

# The Role of Finerenone in Optimizing Cardiovascular-Kidney-Metabolic Health: Everything PCPs Should Know

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## KEY TAKEAWAYS

- Cardiovascular, kidney, and metabolic (CKM) syndrome is a complex health disorder attributable to the substantial overlap and connections among obesity, diabetes, chronic kidney disease, and cardiovascular disease resulting from shared risk factors, and interconnected, interdependent pathophysiology.
- Primary care professionals (PCPs) should detect CKM syndrome early and aggressively treat all patients who are at risk.
- Nonsteroidal mineralocorticoid receptor antagonists like finerenone can favorably affect the progression of CKM syndrome at each stage.
- PCPs should become familiar with the benefits of a 4-pillar approach across different management phases of CKM syndrome.

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## BACKGROUND

Substantial overlap exists among cardiovascular, kidney, and metabolic (CKM) diseases because of shared risk factors and an interconnected, interdependent pathophysiology. As one condition worsens, it increases the risk and severity of others, leading to a cycle of worsening outcomes and a higher risk for mortality.<sup>1,2</sup> Conceptual frameworks and expanded tools can enhance the appreciation and comprehension of physiological changes, diagnosis, and treatment of patients with underlying diabetes, chronic kidney disease (CKD), and/or cardiovascular disease (CVD) among health care providers. In this effort, the American Heart Association Presidential Advisory introduced a new concept of CKM syndrome, defined as a health disorder attributable to connections among obesity, diabetes, CKD, and CVD, including atherosclerotic cardio-

vascular disease and heart failure.<sup>3</sup> CKM syndrome stages were defined to reflect the pathophysiology, spectrum of risk, and opportunities for prevention and care optimization by health care providers, including primary care professionals (PCPs) who have a significant role in integrating the available therapeutic options and different guidelines into their clinical practice (TABLE).<sup>11-18</sup> The age-adjusted prevalence of advanced CKM syndrome stages (ie, stages 3 and 4) among US adults 20 years or older is 14.6%, which did not improve between 2011 and 2020.<sup>4-7</sup>

Finerenone, a nonsteroidal mineralocorticoid receptor antagonist (nsMRA), is one of the therapeutic pillars available for CKD associated with type 2 diabetes or diabetic kidney disease (DKD) that can favorably affect CKM syndrome progression at stages 1-4 (TABLE).<sup>5,9,10</sup> Evidence suggests that

**TABLE. Definitions of CKM syndrome stages**

CKM stages	Definition	Potential role of finerenone
<b>Stage 0: No CKM risk factors</b>	Normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD	
<b>Stage 1: Dysfunctional adiposity</b>	BMI $\geq 25$ , waist circumference $\geq 88/102$ cm in women/men, <sup>a</sup> fasting blood glucose $\geq 100$ to 124 mg/dL, or HbA1c between 5.7% and 6.4% (prediabetes)	Preventing the metabolic alterations in obesity observed from animal studies using MRA <sup>11,12</sup>
<b>Stage 2: Metabolic risk factors and CKD</b>	Hypertriglyceridemia $\geq 135$ mg/dL, hypertension, diabetes, MetS, <sup>b</sup> or CKD (moderate to high risk per KDIGO classification)	Decreasing CKD risk category at early stages among patients with diabetes by decreasing UACR and preserving eGFR <sup>13,14</sup>
<b>Stage 3: Subclinical CVD in CKM or risk equivalent</b>	Individuals with metabolic risk factors who have subclinical ASCVD by imaging, subclinical HF: diagnosed by elevated biomarkers (NT-proBNP $\geq 125$ pg/mL, or hs-troponin <sup>c</sup> ), or combination of the 2, indicating highest HF risk in echocardiography	Same as stage 2 + decreasing the risk for incident HF hospitalization <sup>15</sup>
	High predicted 10-year CVD risk ( $\geq 20\%$ ), <sup>d</sup> or very high risk CKD per KDIGO classification	
<b>Stage 4: Clinical CVD in CKM</b>	<b>4a:</b> ASCVD or heart failure without kidney failure	Beneficial role irrespective of prevalent ASCVD <sup>16</sup>
	<b>4b:</b> ASCVD or heart failure with kidney failure	Potential role in treating HFrEF <sup>17</sup> and HFmr/pEF <sup>18</sup>

<sup>a</sup>Or BMI  $\geq 23$  kg/m<sup>2</sup> or waist circumference  $\geq 80/90$  cm in women/men of Asian ancestry.

