesis, dysgenesis, hypoplasia, or sickle cell disease.

**TABLE 1.** Baseline Characteristics Among Patients With Incident CKD and T2D, Without ACEi/ARB in Baseline Period, Stratified by ACEi or ARB Initiation Within 1 Year of Follow-up (N=15,400)

Demographics	ACEi or ARB initiation <sup>a</sup> within 1 year (N = 2641)	No ACEi or ARB initiation within 1 year (N = 12,759)
<b>Age</b>		
Mean (SD)	68.73 (12.04)	72.88 (10.51)
Median (IQR)	70 (63, 77)	74 (68, 81)
<b>Sex, n (%)</b>		
Male	1187 (44.9)	5389 (42.2)
Female	1451 (54.9)	7368 (57.7)
Unknown	3 (0.1)	2 (0.0)
<b>Race/ethnicity, n (%)</b>		
White	1349 (51.1)	7424 (58.2)
Asian	134 (5.1)	455 (3.6)
Black	282 (10.7)	1219 (9.6)
Hispanic	468 (17.7)	1469 (11.5)
Missing or unknown	408 (15.4)	2192 (17.2)
<b>Region, n (%)</b>		
Northeast	301 (11.4)	1879 (14.7)
Midwest	265 (10.0)	1338 (10.5)
South	1367 (51.8)	6617 (51.9)
West	703 (26.6)	2897 (22.7)
Missing or unknown	5 (0.2)	28 (0.2)
<b>Provider specialty, n (%)</b>		
Endocrinologist	63 (2.4)	273 (2.1)
Nephrologist	5 (0.2)	42 (0.3)
Cardiologist	61 (2.3)	333 (2.6)
General practitioner/internist	1251 (47.4)	5793 (45.4)
Urologist	7 (0.3)	52 (0.4)
Inpatient facility	63 (2.4)	359 (2.8)
Outpatient facility	49 (1.9)	212 (1.7)
Other/unknown provider specialty	1411 (53.4)	6634 (52.0)
<b>Comorbidity score</b>		
Charlson–Deyo comorbidity score		
Mean (SD)	2.05 (1.47)	2.24 (1.52)
Median (IQR)	2 (1, 3)	2 (1, 3)
Index CKD stage		
eGFR stage, <sup>b</sup> n (%)		
Stage 1	271 (10.3)	576 (4.5)
Stage 2	303 (11.5)	885 (6.9)
Stage 3a	1215 (46.0)	7889 (61.8)
Stage 3b	281 (10.6)	1615 (12.7)
Stage 4	39 (1.5)	186 (1.5)
Stage 5	4 (0.2)	36 (0.3)
Missing	528 (20.0)	1572 (12.3)

*(Continued)*

includes additional detail regarding inclusion and exclusion criteria and the study design.

## Exposures and Outcomes

The outcome of interest was ACEi or ARB initiation, defined as a pharmacy claim for an ACEi or an ARB during the follow-up period (**Table 1**). Patients' demographics, including age, sex, race/ethnicity, and US region, and CKD stage-defining variables assessed on the index date were reported. Prevalence of baseline comorbidities and medication use were measured during the baseline period. Provider specialty on the index date was described. A full list of variables is provided in **eAppendix Table 1** (eAppendices available at [ajmc.com](http://ajmc.com)). Treatment patterns with ACEis or ARBs during the first year after meeting CKD criteria were described, including the number and proportion of patients initiating treatment and treatment duration.

## Statistical Analysis

Logistic regression was used to identify baseline characteristics and medication use associated with ACEi or ARB treatment initiation. Bivariate associations are presented for all covariates included in the model. A backward selection model was used for the selection of predictors in the final model. The Akaike information criterion (a method used in model selection that estimates the relative quality of statistical models relative to each other) was used to evaluate model performance.<sup>19</sup> Effect estimates were reported as odds ratios and 95% confidence intervals. Two-sided *P* values with an  $\alpha = .05$  were also reported. No imputation of missing values was performed. The extent of missingness was reported in descriptive tables.

A sensitivity analysis was conducted to evaluate the impact of known contraindications for ACEis or ARBs at treatment initiation. Analyses were stratified by timing of ACEi or ARB initiation. The following variables were considered separately if they occurred in the 365 days before the index date or at any time prior to the index date: ACEi or ARB toxicity, angioedema, aortic stenosis, hyperkalemia, hypotension, shock, and renal disease/dysfunction. All statistical

analyses were performed using the Aetion Evidence Platform version 3.7.<sup>20</sup>

## Results

### Patient Characteristics

Of the 52,817 patients with incident CKD in T2D with 1 year of follow-up, 70.8% (n=37,417) were using an ACEi or ARB at baseline. Of the remaining 15,400 patients, 2641 (17%) initiated therapy within 1 year of cohort entry (Figure 1). Table 1 details the baseline characteristics of the study population. Patients initiating therapy were, on average, slightly younger than those who did not initiate therapy (70 vs 74 years, respectively) and had earlier stages of CKD based on eGFR laboratory results. Approximately 80% of patients in both groups had preexisting hypertension.

### Treatment Patterns

Compared with initiates, patients who did not begin therapy with ACEis or ARBs had a lower prevalence of first- and second-line antidiabetic medication use (Figure 2A). Common second-line treatments were sulfonylurea, dipeptidyl-peptidase-4 inhibitors, and basal insulin (Figure 2B). In addition, baseline medication use in this population reflected the management of multiple cardiovascular-related comorbidities, with frequent use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors,  $\beta$ -blockers, calcium channel blockers, thiazide diuretics, and loop diuretics (Figure 2C). After initiation of ACEis or ARBs, 1369 (55%) patients discontinued treatment within the first year of follow-up, with an average time to discontinuation of 5 months.

### Characteristics Associated With ACEi or ARB Initiation

In the bivariate assessment, attributes associated with lower likelihood of treatment initiation included male sex, White race, Northeast region, more advanced CKD (eGFR stages 2-5), UACR category A1, and MRA use (Table 2). Characteristics associated with higher likelihood of ACEi or ARB initiation included obesity, use of antidiabetic medications, and

**TABLE 1. (CONTINUED)** Baseline Characteristics Among Patients With Incident CKD and T2D, Without ACEi/ARB in Baseline Period, Stratified by ACEi or ARB Initiation Within 1 Year of Follow-up (N=15,400)

Demographics	ACEi or ARB initiation <sup>a</sup> within 1 year (N = 2641)	No ACEi or ARB initiation within 1 year (N = 12,759)
<b>Albuminuria category,<sup>c</sup> n (%)</b>		
A1	129 (4.9)	794 (6.2)
A2	1046 (39.6)	3006 (23.6)
A3	192 (7.3)	464 (3.6)
Missing	1274 (48.2)	8495 (66.6)
<b>Comorbidities, n (%)</b>		
Acute coronary syndrome	75 (2.8)	376 (2.9)
Acute kidney injury	66 (2.5)	368 (2.9)
Anemia	423 (16.0)	2542 (19.9)
Angina pectoris	504 (19.1)	2946 (23.1)
Atrial fibrillation	246 (9.3)	1658 (13.0)
Chronic lung/pulmonary disease	502 (19.0)	2680 (21.0)
Coronary artery disease	347 (13.1)	2147 (16.8)
Depression	259 (9.8)	1578 (12.4)
Diabetic retinopathy	408 (15.4)	1969 (15.4)
Edema	243 (9.2)	1365 (10.7)
Fatigue and sleep-related disorders	624 (23.6)	3282 (25.7)
Heart failure	231 (8.7)	1270 (10.0)
Hyperkalemia	44 (1.7)	250 (2.0)
Hyperlipidemia	2078 (78.7)	10,268 (80.5)
Hypertension	2022 (76.6)	10,219 (80.1)
Hypokalemia	95 (3.6)	471 (3.7)
Hyponatremia	50 (1.9)	288 (2.3)
Microvascular complications	836 (31.7)	4031 (31.6)
Myocardial infarction	31 (1.2)	173 (1.4)
Obesity	602 (22.8)	2522 (19.8)
Pain disorders	1726 (65.4)	8856 (69.4)
Peripheral vascular disease	397 (15.0)	2183 (17.1)
Resistant hypertension	61 (2.3)	320 (2.5)
Respiratory failure	47 (1.8)	273 (2.1)
Sleep apnea	271 (10.3)	1366 (10.7)
Stroke	94 (3.6)	570 (4.5)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation; T2D, type 2 diabetes; UACR, urinary albumin to creatinine ratio.