<sup>b</sup>MetS is defined by the presence of 3 or more of the following: (1) waist circumference  $\geq 88$  cm for women and  $\geq 102$  cm for men; (2) HDL cholesterol  $<40$  mg/dL for men and  $<50$  mg/dL for women; (3) triglycerides  $\geq 150$  mg/dL; (4) elevated blood pressure (systolic blood pressure  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 80$  mm Hg and/or use of antihypertensive medications); and (5) fasting blood glucose  $\geq 100$  mg/dL.

<sup>c</sup>hs-troponin (high sensitivity troponin) T  $\geq 14$  ng/L for women and  $\geq 22$  ng/L for men or hs-troponin I  $\geq 10$  ng/L for women and  $\geq 12$  ng/L for men.

<sup>d</sup>Calculated using the American Heart Association PREVENT risk calculator (<https://professional.heart.org/en/guidelines-and-statements/prevent-calculator>).

**Abbreviations:** ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CKM, cardiovascular, kidney, and metabolic; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmr/pEF, heart failure with preserved or midrange ejection fraction; KDIGO, Kidney Disease Improving Global Outcomes; MetS, metabolic syndrome; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; UACR, urinary albumin-to-creatinine ratio.

finerenone may be beneficial in the patient journey across CKM syndrome stages in tandem with other therapeutic pillars, such as maximally dosed renin-angiotensin-aldosterone-system inhibitors (RAAsi), sodium-glucose cotransporter 2 inhibitors (SGLT2is), and/or glucagon-like peptide-1 receptor agonists (GLP-1 RAs). In this article, a hypothetical case is used to demonstrate how to optimize the role of finerenone in different management phases that include risk stratification, finerenone initiation, patient monitoring, and involvement of an interdisciplinary care team.

### CASE STUDY

K.A. is a 60-year-old male diagnosed with type 2 diabetes (T2D) 10 years ago and hypertension 5 years ago. He recently moved from another state and has no history of atherosclerotic cardiovascular disease. He is not experiencing any particular symptoms.

#### Examination:

No jugular vein distention, other signs of heart failure, or signs of peripheral arterial disease.

*Blood Pressure:* 120/80    *Heart Rate:* 70    *BMI:* 32.7

*Weight:* 89 kg (196 lb)    *Height:* 1.65 m (65 in)

#### Lab results:

*Serum creatinine:* 1.7 mg/dL    *eGFR:* 52 mL/min/1.73 m<sup>2</sup>

*BUN:* 40 mg/dL

*Total cholesterol:* 140 mg/dL    *Triglyceride:* 100 mg/dL

*LDL:* 65 mg/dL

*HDL:* 40 mg/dL

*UACR:* 340 mg/g (38.42 mg/mmol)

*Na:* 140 mmol/L

*K:* 4.2 mmol/L    *HbA1c:* 7%

*NT-proBNP:* 70 pg/mL

#### Current medication:

Optimum dose of RAAsi (perindopril 8 mg once daily)

*Rosuvastatin:* 20 mg; *Metformin:* 500 mg twice daily;