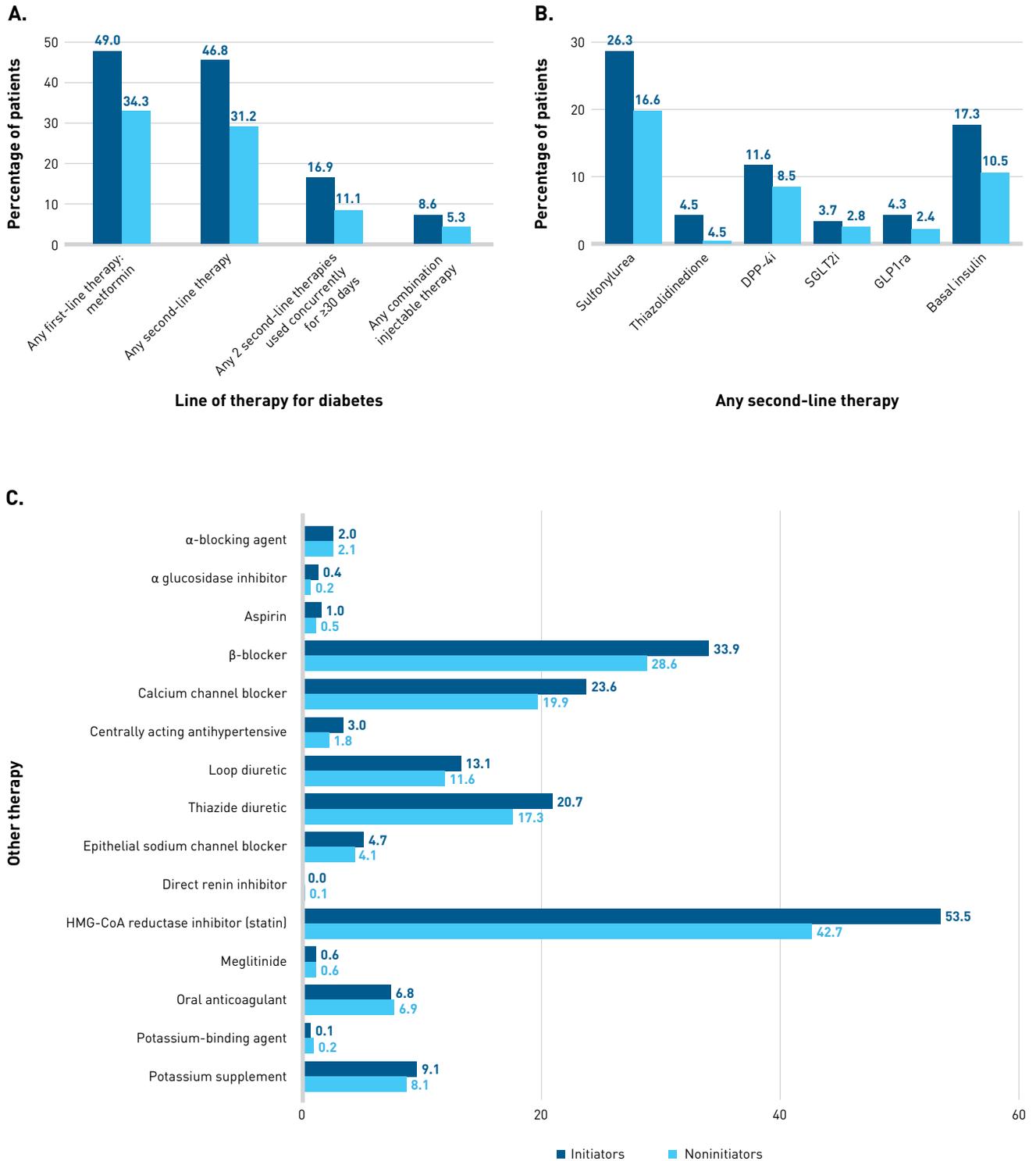
<sup>a</sup>Successful ACEi or ARB initiation was defined as any pharmacy claim during follow-up for an ACEi (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, tran-dolapril) or an ARB (candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan).

<sup>b</sup>Stage 1, eGFR  $\geq$ 90 mL/min/1.73 m<sup>2</sup> and UACR  $\geq$ 30 mg/g; stage 2, eGFR 60-89 mL/min/1.73 m<sup>2</sup> and UACR  $\geq$ 30 mg/g; stage 3a, eGFR 45-59 mL/min/1.73 m<sup>2</sup>; stage 3b, eGFR 30-44 mL/min/1.73 m<sup>2</sup>; stage 4, eGFR 15-29 mL/min/1.73 m<sup>2</sup>; stage 5, <15 mL/min/1.73 m<sup>2</sup>.

<sup>c</sup>A1, UACR <30 mg/g and eGFR <60 mL/min/1.73 m<sup>2</sup>; A2, UACR 30-299 mg/g; A3, UACR  $\geq$ 300 mg/g.

Demographics, eGFR stage, and albuminuria category were assessed on index date. Comorbidities, therapies, and subgroup criteria were assessed over a 365-day baseline period.

**FIGURE 2.** Baseline Medication Use Among Patients with Incident CKD and T2D Without ACE/ARB in Baseline Period, Stratified by ACEi/ARB Initiation Within 1 Year of Follow-up (N = 15,400)



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP1ra, glucagon-like peptide-1 receptor agonist; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A reductase; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes.

**TABLE 2.** Likelihood of Failing to Initiate Treatment With ACEis or ARBs Within 1 Year of Follow-up Among Patients With Incident CKD and T2D Without ACEi or ARB in Baseline Period (N=15,400): Bivariate Model<sup>a</sup>

Demographics	Univariate ORs (95% CI)	P value
Age	1.03 (1.03-1.04)	<.001
<b>Sex, n (%)</b>		
Male	1 (Reference)	—
Female	0.89 (0.82-0.97)	.009
Unknown	0.13 (0.02-0.79)	.026
<b>Race/ethnicity, n (%)</b>		
White	1 (Reference)	—
Asian	0.54 (0.42-0.69)	<.001
Black	0.68 (0.55-0.84)	<.001
Hispanic	0.50 (0.41-0.60)	<.001
Unknown	0.85 (0.71-1.01)	.068
<b>Region, n (%)</b>		
Northeast	1 (Reference)	—
Midwest	0.81 (0.68-0.97)	.020
South	0.78 (0.68-0.89)	<.001
West	0.66 (0.57-0.76)	<.001
Missing	0.90 (0.34-2.34)	.824
<b>Provider specialty, n (%)</b>		
Endocrinologist	0.89 (0.68-1.18)	.431
Nephrologist	1.74 (0.69-4.40)	.242
Cardiologist	1.13 (0.86-1.49)	.374
General practitioner/internist	0.92 (0.85-1.00)	.065
Urologist	1.54 (0.70-3.39)	.284
Inpatient facility	1.18 (0.90-1.55)	.220
Outpatient facility	0.89 (0.65-1.22)	.483
Missing	0.94 (0.87-1.03)	.180
<b>Index CKD stage</b>		
eGFR stage <sup>b</sup>		
Stage 1	1 (Reference)	—
Stage 2	1.37 (1.13-1.67)	.001
Stage 3a	3.05 (2.61-3.57)	<.001
Stage 3b	2.70 (2.23-3.28)	<.001
Stage 4	2.24 (1.54-3.26)	<.001
Stage 5	4.23 (1.49-12.02)	.007
Missing	1.40 (1.18-1.67)	<.001
UACR category <sup>c</sup>		
A1	1 (Reference)	—
A2	0.47 (0.38-0.57)	<.001
A3	0.39 (0.31-0.50)	<.001
Missing	1.08 (0.89-1.32)	.421

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; T2D, type 2 diabetes; UACR, urinary albumin to creatinine ratio.

<sup>a</sup>Table includes only select ORs; ORs for comorbidities, antidiabetic medications, and other therapies can be found in eAppendix Table 2.

<sup>b</sup>Stage 1, eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup> and UACR  $\geq 30$  mg/g; stage 2, eGFR 60-89 mL/min/1.73 m<sup>2</sup> and UACR  $\geq 30$  mg/g; stage 3a, eGFR 45-59 mL/min/1.73 m<sup>2</sup>; stage 3b, eGFR 30-44 mL/min/1.73 m<sup>2</sup>; stage 4, eGFR 15-29 mL/min/1.73 m<sup>2</sup>; stage 5,  $<15$  mL/min/1.73 m<sup>2</sup>.

<sup>c</sup>A1, UACR  $<30$  mg/g and eGFR  $<60$  mL/min/1.73 m<sup>2</sup>; A2, UACR 30-299 mg/g; A3, UACR  $\geq 300$  mg/g.

the use of most cardiovascular agents except for MRAs (eAppendix Table 2). Key predictors of ACEi or ARB treatment initiation in the final model are presented in Table 3. Characteristics associated with lower likelihood of treatment initiation included White race, Northeast region, presence of atrial fibrillation, depression, pain disorders, coronary artery disease, and MRA use. Those meeting criteria for resistant hypertension and users of SGLT2is were 45% and 63% less likely to initiate therapy, respectively. Users of  $\beta$ -blockers, centrally acting antihypertensives, and statins were more likely to initiate ACEis or ARBs.

### Contraindications

Among patients who met criteria for CKD in T2D and had no baseline ACEi or ARB use, the presence of potential ACEi or ARB contraindications did not differ by whether patients initiated therapy with ACEis or ARBs within 1 year of follow-up (eAppendix Table 3). At least 1 contraindication was observed among approximately 20% of patients whether they received ACEis or ARBs or not, in 6% of patients with evidence of hyperkalemia prior to index (by diagnosis or laboratory test result), and in less than 10% of patients with evidence of hypotension. These findings suggest that failure to initiate treatment with an ACEi or ARB within 1 year may not be attributed to a previous contraindication alone.

### Discussion

This study described characteristics associated with initiation of treatment with ACEis or ARBs within 1 year after meeting the criteria for CKD among patients with T2D. Approximately two-thirds of newly identified patients with CKD were already receiving ACEis or ARBs at the time of diagnosis; of the remaining one-third, only 17% of patients initiated therapy within 1 year, despite a similarly high prevalence of hypertension in that group. It is possible that some patients did not initiate these therapies due to use of other medications, in particular those with resistant hypertension, which was associated with a lower likelihood of beginning ACEi or ARB therapy. In our analysis, patients

**TABLE 3.** Likelihood of Failing to Initiate Treatment With ACEi or ARB Within 1 Year of Follow-up Among Patients With Incident CKD and T2D Without ACEi or ARB in Baseline Period (N=15,400): Final Multivariate Model After Backward Selection

Demographics	Final multivariate ORs after backward selection [95% CI]	P value
Age (years)	1.02 (1.02-1.02)	<.001
<b>Race/ethnicity</b>		
White	1 (Reference)	—
Asian	0.76 (0.58-0.99)	.040
Black	0.80 (0.64-1.00)	.049
Hispanic	0.69 (0.56-0.84)	<.001
Unknown	0.88 (0.74-1.06)	.178
<b>Region</b>		
Northeast	1 (Reference)	—
Midwest	0.83 (0.69-1.00)	.052
South	0.87 (0.75-1.00)	.046
West	0.80 (0.69-0.93)	.005
Missing	1.01 (0.38-2.70)	.978
<b>Provider specialty</b>		
General practitioner/internist	0.85 (0.77-0.92)	<.001
<b>UACR category<sup>a</sup></b>		
A1	1 (Reference)	—
A2	0.55 (0.45-0.68)	<.001
A3	0.48 (0.37-0.62)	<.001
Missing	1.02 (0.84-1.25)	.816
<b>Comorbidity score</b>		
Deyo comorbidity score	1.04 (1.01-1.08)	.024
<b>Comorbidities</b>		
Atrial fibrillation	1.17 (1.00-1.36)	.053
Coronary artery disease	1.16 (1.01-1.32)	.033
Depression	1.29 (1.12-1.50)	.001
Fatigue and sleep-related disorders	0.93 (0.83-1.03)	.148
Heart failure	0.86 (0.72-1.02)	.086
Pain disorders	1.11 (1.01-1.22)	.032
Resistant hypertension	1.45 (1.06-1.97)	.019
<b>Antidiabetic medications</b>		
Metformin	0.92 (0.82-1.02)	.125
Sulfonylurea	0.84 (0.74-0.95)	.007
DPP-4i	1.12 (0.96-1.31)	.146
SGLT2i	1.63 (1.26-2.12)	<.001
Number of different antidiabetic medications	0.85 (0.79-0.90)	<.001
<b>Other therapy</b>		
Aspirin	0.68 (0.42-1.10)	.115
β-Blocker	0.82 (0.74-0.91)	<.001
Centrally acting antihypertensive	0.67 (0.50-0.88)	.004

(Continued)

who did not initiate ACEis or ARBs within follow-up were more likely to be White; reside in the northeastern United States; have normal to mildly increased persistent albuminuria (UACR category A1); have a higher number of comorbidities, including atrial fibrillation, coronary artery disease, depression, pain disorders, and resistant hypertension; and have a prescription for SGLT2is.