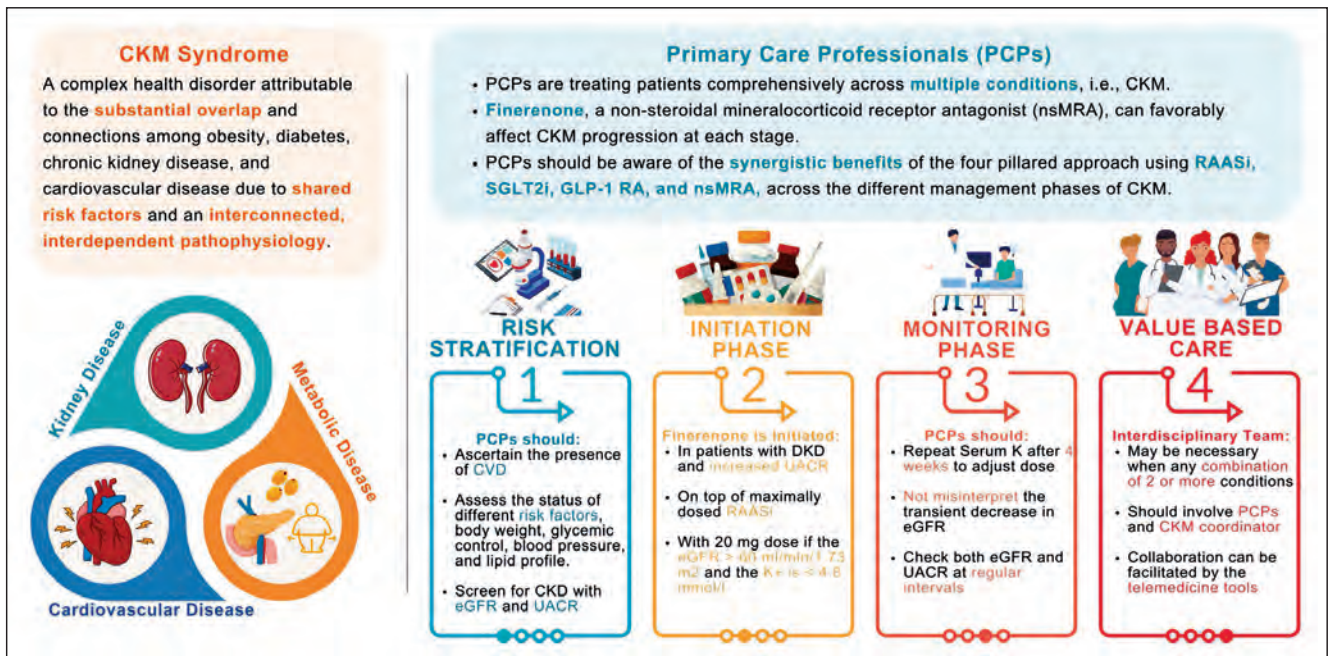
*Empagliflozin:* 25 mg once daily

#### Primary care professional decision:

Started finerenone 10 mg and advised to repeat K after 1 month

**Abbreviations:** BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; K, potassium; LDL, low-density lipoprotein; UACR, urine albumin-creatinine ratio.

## GRAPHIC ABSTRACT



**Abbreviations:** CKM, cardiovascular, kidney, and metabolic; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; RAASi, renin-angiotensin aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

## RISK STRATIFICATION PHASE: ROLE OF PCPS

## CASE COMMENT:

K.A. had stage 2 CKM syndrome; he had metabolic risk factors and high-risk CKD attributed mainly to the elevated UACR (FIGURE 1).<sup>5</sup> However, he should be screened for the presence of subclinical CVD if there is a suggestive clinical presentation or elevated cardiac biomarkers, and the 10-year CVD predicted score should be calculated using the American Heart Association PREVENT online risk calculator (<https://professional.heart.org/en/guidelines-and-statements/prevent-calculator>) to confirm that K.A. is not in stage 3 CKM syndrome.

To define the stage of CKM syndrome, PCPs have to ascertain the prevalence of CVD and assess the status of different risk factors, including body weight, glycemic control, blood pressure, and lipid profile. In addition to the metabolic CVD risk factors, screening for CKD with eGFR, estimated glomerular filtration rate (eGFR) and UACR is mandatory because CKD can modify the CKM syndrome stage (TABLE).<sup>11-18</sup> CKD should be evaluated by using the Kidney Disease Improving Global Outcomes (KDIGO) Heatmap that classifies patients with CKD according to the level of UACR and eGFR (FIGURE 1). In clinical practice, glomerular filtration rate is typically estimated from serum creatinine concentration and/or cystatin-C using a race-free eGFR equation developed by the CKD Epidemiology Collaboration in 2021.<sup>19</sup> The National Kidney Foundation

recommended replacing race-based equations with a new equation and provided a web-based tool for determining the eGFR from serum creatinine<sup>20</sup> ([https://www.kidney.org/professionals/kdoqi/gfr\\_calculator](https://www.kidney.org/professionals/kdoqi/gfr_calculator)). UACR is the preferred and most predictive measure for CKD staging and CVD risk assessment,<sup>21</sup> and the effect of a medication like finerenone against CKD progression is largely mediated by UACR reduction.<sup>22</sup>