Based on published literature suggesting safety issues as a barrier to ACEi or ARB treatment initiation, we considered the presence of relative contraindications to ACEi or ARB therapy (eg, hyperkalemia, hypotension)<sup>21-25</sup>; however, the similar prevalence of contraindications among initiates and noninitiates suggests that contraindications alone may not explain the failure to initiate ACEis or ARBs in our study population.

Although advanced eGFR stage at the time of patient identification was associated with a lower likelihood of treatment initiation with ACEis or ARBs in the bivariate model, this association did not persist in the final model. However, we observed an association with UACR category, suggesting that UACR category A1 was associated with failure to initiate treatment within 1 year of follow-up. This incongruity may reflect the differing medical evidence regarding treatment to reduce eGFR compared with proteinuria. The guidelines from Kidney Disease: Improving Global Outcomes recommend that ACEis or ARBs be titrated to the highest approved dose that is tolerated regardless of albuminuria level, whereas published results from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and the Irbesartan Diabetic Nephropathy Trial (IDNT) emphasize the benefits of ACEi or ARB therapy in patients with severely increased albuminuria.<sup>11,13,26</sup> ACEi therapy is often not started in patients with advanced CKD, but these individuals may derive the greatest benefit.<sup>12</sup> In the RENAAL study and IDNT, patients were initiated on ARB therapy when their creatinine levels reached 3.0 mg/dL, and the medication was continued despite rising creatinine values.<sup>11,13</sup> These varying medical opinions on

the use of ACEis or ARBs in advanced CKD may affect prescribing patterns.

In addition, our final multivariate predictive model showed that while sulfonyleurea use was associated with ACEi or ARB treatment, SGLT2i use was associated with a lower likelihood of ACEi or ARB treatment initiation within 1 year of meeting CKD criteria. However, it should be noted that this study included a small number of patients taking SGLT2i (n = 455). The association of SGLT2i use and failure to initiate ACEi or ARB therapy most likely reflects the burgeoning evidence of the renal-protective effects of this second-line antidiabetic treatment on kidney disease progression<sup>27,28</sup> and the likely choice of SGLT2is to provide renal-protective benefits in patients who cannot take ACEis or ARBs. The association of the use of other cardiovascular agents with ACEi or ARB initiation—except for MRAs—aligns with the addition of ACEis or ARBs to prior antihypertensive therapies, or treatment augmentation, for better blood pressure control.

Several published studies also highlight suboptimal prescribing of ACEis or ARBs in high-risk patients with diabetes when evaluating real-world determinants of ACEi or ARB utilization. Among Medicare Part D enrollees, 43.1% of patients with diabetes and renal disease used ACEis or ARBs; the percentage increased to 63.0% in patients with diabetes, renal disease, and hypertension.<sup>29</sup> Patient characteristics associated with ACEi or ARB use in this Medicare D population were female sex, non-White race, age at least 65 years, and specific comorbidities (eg, hypercholesterolemia, heart failure, and myocardial infarction), which correspond closely to predictors identified in this study. While these studies found that non-White race predicted ACEi or ARB use, a 2004 study of Kaiser Permanente Northern California Diabetes Registry data found similar levels of ACEi or ARB utilization in Black and White patients with T2D (63% vs 61%, respectively). However, Black patients with T2D with albuminuria had significantly lower ACEi/ARB use than their White counterparts (47% vs 56%, respectively).<sup>30</sup> The lack of pronounced racial disparity with respect to ACEi or ARB therapy in our analysis and the Medicare D analysis may be due to a greater awareness of high-risk ethnic groups among physicians.

Differing from the Medicare D analysis, none of the individual comorbidities in our analysis predicted ACEi or ARB use after CKD diagnosis among patients with T2D without evidence of ACEi or ARB use during baseline. Heart failure was suggestive of an association (odds ratio, 0.86; 95% CI, 0.72-1.02) but it was not significant in the final model; moreover, several individual comorbidities (ie,

**TABLE 3. (Continued)** Likelihood of Failing to Initiate Treatment With ACEi or ARB Within 1 Year of Follow-up Among Patients With Incident CKD and T2D Without ACEi or ARB in Baseline Period (N=15,400): Final Multivariate Model After Backward Selection

Demographics	Final multivariate ORs after backward selection (95% CI)	P value
<b>Diuretic</b>		
Loop diuretic	0.84 (0.72-0.97)	.017
Thiazide diuretic	0.88 (0.79-0.99)	.036
Direct renin inhibitor <sup>b</sup>	—	—
HMG-CoA reductase inhibitor (statin)	0.83 (0.76-0.92)	<.001
MRA	1.40 (1.07-1.82)	.013

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A reductase; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urinary albumin to creatinine ratio.

<sup>a</sup>A1, UACR <30 mg/g and eGFR <60 mL/min/1.73 m<sup>2</sup>; A2, UACR 30-299 mg/g; A3, UACR ≥300 mg/g.

<sup>b</sup>Direct renin inhibitors did not converge because there were 18 users who did not initiate and 0 users who initiated by 1 year.

Demographics, eGFR stage, and albuminuria category were assessed on index date. Comorbidities, therapies, and subgroup criteria were assessed over a 365-day baseline period.

coronary artery disease, depression, atrial fibrillation, pain disorders, and resistant hypertension) were associated with a lower likelihood of ACEi or ARB treatment initiation in our analysis. The final model showed that the use of several cardiovascular-related medications (eg,  $\beta$ -blockers, centrally active antihypertensives, diuretics, and statins) was associated with a higher likelihood of ACEi or ARB treatment initiation.

### Limitations

This study had several limitations. First, laboratory results in administrative claims data were incomplete and available for only a subset of patients who received testing at a participating laboratory. Laboratory results that were performed in a hospital setting or directly at the physician's office are most likely under-represented. Laboratory participation was assumed to be random; thus, selection bias was not a concern. Second, we refer to eGFR and UACR laboratory results as the gold standard for the identification of renal disease. However, there are circumstances in which any creatinine-based estimate of kidney function, including eGFR, should not be used; thus, some patients may have been misclassified. For example, creatinine-based estimates should be avoided in patients in the following circumstances: people with changing serum creatinine levels; people with acute kidney injury; those with extremes in muscle mass, body size, or altered diets; and individuals taking medications that affect excretion of creatinine. Third, the logistic regression model attempted to relate potential predictors to the likelihood of ACEi or ARB initiation. To this end, we cannot rule out the possibility of unmeasured confounding of the estimated associations or unmeasured

predictors of differential dropout, which may bias our estimates. Fourth, the study included patients without albuminuria and/or hypertension for whom ACEi or ARB therapy is not indicated according to current guidelines. However, the proportion of such patients was assumed to be low, because 80.1% of noninitiates had a diagnosis for hypertension and approximately 81.4% had a diagnosis for albuminuria (assuming that the distribution is the same in those with missing information for UACR). Finally, the study required patients to have continuous enrollment in their health plan for a fixed follow-up time, potentially introducing selection bias by excluding patients who did not survive or were not enrolled for a minimum period of follow-up.

## Conclusions

This study estimated that one-third of patients with T2D are not receiving ACEis or ARBs at the time of newly diagnosed CKD, and a large proportion of them do not initiate the guideline-recommended ACEi or ARB therapy within 1 year of diagnosis. Characteristics associated with a lower likelihood of ACEi or ARB initiation among nonusers include less advanced albuminuria, use of MRAs and SGLT2is, and comorbid conditions such as coronary artery disease, depression, and resistant hypertension. Given that failure to initiate treatment in these patients may adversely affect disease progression, these findings highlight the need for new therapies that can slow the progression of newly diagnosed CKD in T2D. Future research to better understand the impact of this treatment delay on patient outcomes and the reasons for not receiving ACEis or ARBs as indicated by guidelines will benefit a growing population of patients with newly diagnosed CKD in T2D who have a demonstrated unmet need. ■

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# Medical Costs for Managing Chronic Kidney Disease and Related Complications in Patients With Chronic Kidney Disease and Type 2 Diabetes

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## Introduction

Chronic kidney disease (CKD) is prevalent, and it is estimated that it will affect about 15% of adults or 37 million people in the United States in 2021.<sup>1</sup> Diabetes is one of the leading causes of CKD and kidney failure. About 1 in 3 US adults with diabetes has CKD, and CKD with diabetes accounts for approximately 39% of end-stage renal disease (ESRD) cases in the United States.<sup>1</sup> Moreover, CKD is associated with an increased risk of cardiovascular (CV) diseases and all-cause mortality.<sup>2</sup> The risk of heart failure, atrial fibrillation, stroke, and coronary heart disease is approximately double in patients with CKD.<sup>3-7</sup> The adjusted mortality is also twice as high among Medicare beneficiaries with CKD compared with those without CKD.<sup>8</sup>

CKD poses a substantial economic burden. Medicare spending for all beneficiaries who had CKD exceeded \$120 billion in 2017, representing 33.8% of total Medicare fee-for-service spending.<sup>9</sup> On an individual level, annual Medicare spending was \$16,112 per patient for those with CKD and increased to \$19,739 per patient for those with CKD and diabetes.<sup>9</sup> In addition to general CKD management, addressing CV complications can be costly. Approximately 29% of the total inpatient hospitalization spending for those with CKD resulted from admissions to treat CV complications.<sup>9</sup> Heart failure was associated with an incremental per-person per-year Medicare cost of \$19,944 among patients with CKD.<sup>8</sup> Hyperkalemia is another complication that is common among patients with CKD, and it is associated with substantial health care costs.<sup>10,11</sup> Specifically, hyperkalemia was associated with an increased 1-year cost of \$21,857 in patients with CKD and \$20,657 in patients with diabetes.<sup>10</sup>

Current treatment strategies for patients with CKD and type 2 diabetes (T2D) focus on CV risk reduction, blood pressure control, glycemic control, and lipid-lowering therapy.<sup>12</sup> For example, the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the use of renin-angiotensin-aldosterone system-blocking agents including angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) in patients with CKD and diabetes who have hypertensive symptoms.<sup>13</sup> Available evidence strongly indicates that the use of ACEis or ARBs yields a significant renal protective effect, reducing albuminuria and

## ABSTRACT

**Objective:** To provide cost estimates for chronic kidney disease (CKD) management and major CKD complications among patients with CKD and type 2 diabetes (T2D).

**Study Design:** A retrospective cohort study of 52,599 adults with CKD and T2D using Optum Clinformatics claims data from 2014 to 2019.

**Methods:** Medical costs associated with CKD management, renal replacement therapies (RRTs), major CKD complications (eg, myocardial infarction, stroke, heart failure, atrial fibrillation, and hyperkalemia), and death were estimated using generalized estimating equations adjusting for baseline demographics, complications, and medical costs. Costs for CKD management, RRT, and major CKD complications were assessed in 4-month cycles. Mortality costs were assessed in the month before death.

**Results:** The estimated 4-month CKD management costs ranged from \$7725 for stage I to II disease to \$11,879 for stage V (without RRT), with high additional costs for dialysis and kidney transplantation (\$87,538 and \$124,271, respectively). The acute event costs were \$31,063 for heart failure, \$21,087 for stroke, and \$21,016 for myocardial infarction in the first 4 months after the incident event, which all decreased substantially in subsequent 4-month cycles. The acute event costs of atrial fibrillation and hyperkalemia were \$30,500 and \$31,212 with hospitalization, and \$5162 and \$1782 without. The costs associated with cardiovascular-related death, renal-related death, and death from other causes were \$17,031, \$12,605, and \$9900, respectively.

**Conclusions:** Management of CKD and its complications incurs high medical costs for patients with CKD and T2D. Results from this study can be used to quantify the economic profile of emerging treatments and inform decision-making.

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For author information and disclosures, see end of text.

the risk of ESRD in this patient group.<sup>12</sup> Several emerging treatments, such as finerenone and sodium-glucose cotransporter-2 inhibitors (SGLT2is), have demonstrated clinical benefits in terms of preventing CV diseases in patients with CKD and T2D, slowing down the progression of kidney disease, and reducing the risk of death.<sup>14-18</sup>

To evaluate whether these clinical benefits translate to real-world economic benefit (ie, cost-effectiveness), it is essential to quantify the key cost components associated with the management of CKD and related complications in patients with CKD and T2D. However, knowledge gaps exist regarding the health care costs associated with general CKD management at different disease stages and major complications (including myocardial infarction [MI], heart failure, stroke, atrial fibrillation, and hyperkalemia) in patients with CKD and T2D. This study aims to provide the most up-to-date estimates of cost components related to general CKD management and major CKD complications using a regression-based approach. Results will facilitate the parameterization of economic models and quantify the economic burden in this population using the most recent data.

## Methods

### Study Design and Population

This retrospective cohort study identified adult patients with T2D and CKD using Optum Clinformatics claims data from 2014 to 2019. The Optum claims database is a single-payer source of administrative health claims with approximately 15 to 20 million annual covered enrollees across all states in the United States. Enrollees may be covered by commercial health plans or Medicare Advantage. The administrative claims were submitted for payment by providers and pharmacies and were verified, adjudicated, and de-identified.

T2D was identified using a modified version of the Electronic Medical Records and Genomics algorithm, developed to identify patients with T2D in electronic medical records with high specificity.<sup>19</sup> Patients without observed insulin use were required to have at least 1 medical claim with a T2D diagnosis and at least 1 prescription claim for antidiabetic medication. Patients with observed insulin use were required to have (1) at least 1 medical claim with a T2D diagnosis and at least 1 prescription claim for antidiabetic therapy prior to the first insulin prescription; or (2) at least 2 T2D diagnoses on different dates among those without antidiabetic prescription claims. Patients with records of other types of diabetes (including type 1 diabetes, diabetes due to underlying conditions, drug- or chemical-induced diabetes, and other specified diabetes) were excluded.

CKD was identified using at least 1 inpatient or at least 2 outpatient CKD claims on distinct dates. Evidence of CKD included having diagnosis codes for CKD or ESRD, or procedure codes for renal replacement therapies (RRT), including dialysis and kidney transplantation. Only patients with known CKD stage based on diagnosis codes were included.

The study index date was defined as the first date when both T2D and CKD definitions were met. Patients were required to have continuous enrollment for 1 year before (baseline period) and at least 4 months after the index date. Patients covered by health maintenance organizations during the baseline or study period were excluded from the study sample because their recorded health care expenditures may not accurately reflect their medical care usage.

### Study Outcomes

This study assessed medical costs from the payer's perspective, from the patient's index date to disenrollment, death, or end of data availability. Cost components included CKD management, RRT, major CKD complications, and death. The costs for CKD management, RRT, and major CKD complications were reported in 4-month cycles, which was a commonly evaluated cycle length in clinical trials in this population.<sup>15,17</sup> Mortality costs were assessed in the month prior to death.

The costs of general CKD management were estimated by CKD stage, classified as stage I to II, stage III, stage IV, and stage V without RRT.<sup>20</sup> The costs of RRT were assessed separately, including dialysis costs and kidney transplantation costs. Major CKD complications included MI, heart failure (with hospitalization), stroke, hyperkalemia (with and without hospitalization), and atrial fibrillation (with and without hospitalization). Death was classified as CV-related, renal-related, or from other causes based on the primary diagnosis or procedure codes during hospitalization in the month of death because direct information on the cause of death was not available.

Events of interest were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* and *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* diagnosis codes, and Current Procedural Terminology, Healthcare Common Procedure Coding System, and *ICD-9-CM* or *ICD-10* Procedure Coding System procedure codes. All medical costs were inflated to 2020 US\$ using the medical care component of the Consumer Price Index.

### Statistical Analysis

Descriptive analyses were performed for patient characteristics during baseline. Mean and standard deviation were reported for continuous variables, and frequency counts and percentages were used for categorical variables. Median and interquartile range were calculated for baseline medical costs.

A generalized estimating equation (GEE) regression with a normal distribution and an exchangeable correlation structure was used to model the monthly costs associated with the management of CKD, RRT, major CKD complications, and death, adjusting for age at index date, sex, baseline complications, and baseline medical costs (detailed model specification information is displayed in

**FIGURE 1.** Generalized Estimating Equation Model

$$\text{Monthly cost}_{ij} =$$

$$\underbrace{\beta_0 + \beta_1 \text{age}_i + \beta_2 \text{sex}_i + \beta_3 \text{BL\_MI}_i + \beta_4 \text{BL\_stroke}_i + \beta_5 \text{BL\_HF}_i + \beta_6 \text{BL\_hyperkalemia}_i + \beta_7 \text{BL\_AFib}_i + \beta_8 \text{BL\_costs}_i}_{\text{BL characteristics (time-invariant)}}$$

$$+ \underbrace{\beta_9 \text{CKD\_stage3}_{ij} + \beta_{10} \text{CKD\_stage4}_{ij} + \beta_{11} \text{CKD\_stage5\_without\_RRT}_{ij}}_{\text{CKD stage (time-varying)}}$$

$$+ \underbrace{(\beta_{12} \text{P1\_MI}_{ij} + \beta_{13} \text{P2\_MI}_{ij} + \beta_{14} \text{P3\_MI}_{ij}) + (\beta_{15} \text{P1\_stroke}_{ij} + \beta_{16} \text{P2\_stroke}_{ij} + \beta_{17} \text{P3\_stroke}_{ij}) + (\beta_{18} \text{P1\_HF}_{ij} + \beta_{19} \text{P2\_HF}_{ij} + \beta_{20} \text{P3\_HF}_{ij})}_{\text{Complications with acute and postacute costs (time-varying)}}$$

$$+ \underbrace{(\beta_{21} \text{P1\_dialysis}_{ij} + \beta_{22} \text{P2\_dialysis}_{ij} + \beta_{23} \text{P3\_dialysis}_{ij}) + (\beta_{24} \text{P1\_KT}_{ij} + \beta_{25} \text{P2\_KT}_{ij} + \beta_{26} \text{P3\_KT}_{ij})}_{\text{RRT (time-varying)}}$$

$$+ \underbrace{(\beta_{27} \text{P1\_hyperkalemia}_{ij} + \beta_{28} \text{P2\_hyperkalemia}_{ij}) + (\beta_{29} \text{P1\_AFib}_{ij} + \beta_{30} \text{P2\_AFib}_{ij})}_{\text{Complications with acute costs only (time-varying)}}$$

$$+ \underbrace{\beta_{31} \text{CV\_death}_{ij} + \beta_{32} \text{renal\_death}_{ij} + \beta_{33} \text{other\_death}_{ij}}_{\text{Death (time-varying)}}$$

AFib, atrial fibrillation; BL, baseline; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; KT, kidney transplantation; MI, myocardial infarction; RRT, renal replacement therapy.  
 i, patient i; j, month j  
 P1: in the month of the event  
 P2: in the next 3 months after the incident month  
 P3: after the first 4-month cycle

**Figure 1).** A GEE regression model is a technique for obtaining regression estimates in multilevel data. It was used to account for the within-subject correlations in our longitudinal claims data with repeated measurements. CKD management costs (excluding costs associated with RRT, major CKD complications, and death) were estimated on a monthly basis and were summarized in a 4-month period for CKD stages I to II through V without RRT. The costs for major CKD complications (eg, MI, heart failure, stroke), dialysis, and kidney transplantation were estimated for 2 phases. Acute costs included the costs occurring during the month of the event onset and the subsequent 3 months (ie, 4 months in total); postacute costs included costs during subsequent follow-up and were reported in 4-month cycles. Similar to Kähm et al, these later months were assumed to reflect the ongoing impact of the complication, regardless of whether the particular event recurred following the incident month.<sup>21</sup> Only acute costs were estimated for hyperkalemia and atrial fibrillation due to their relatively short-term impact on costs.

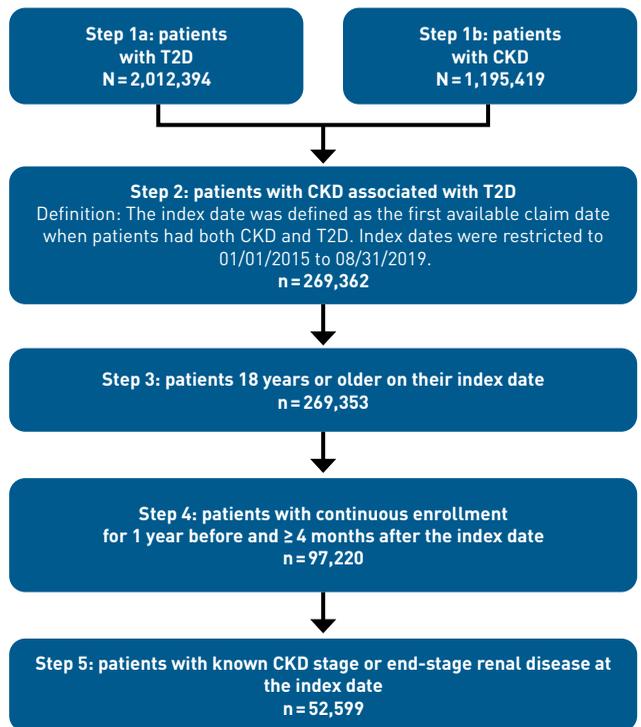
SAS 9.4 software (SAS Institute, Cary, NC) was used for all statistical analyses.

**Results**

**Sample and Patient Characteristics**

The study sample included 52,599 adult patients with T2D and CKD (**Figure 2**). **Table 1** describes patients' baseline demographics

**Figure 2.** Sample Selection



CKD, chronic kidney disease; T2D, type 2 diabetes.

**TABLE 1.** Patient Baseline Characteristics

Patients with T2D and CKD N = 52,599	
Demographic information at index date	
Age (years), mean (SD)	71.38 (9.78)
Female, n (%)	25,533 (48.54%)
Race, n (%)	
White	31,332 (59.57%)
Black	8173 (15.54%)
Hispanic	6291 (11.96%)
Asian	1645 (3.13%)
Unknown	5158 (9.81%)
Region, n (%)	
South	28,419 (54.03%)
Midwest	12,844 (24.42%)
Northeast	5977 (11.36%)
West	5342 (10.16%)
Other/unknown	17 (0.03%)
Insurance type, n (%)	
Medicare Advantage	42,249 (80.32%)
Commercial	10,369 (19.71%)
CKD stage, n (%)	
CKD stage I	2796 (5.32%)
CKD stage II	10,955 (20.83%)
CKD stage III	35,696 (67.86%)
CKD stage IV	2420 (4.60%)
CKD stage V and ESRD	732 (1.39%)
Comorbidities, n (%)	
Hypertension	48,639 (92.47%)
Hyperlipidemia	44,364 (84.34%)
Diabetes-related microvascular complications	16,695 (31.74%)
Ischemic heart diseases	15,720 (29.89%)
Myocardial infarction	3687 (7.01%)
Anemia	14,420 (27.41%)
Obesity	12,590 (23.94%)
Chronic pulmonary diseases	11,746 (22.33%)
Peripheral vascular diseases	9103 (17.31%)
Heart failure	8157 (15.51%)
Edema	7628 (14.50%)
Atrial fibrillation	6893 (13.10%)
Hyperkalemia	3181 (6.05%)
Stroke	2443 (4.64%)
Health care costs (2020 US\$)	
Medical costs	
Mean ± SD	16,995 ± 45,670
Median	4786
IQR	(1675, 14,684)

CKD, chronic kidney disease; ESRD, end-stage renal disease; IQR, interquartile range; SD, standard deviation; T2D, type 2 diabetes.

and clinical characteristics. Patients were 71 years of age on average; 49% were female and 60% were White. The majority of patients were covered by Medicare Advantage (80%). Most patients had a CKD diagnosis at index date indicating CKD stage III (68%), followed by stage II (21%). Diagnoses of hypertension (92%) and hyperlipidemia (84%) were very common in the study sample, which also had a relatively high prevalence of recorded microvascular complications (32%), ischemic heart diseases (30%), and anemia (27%). For the major CKD complications of interest, the prevalence was moderate to low during the 1-year baseline period: heart failure (16%), atrial fibrillation (13%), MI (7%), hyperkalemia (6%), and stroke (5%). Baseline all-cause medical costs were \$16,995 annually on average.

### Cost Estimates

**Table 2** shows the cost estimates for CKD management, RRT, major CKD complications, and death. The estimated 4-month CKD management costs for stage I to II were \$7725 and increased to \$11,879 for stage V (without RRT), with the largest increase (+\$1881) from stage III to IV. The estimated acute event costs for dialysis and kidney transplantation were \$87,538 and \$124,271, respectively. The costs decreased substantially to \$49,573 and \$7079 in the subsequent 4-month cycles, respectively.

For major CKD complications, the estimates of acute cost in the first 4 months after the incident event were \$21,016 for MI, \$21,087 for stroke, and \$31,063 for heart failure. For patients who experienced a hospitalization with atrial fibrillation, their acute costs were nearly 6 times higher than those without a hospitalization (\$30,500 vs \$5162). Similarly, the acute cost of hyperkalemia was \$31,212 with hospitalization and \$1782 without. In subsequent 4-month cycles, the cost of major CKD complications decreased to \$4931 for heart failure, \$2327 for stroke, and \$1941 for MI. In the month before death, the costs associated with CV-related death, renal-related death, and death from other causes were \$17,031, \$12,605, and \$9900, respectively.

### Discussion

This study summarizes the real-world economic impact associated with CKD management, RRT, major CKD complications, and death in patients with CKD and T2D, using a large US administrative claims database. The results show that costs associated with CKD management increase with disease severity, and the costs were substantially higher with RRT. CKD complications were associated with high costs during the initial months, with acute costs nearly double or triple the amount associated with regular CKD management without RRT. In addition, both CV-related and renal-related death incurred high costs in this patient population.

Given the rising prevalence of T2D and the high prevalence of CKD among patients with T2D, slowing down CKD progression and

preventing these costly complications can substantially reduce the economic burden associated with this population.<sup>1,22</sup> For example, by reducing the incidence of heart failure by 1 percentage point among patients with T2D and CKD, a Medicare Advantage plan of 1 million enrollees could save more than \$18.6 million in acute costs (using the estimated acute cost for heart failure [\$31,063]).<sup>23,24</sup> Similarly, if a treatment can yield a percentage point reduction in the incidence of patients progressing to dialysis, the health care plan can save approximately \$52 million in dialysis initiation costs and \$30 million in each subsequent 4-month cycle.

This study found acute costs of major complications commonly seen in CKD and T2D to be much higher than postacute costs, which is largely consistent with results reported in published studies. For example, a retrospective analysis of 2002 to 2009 Medicare claims data among older MI survivors reported a mean health care cost of \$21,416 during the calendar quarter of the MI and \$3574 for each calendar quarter post MI.<sup>25</sup> A systematic literature review of journal articles published between 2014 and 2020 on heart failure–related costs reported a mean cost of \$11,315 during the first month after a heart failure event, and a mean monthly cost during the entire first year post heart failure of \$2427.<sup>26</sup> Another retrospective analysis assessed the cost of hyperkalemia using the MarketScan claims database; the 1-month cost after a hyperkalemia event was \$5994 and the average monthly cost within the first year was \$2654.<sup>10</sup> Our results were largely in line with these previous findings in patients with CKD and T2D after controlling for patients' baseline demographics and complications.

Patients with CKD and T2D should be treated with a comprehensive strategy to reduce the risk of kidney disease progression and CV disease; the strategy usually includes blood pressure control by ACEis or ARBs, glycemic control by metformin and other antihyperglycemics, antiplatelet therapy with aspirin in those with established CV disease, and various lifestyle interventions.<sup>13</sup> Several emerging treatments demonstrated promising efficacy in preventing CV- and renal-related events in recent trials. Canagliflozin, dapagliflozin, and empagliflozin, the first 3 SGLT2is approved by the United States Food and Drug Administration (FDA), were shown to decrease the risk of renal and CV outcomes in patients with CKD and T2D.<sup>14-16,18</sup> Finerenone, a first-in-class nonsteroidal, selective mineralocorticoid receptor antagonist recently approved by the FDA in adults with CKD and T2D, was also shown to lower the risk of renal and CV outcomes in this patient population in the FIDELIO-DKD trial (NCT02540993).<sup>17,27</sup> To formally evaluate the different roles that these emerging treatments can fill in the management of CKD and T2D, rigorous economic models are needed to systematically assess their cost-effectiveness, especially potential cost reductions in the setting of common CKD complications. The current study provides accurate estimates for the key cost components relevant to managing

**TABLE 2.** Cost Estimates for CKD Management, RRT, Major CKD Complications, and Death

Unit cost (2020 US\$)	All patients N = 52,599	
	4-month acute (SE)	4-month ongoing/postacute (SE)
<b>CKD management</b>		
CKD stage I and II	N/A	\$7725 (\$597)
CKD stage III	N/A	\$8928 (\$640)
CKD stage IV	N/A	\$10,809 (\$668)
CKD stage V (without RRT)	N/A	\$11,879 (\$937)
Dialysis	\$87,538 (\$6691)	\$49,573 (\$2476)
Kidney transplantation	\$124,271 (\$37,052)	\$7079 (\$1422)
<b>Major CKD complications</b>		
Myocardial infarction	\$21,016 (\$811)	\$1941 (\$367)
Heart failure	\$31,063 (\$823)	\$4931 (\$347)
Stroke	\$21,087 (\$975)	\$2327 (\$505)
Hyperkalemia		
Hyperkalemia with hospitalization	\$31,212 (\$2135)	N/A
Hyperkalemia without hospitalization	\$1782 (\$378)	N/A
Atrial fibrillation		
Atrial fibrillation with hospitalization	\$30,500 (\$1388)	N/A
Atrial fibrillation without hospitalization	\$5162 (\$666)	N/A
<b>1-month (SE)</b>		
<b>Death costs</b>		
CV-related	\$17,031 (\$1782)	N/A
Renal-related	\$12,605 (\$2380)	N/A
Other causes	\$9900 (\$504)	N/A

CKD, chronic kidney disease; CV, cardiovascular; N/A, not applicable; RRT, renal replacement therapy; SE, standard error.

patients with CKD and T2D from a US payer's perspective, which can be used to facilitate the parameterization of such cost-effectiveness models.

**Limitations**

The findings of this study need to be seen in light of several limitations. First, although this study used GEE regression analysis to provide cost estimates, adjusting for patient demographics, baseline complications, and baseline medical costs, the model did not control for other chronic comorbidities, such as hypertension and hyperlipidemia. This is not expected to impact the results significantly, given that age is a strong predictor of comorbidities.<sup>21</sup> Nonetheless, there may be remaining confounding due to clinical characteristics (eg, disease duration and smoking status)

that cannot be observed in retrospective claims data.<sup>21</sup> Second, this study was subject to the typical limitations of retrospective studies based on health care claims data, such as possible errors or omissions of claims. Certain comorbidities may be underestimated due to coding incompleteness, inaccuracies, or misclassification. CV-related or renal-related death was assigned based on the primary diagnosis or procedure codes during the hospitalization in the month of death, given that the cause of death cannot be evaluated directly in claims data. In addition, the cost items in this study reflect the adjudicated reimbursement rate, instead of actual cost. It is possible that some medical items were not claimed and thus not captured in the data. Third, the Optum Clinformatics claims data used in this study were from a single payer source (eg, UnitedHealth Group). Formularies of this specific payer may have impacted health care resource utilization and medical costs incurred. Future studies are needed to evaluate whether results of this study would be transferable to other payers. Fourth, patients in this study were enrolled in commercial plans or Medicare Advantage, and were required to have a known CKD stage based on diagnosis codes. The cost estimates may only apply to patients meeting the study criteria.

## Conclusions

CKD incurs high health care costs in adult patients with T2D, which increase with more severe disease stages. RRT and management of major CKD complications, especially during the acute period immediately after the onset of the complications, are the most expensive components. The results demonstrate the imminent need for appropriate monitoring and treatment to avoid downstream costs in this patient population. The cost estimates from this study may also support the parametrization of economic models and help clinicians, payers, and other health care decision-makers determine the cost-effectiveness of interventions for CKD and T2D. ■

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# FINE-CKD Model to Evaluate Economic Value of Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes

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## Introduction

The global prevalence of chronic kidney disease (CKD) is approximately 11%, and in 2017, CKD was one of the most common diseases worldwide.<sup>1-3</sup> CKD is a progressive and irreversible disease, causing gradual loss of kidney function, thereby increasing the risk of kidney failure (end-stage kidney disease [ESKD]). CKD staging is based on clinical indicators, including estimated glomerular filtration rate (eGFR) stage (G1-G5), and albuminuria level (A1-A3).

In relation to the total population of patients with type 2 diabetes (T2D), patients with concomitant CKD represent approximately 40%. However, the prevalence of CKD in patients with T2D is likely underestimated because many subjects have not received a diagnosis.<sup>4,5</sup> In addition to promoting ESKD risk, CKD increases the risk of cardiovascular (CV) events<sup>6</sup> and mortality<sup>7,8</sup> and reduces quality of life (QOL).<sup>9</sup>

The current standard of care (SOC) for patients with CKD and T2D includes lifestyle modifications and pharmacotherapy with glucose-lowering and antihypertensive agents, focusing on slowing progression of the disease, preventing ESKD, and reducing the risk of CV events and mortality.<sup>10,11</sup> Unfortunately, current treatment modalities are inadequate in achieving these goals, and CKD in T2D remains a condition with high unmet needs.

CKD in patients with T2D is associated with substantial health care costs related to the complex management of the disease and its complications. Along with the deterioration of kidney function and progression to more advanced CKD stages, these patients also tend to experience longer hospital stays and increased medical costs.

Finerenone is a new, selective, nonsteroidal mineralocorticoid receptor (MR) antagonist with higher antagonistic potency for MR and lower relative affinity to other steroid hormone receptors when compared with other MR antagonists.<sup>12-14</sup> The FIDELIO-DKD (NCT02540993) trial showed that use of finerenone on top of SOC, compared with SOC alone, provides a reduction in the risk of CKD progression of 18% and a reduction in the risk of CV complications of 14% within a median follow-up of 2.6 years. In addition, finerenone was shown to be well-tolerated with a modest increase in hyperkalemia leading to discontinuation.<sup>12-14</sup>

## ABSTRACT

**BACKGROUND:** Chronic kidney disease (CKD) is a progressive and irreversible disease often associated with type 2 diabetes (T2D). CKD is associated with an elevated risk of cardiovascular (CV) events, increased mortality, and diminished quality of life. Finerenone is a new treatment for patients with CKD and T2D that delays CKD progression and reduces CV complications.

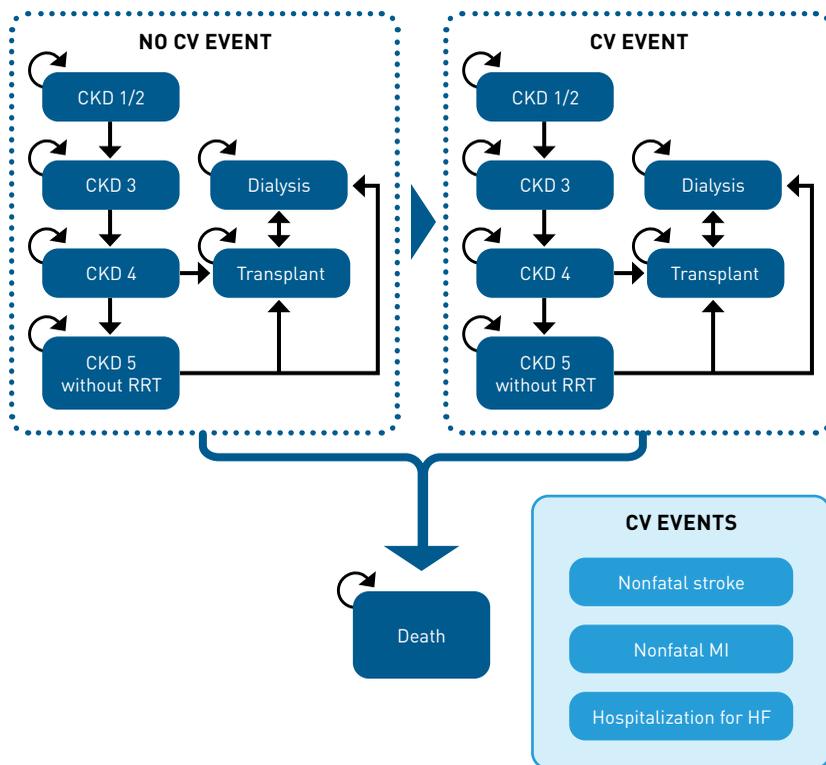
**OBJECTIVE:** To describe the approach and structure of a cost-effectiveness model for finerenone for patients with CKD and T2D and compare it with existing economic models in CKD.

**METHODS:** A de novo cost-effectiveness model (FINE-CKD model), reflective of FIDELIO-DKD results, was developed for finerenone. The FINE-CKD model was designed and implemented in accordance with published guidance on modeling and was developed with input from economic and clinical experts. The final model approach was evaluated against existing modeling structures in CKD identified through a systematic literature review.

**RESULTS AND CONCLUSIONS:** The FINE-CKD model structure follows recommended modeling guidelines and has been designed in accordance with the best practices of modeling in CKD, while also incorporating important features of the FIDELIO-DKD design and results. The approach is consistent with the published literature, ensuring transparency and minimizing uncertainty that can arise from unnecessary complexity. The FINE-CKD model allows for reliable assessment of benefits and costs related to the use of finerenone in patients with CKD and T2D, and it is a reliable assessment of cost-effectiveness.

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**FIGURE 1.** The FINE-CKD Model Structure<sup>a</sup>

CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; RRT, renal replacement therapy.

<sup>a</sup>The model structure reflects CKD progression. The model allows for transitions between any 2 CKD health states based on the FIDELIO-DKD data.

In many countries, public funding decisions for interventions such as finerenone are based on health economic evidence, requiring cost-effectiveness models to estimate long-term costs and effects. Accordingly, our objective was to present the structure of the cost-effectiveness model for finerenone and compare it with other economic evaluations in CKD available in the literature. While development of a de novo model for finerenone was deemed necessary to reflect and incorporate the FIDELIO-DKD results fully, a new model should be consistent with best practices of economic modeling in CKD.

### FINE-CKD Model

The FINE-CKD model was designed, programmed, and populated with data in accordance with National Institute for Health and Care Excellence recommendations and ISPOR-SMDM guidance on modeling for economic evaluation.<sup>15</sup> The development of the model was supported by consultations with economic and clinical experts. The model was implemented in Microsoft Excel 2016, supported by Visual Basic for Applications (VBA).

The FINE-CKD model uses a Markov modeling approach with the structure presented in **Figure 1**. A Markovian approach was deemed an appropriate framework for modeling the relationship between CKD progression and the incidence of CV events because this approach allows for events to occur over time using regular cycles.

To assess cost-effectiveness of finerenone, the FINE-CKD model is based on FIDELIO-DKD, a randomized controlled trial (RCT) that showed that finerenone slows the progression of kidney disease in patients with a clinical diagnosis of CKD and T2D. The secondary outcome of interest in FIDELIO-DKD was the impact of finerenone on the reduction of CV events and death. The finerenone model, therefore, focused on these important dimensions of clinical value (CKD, CV events, and death).

The model health states must represent the main stages in the patients' disease progression. Similarly, they should reflect the patient's condition at any time point, as well as the impact of treatment. Therefore, the health states of the FINE-CKD model should represent the key outcomes of FIDELIO-DKD and should be in line with both the potentially important benefits and the safety concerns of finerenone. As such, the model health states were defined according to the stage of kidney disease and history of CV events. Four stages of CKD progression were considered: CKD 1/2, CKD 3, CKD 4, and CKD 5 without renal replacement therapy (RRT), in addition to 2 stages for patients with ESKD (dialysis and transplant). Patients start the model in one of the CKD stages. Patients remain in the same CKD stage, or move to a more/less advanced CKD stage. In each CKD stage patients can experience a modeled CV event (nonfatal myocardial infarction [MI], nonfatal stroke, hospitalization for heart failure [HF]) or death. The model considers 6 corresponding health states for patients after the first CV event observed within the model (ie, CKD 1/2 post CV event, CKD 3 post CV event, CKD 4 post CV event, CKD 5 without RRT post CV event, dialysis post CV event, transplant and CV event). Once patients experience a first CV event, they move to the post CV event health state and are not able to move back to the health state without a history of CV events. Patients can change CKD stage and experience a first CV event in the same 4-month model cycle (ie, a patient from CKD stage 3 can move to CKD stage 4 post CV event). Transitions between all CKD stages are allowed. The assessment of end points occurred every 4 months in the FIDELIO-DKD trial. To reflect the

**FIGURE 2.** Main Characteristics of CKD and T2D Models

Model type	Time horizon	Cycle length	Health states	CV events
<ul style="list-style-type: none"> <li>• Markov or semi-Markov alone (n=39)</li> <li>• Decision tree and Markov model (n=7)</li> <li>• Patient simulation model (n=4)</li> <li>• Discrete state simulation (n=3)</li> <li>• No information (n=6)</li> </ul>	<ul style="list-style-type: none"> <li>• Lifetime (n=38)</li> <li>• 10 or 7 years (n=7)</li> <li>• 5 years (n=4)</li> <li>• 1, 2, or 3 years (n=6)</li> <li>• No information (n=7)</li> </ul>	<ul style="list-style-type: none"> <li>• 1 month (n=11)</li> <li>• 3 months (n=4)</li> <li>• 6 months (n=1)</li> <li>• 12 months (n=25)</li> <li>• No information (n=20)</li> </ul>	<ul style="list-style-type: none"> <li>• Based on CKD stages in accordance with eGFR (n=22)</li> <li>• Based on albuminuria stages (n=3)</li> <li>• Based on CKD stages in accordance with eGFR and albuminuria (n=11)</li> </ul>	<ul style="list-style-type: none"> <li>• Considered as a separate health state (n=12)</li> <li>• Considered as an event (n=10)</li> </ul>

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes.

disease progression in alignment with the trial evidence, a 4-month cycle length was used.

In relation to CKD progression, the 2 main predictors for changes in CKD stages are the stage a patient is currently in and the duration they have been in that stage. Transition probabilities between CKD stages in the model, however, depend only on the current stage the patient is in (ie, these transition probabilities are constant over time). The CKD stage can be defined by eGFR and albuminuria level. FIDELIO-DKD included eGFR as a part of the primary outcome, thereby leading to an expectation of the model to estimate the impact of the treatment on changes in this parameter. FIDELIO-DKD provides granular eGFR data, whereas albuminuria was considered only as an explanatory end point. Therefore, the model health states were defined based on the eGFR. Observed changes in eGFR supplemented by subgroup analyses considering albuminuria were deemed sufficient.

In the case of CV events or death, many prognostic factors can be theoretically considered. Nonetheless, there is an established relationship between CKD stage and CV events (fatal or otherwise). As such, the FINE-CKD model focuses on the link between CKD stage and these events rather than extending this to explicit consideration of other risk factors for which no impact of finerenone has been proven.

Generally, patients are permitted within the model to start dialysis after progression to CKD 5, at which point they are eligible for kidney transplant. In practice, because a proportion of patients undergo transplant before dialysis (eg, living donations), the model allows for transplants before dialysis in either CKD stage 4 or CKD stage 5. Additionally, a small percentage of patients undergo dialysis before CKD 4. The model also allows patients to start dialysis again from a transplant state to reflect the risk of graft failure. At any point in the model, patients can die.

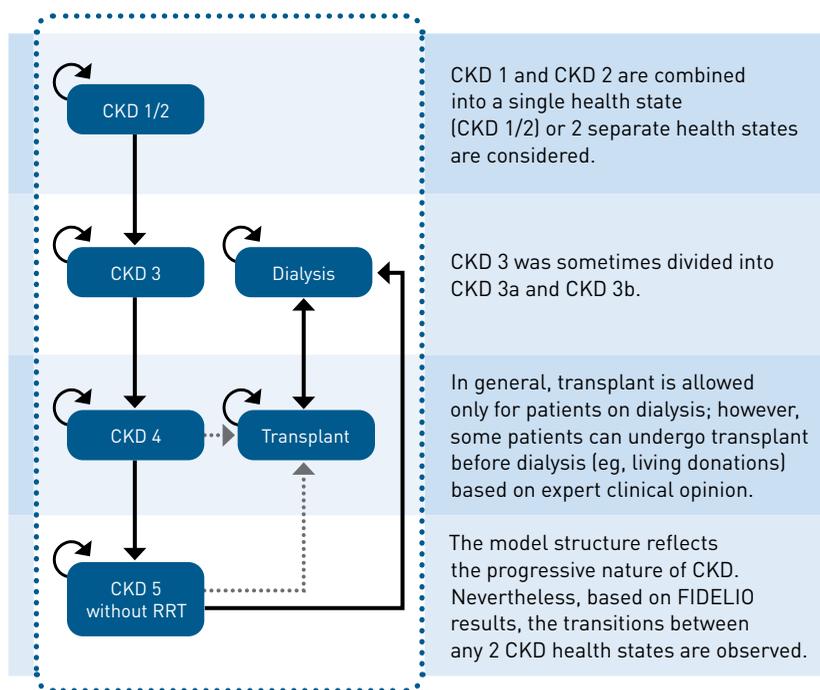
Transition probabilities between health states are primarily based on patient-level data from FIDELIO-DKD. Such an approach to modeling CKD progression allows the model to reflect the fluctuations in eGFR over the time. The model is not limited only to considering deterioration of the disease; rather, it reflects the actual trial data. Additionally, data from the literature were applied to estimate long-term outcomes, accounting for increased CV event and mortality risks due to age.

Subsequent CV events are considered in the model within the post-CV event health states. These events are modeled based on the incidence of components of the key secondary end point in FIDELIO-DKD, which did not capture whether CV events were index events or otherwise. The associated costs and disutilities of subsequent CV events were also captured by the model.

The model simulates patients' trajectories over a lifetime horizon, which is reflective of the chronic nature of CKD in T2D. Patients may die in any health state in the model. In line with the FIDELIO-DKD protocol, different reasons for deaths are accounted for and implemented in the model. These comprise renal death and CV death as well as additional background mortality.

### Existing Economic Models in CKD

To design and assess the approach of the FINE-CKD model structure against all relevant cost-effectiveness models available in the public domain, a systematic literature review was conducted. All economic models considering a population of patients with CKD were included, irrespective of the form of economic evaluation used. To consider as broad a population as possible, no restriction on diabetes status was applied. In addition, no restriction was made on interventions, geographical scope, or time frame. The search strategy and PRISMA diagram are presented in [eAppendix](#) (eAppendices available at [ajmc.com](http://ajmc.com)).

**FIGURE 3.** Most Commonly Used Model Structure for CKD Progression

CKD, chronic kidney disease; RRT, renal replacement therapy.

The review of literature in selected databases identified a total of 15,147 references after the deduplication process ([eAppendix Figure 1](#), and [eAppendix Tables 1 and 2](#)). After screening for titles and abstracts, 14,422 records were excluded. Full texts were then assessed for eligibility, and an additional 670 articles were excluded. The final selection included 55 publications. Additionally, after searching the Health Technology Assessment databases, 6 more reports were included. Finally, 61 studies were extracted. [eAppendix Tables 3, 4, and 5](#) present the main characteristics, including 61 studies.

The majority of models applied a lifetime time horizon ( $n = 38$ ). Generally, published models utilized frameworks based on eGFR and/or albuminuria, with 2 main core structures identified: patient-level models (ie, microsimulation models involving albuminuria and/or eGFR) and cohort-level Markov models, utilizing CKD stages to model CKD progression.

Most models assumed that CKD was progressive and irreversible and included the possibility for patients to experience renal replacement therapy when they reach ESKD in the form of dialysis or transplant. CV complications of CKD were considered in 22 models, including 12 models in which CV events were represented by separate health states. In addition to eGFR, albuminuria was considered as a predictor of CKD progression in some models, explicitly impacting the risk of CV events.

Among the included cost utility analyses and cost-effectiveness analyses (CEAs), there were 39 cohort Markov or semi-Markov models, 7 decision trees together with Markov models, 4 patient-level simulation models, 3 discrete-event simulation models, and 6 studies in which the model type was not provided. The remaining 2 publications described cost-benefit analyses.

Based on the analysis of the models identified, the published literature appears to support the use of both a cohort Markov framework and a patient-level microsimulation model. These options are discussed in turn below.

### Cohort Markov models

While variations in structure were evident in the Markov models identified, these models mainly considered the progressive nature of the disease with patients transitioning forward through CKD stages, with most studies not allowing for improvement over time. Health states were based on eGFR in line with KDIGO stratifications (from G1-G5), stage G1 and G2 being sometimes combined, and stage G3 sometimes, although rarely, disaggregated into stages G3a and G3b.

These models predicted CKD outcomes using rates of sustained eGFR decline or transition probabilities.

The most common cycle length was 1 year (with the exception of 11 models with a cycle length of 1 month, 4 models with 3-month cycles, and 1 model with 6-month cycles).

Of the models employing a Markov structure, one of the most relevant and recent was an analysis published in 2019 by Go et al to compare CKD screening strategies with no screening. The model was applied to the general Korean population with annual cycles over the lifetime of the cohort.<sup>16</sup> The model included 8 CKD-related health states. These were defined in a similar way to FINE-CKD in terms of CKD stage (G1/G2, G3, G4, G5), and there were broad similarities in the way the acute and postacute stages of transplant were distinguished, though Go et al applied a 1-year acute period rather than a 4-month period. Go et al applied more granularity than the FINE-CKD model in terms of both dialysis (distinguishing between hemodialysis and peritoneal dialysis) and CV complications (distinguishing not only between acute and postacute, as in FINE-CKD, but also between MI and stroke). Dialysis and CV complications are aggregated in the FINE-CKD model by applying weighted averages of each component. The incidence of CKD G3 was estimated based on National Health Insurance Scheme claims data, whereas the progression of CKD was assigned based on the literature with the inclusion of relative risk for patients with diabetes.

One simplification relative to FINE-CKD is that only the progressive character of CKD was reflected in the model (ie, no improvement was possible). In contrast with the approach taken in FINE-CKD, it was assumed that all CKD G5 patients began RRT in the next cycle. Treatment effects on CKD progression were included by applying a reduction to the rate of transition to more advanced CKD stages. This contrasts with the approach of FINE-CKD, which applies transition probabilities to each arm on the basis of patient-level data from FIDELIO-DKD. The Korean national population-based study was used for obtaining CV risks.

In a UK HTA Assessment Study from 2010, a Markov model was also used to evaluate the cost-effectiveness of early referral strategies in a cohort of patients with CKD who were not known to nephrology services.<sup>17</sup> People with diabetes were excluded because these patients receive annual checks for kidney disease in the UK. A lifetime time horizon was applied using annual cycles. Six main health states were considered: G1/G2, G3a, G3b, G4, ESKD, and death. Though the health states are broadly similar to those used in FINE-CKD, CKD stage 3 was disaggregated, and there was less granularity in terms of ESKD and its associated treatment. In addition to transiting unidirectionally through the CKD stages, patients could transit across comorbidity states as they developed microalbuminuria, proteinuria, and CV disease. Although the latter is explicitly accounted for in the structure of FINE-CKD, the impact of albuminuria and proteinuria would be addressed through scenario analysis of subgroups rather than through the structure of the model. CKD progression was simulated using reported average annual rates of eGFR decline rather than patient-level data observed through a randomized controlled trial, with the level of urine albumin/protein at baseline and calculation of the average proportion of individuals that would be expected to transit annually from each CKD state to the next state also being considered in the UK HTA Assessment Study. Again, trial data were not applied for CV risks as they were in the case of FINE-CKD. Instead, a risk algorithm was used, with adjustments made for sex and hypertension status.

In 2013, Erickson et al published results of a cost-effectiveness analysis of statins for primary prevention of MI and stroke in patients with CKD.<sup>18</sup> This Markov model was developed from the US perspective with 3-month cycles over patients' lifetimes, simulating a population of 65-year-old patients with mild to moderate CKD and moderate hypertension. The model structure, unlike the FINE-CKD structure, did not include health states prior to G3a. CKD progression was based on rates derived from large observational cohorts of comparable patient populations via model calibrations. In contrast with FINE-CKD, only the progressive nature of CKD was included, with no backward transition between CKD stages possible. The modeling of progression in the Erickson et al model differs quite substantially from the FINE-CKD model, with the

probability of progression from stages G3a to G3b, G3b to G4, and G4 to G5 being obtained from a separate microsimulation model implemented in SAS software rather than through a Markov model. Additionally, transitions based on a mean annual rate of eGFR decline were estimated from the published observations rather than via actual eGFR scores observed in a single RCT. Similar to FINE-CKD, patients could also experience CV events (limited to MI and stroke), though instead of basing risks on observed trial data, the baseline probabilities of CV events were derived from Framingham risk scores, which were multiplied by CKD stage-specific hazard ratios to reflect the increased risk in more severe CKD stages.

In 2017, Schlackow et al presented a long-term policy model of CV complications in moderate to advanced CKD.<sup>19</sup> A Markovian structure was used over lifetime, with annual transitions between a limited range of CKD stages (G3b, G4, and G5) relative to FINE-CKD. This model applied interdependence between renal and CV complications (MI, nonhemorrhagic stroke, or arterial revascularization) using individualized risks estimated from 5 years of follow-up data among almost 10,000 patients with moderate to severe CKD. CKD progression was modeled with transition probabilities using a regression-based approach based on observed transitions between CKD stages during annual periods of follow-up in SHARP study.<sup>20</sup> Similar to FINE-CKD, transitions between all CKD stages were captured, including those corresponding to disease improvement. CV events were modeled via parametric proportional hazard multivariate survival models.

### Patient-level microsimulation models

Some models adopted more complex methods, such as patient level ( $n = 4$ ) or discrete event simulations (DES,  $n = 3$ ). These models were mostly used when considering the treatment and consequences of diabetes, with CKD included as a submodel. CKD outcomes were often predicted from annual rates of eGFR decline, eGFR transition probabilities, and/or albuminuria transition probabilities.

A representative example of a microsimulation model is the ECHO-T2DM model.<sup>21</sup> It is a stochastic, multiapplication patient-level model suitable for estimating long-term costs and effects of treatments for T2D. The cycle length was 1 year, and the time horizon was user definable. ECHO-T2DM incorporates key structural features from several well-known T2DM models: the NIH Model, the CORE Diabetes Model, and the Diabetes Decision Analysis and Cost of Type 2 Model, and includes development and progression of key micro- and macrovascular complications and mortality.

The CKD submodule of the ECHO-T2DM model includes both injury (defined by the presence of albuminuria, which is not explicitly considered in the structure of FINE-CKD) and function (described by eGFR, which is considered explicitly in the structure of FINE-CKD). Kidney status is based on KDIGO stages with or without moderately increased or severely increased albuminuria.

The functional dimension of CKD is modeled using default values for annual rate of change in eGFR, sourced from another model of CKD,<sup>22</sup> which may be modified via user-defined eGFR parameters. As with several other studies described above, the application of annual rate of change differs from the transition probability approach applied to the FINE-CKD model. Macrovascular health states consist of ischemic heart disease, MI, stroke, congestive heart failure (CHF), and peripheral vascular disease. While the components of the composite health state differ, the approach is broadly consistent with the aggregation approach used in the FINE-CKD model. Consistent with FINE-CKD, MI and stroke can occur multiple times within the model (although only once each per cycle), and multiple types of macrovascular events can occur in the same cycle. ECHO-T2DM includes 4 different sets of macrovascular risk equations that can be used in the model, but only 1 set of risk equations can be used in a simulation. None of them, however, are specific for CKD.

## Discussion

Several findings from the literature review presented here warrant discussion in the context of the cost-effectiveness model developed for finerenone in the treatment of patients with CKD and T2D (ie, FINE-CKD model).

The identified approaches to model CKD progression all follow the same general model structure whether the population is patients with CKD or patients with diabetes. CKD progression modeling is the most detailed in models focused on CKD patients. In diabetes models, which also include CKD submodels, the structure is similar, but include additional considerations related to diabetes (eg, glycemia) and its complications. As finerenone does not impact T2D progression or glycemia-related parameters, the use of a diabetes model would add unnecessary complexity, while also leading to an oversimplification of CKD progression. Indeed, these models overwhelmingly assume a constant decrease of eGFR, as in the ECHO-T2DM model, which does not reflect natural fluctuations of eGFR over time, as observed in FIDELIO-DKD,<sup>13</sup> and lacks granularity. Such an approach potentially results in an imprecise estimation of how eGFR changes through time, which could have important impacts on the accrual of costs and outcomes related to CKD progression.

Our systematic review confirms previous conclusions by Sugrue et al,<sup>23</sup> who assert that published models typically utilize frameworks based on either eGFR and/or albuminuria, with 2 core structures identified (ie, microsimulation models and cohort-level Markov models using CKD stages to capture disease progression) and with patient trajectories represented as a series of transitions from one CKD stage to another. Sugrue et al advocate for prediction of individual patients' eGFR trajectories (ie, patient-level models used to capture the heterogeneity of CKD progression clinical course), which

may vary substantially across patients and may be influenced by various risk factors, including CV disease and diabetes. Although such heterogeneity may pose challenges to model CKD progression accurately, a Markovian structure considering these factors has been proven to be sufficient in many of the existing models. Given that a Markov modeling approach at the cohort level is able to capture the key considerations, it is preferred to patient-level simulations, since the latter are more difficult to populate and review.<sup>15</sup> Based on these factors, the use of a Markov framework in the FINE-CKD model is justified.

As demonstrated by FIDELIO-DKD,<sup>13</sup> finerenone is expected to have a CV benefit, as evident in the observed reduction in the risk of a composite end point of time to first occurrence of CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF by 14% over 2.6 years. Moreover, it was shown in the trial that finerenone delays CKD progression and reduces the risk of renal events, including ESKD. The impact of finerenone on these outcomes can be captured in the FINE-CKD model in an appropriate way due to the inclusion of relevant model health states. These health states are implemented to reflect the main stages in the patients' disease progression. As the cardiorenal protective properties of finerenone result in delayed progression of CKD and reduced occurrence of CV events, it is important that the FINE-CKD model considers both renal and CV outcomes in the list of health states. As in many identified models, and in line with KDIGO guidelines, the kidney health states were defined according to CKD stage and history of CV events. Indeed, 12 of 22 models consider CV events and include them as separate health states. As in the existing models, different CKD stages from G1 to G5 are considered in the FINE-CKD model. Stage G3 could have been additionally divided into 2 categories; however, this was rarely done in the previous models, and in cases where it was, the disaggregation was most often accompanied by application of the same inputs regarding both resource use and QOL for CKD stages 3a and 3b.

Although adequate modeling of the impact of finerenone on CKD and associated risks is inherently complex, a range of simplifications were applied relative to some of the existing CKD models. Among these, albuminuria is not included explicitly in the model as was the case, for example, in a UK HTA Assessment Study.<sup>17</sup> No separate health states for different types of dialysis or CV events are considered in the FINE-CKD model, while both of these were included by Go et al.<sup>16</sup> These simplifications have been undertaken in the FINE-CKD model for practical reasons, and their impact on model results can be assessed via sensitivity analysis. At the same time, a detailed application of the results of FIDELIO-DKD is considered in the FINE-CKD model by taking full advantage of their granularity in terms of eGFR changes over time. Indeed, the FINE-CKD model considers a relatively short model cycle and allows for all possible transitions between CKD stages, whereas the

focus was solely on the deterioration of the disease in the majority of the existing models.

In conclusion, the FINE-CKD model has been built in accordance with the general practice of modeling in CKD with appropriate focus on the incorporation of the FIDELIO-DKD trial results. Hence, the FINE-CKD model accurately reflects reality in terms of the natural history of CKD while also allowing for reliable assessment of benefits and costs related to the use of finerenone in patients with CKD and T2D. The structure of the FINE-CKD model is that which most adequately addresses the decision problem posed, making the model transparent and reducing uncertainty related to unnecessary complexity. This is, at the same time, the most used and well-validated model type and structure in the published literature, as evident from the systematic literature review described above. Together, these considerations lend substantial weight to the approach of the FINE-CKD model and support its use in assessing the cost-effectiveness of finerenone in patients with CKD and T2D. ■

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