The role of PCPs at this stage is not just to identify risk factors and classify the patient's risk category but also to educate patients and personalize lifestyle modifications that are the foundation for managing diabetes and CKD.<sup>23</sup> Building and maintaining positive health behaviors, such as regular physical exercise, weight management, and smoking cessation, are crucial to achieving personalized treatment goals, including slowing CKM syndrome progression.<sup>24</sup>

## INITIATION PHASE: THERAPEUTIC OPTIONS INITIATED BY PCPS

## CASE COMMENT:

The patient's PCP recommended 10 mg of finerenone because K.A. had a UACR  $>300$  mg/g, despite receiving an SGLT2i and the maximum tolerable dose of RAASi, perindopril 8 mg once daily (ie, angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs]) and had good blood pressure and an HbA1c of 7%. (If the eGFR was  $>60$  mL/min/1.73 m<sup>2</sup> and the K<sup>+</sup> was  $<4.8$  mmol/L, finerenone could be initiated at a higher dose

**FIGURE 1. KDIGO heatmap showing the case scenario baseline and status after 4 months<sup>5</sup>**

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–299 mg/g 3–29 mg/mmol	A3 Severely increased ≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

■ Low risk (if no other markers of kidney disease, no CKD)    ■ High risk  
■ Moderately increased risk    ■ Very high risk

lished more than 20 years ago. These trials demonstrated a 16% to 43% reduction in doubling of serum creatinine, death, or kidney failure over 2 to 3 years.<sup>27–29</sup> In addition to glycemic control by medication with cardiorenal protection like SGLT2is, the maximum dose of RAASi should be the first-line therapy for treating hypertension in patients with diabetes when albuminuria is present.<sup>5,6,23</sup> RAASi is also recommended for patients with DKD and moderately to severely increased UACR (KDIGO classification G1–G4, A2, and A3), even in the absence of high blood pressure.<sup>5,6,23</sup> However, the hazardous effects of aldosterone on CKM syndrome persist despite using RAASi, justifying the addition of a MRA to minimize the residual risk for CKM syndrome progression that exists even while using an SGLT2i.<sup>30,31</sup>

Two large phase 3 trials, FIDELIO-DKD and FIGARO-DKD, and their pooled analysis, FIDELITY, demonstrated the compelling evidence of a nsMRA, finerenone, in reducing the risk for CKD and CVD progression in a broad range of patients with DKD who were on maximum tolerable dose of RAASi.<sup>32–34</sup> Although a small number of patients (6.7% to 7.2%) were receiving SGLT2i or GLP-1 RA therapy, they also saw

Cause refers to the cause of CKD as ascertained by the clinician. Most patients who fit into the CKM staging framework will have CKD attributable to diabetes, hypertension, and other metabolic risk factors. \*PCPs may wish to discuss with their nephrology service, depending on local practice patterns on monitoring or referring. **Numbers: Represent a recommendation for the number of times per year the patient should be monitored.<sup>5</sup>**

**Abbreviations:** CKD; chronic kidney disease; CKM; cardiovascular, kidney, metabolic; eGFR; estimated glomerular filtration rate; PCP, primary care provider

Adapted from KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.

[ie, 20 mg]). Serum potassium and eGFR should be repeated after 4 weeks to adjust the dose accordingly. Note that up to a 30% reduction in eGFR initially is acceptable. Blood pressure and lipid profile levels did not mandate intensifying the relevant medications; however, adding other glucose-lowering medications to achieve better glycemic control is reasonable.

Several updated guidelines are available to guide therapy for patients with CKM syndrome. Alongside the annual publication of the Standards of Care in Diabetes guideline by the American Diabetes Association (ADA), KDIGO published its 2024 guideline, and both organizations endorsed their consensus report about diabetes management in CKD, which was published in 2022.<sup>5,6,23</sup> However, a significant barrier to implementing the recommendations in primary care is the lack of guidance on how PCPs can effectively implement the guidelines in their real-world practices.<sup>25</sup> The prescription pattern analysis at a single institution revealed that finerenone was prescribed more frequently by specialists than PCPs.<sup>26</sup>

RAASi are considered the first-line therapy for patients with diabetes and CKD based on clinical trials that were pub-

benefit.<sup>35,36</sup> During a median follow-up of 2.6 years, the finerenone group showed 18% lower risk for a composite of kidney failure, 40% or more decline in eGFR, or death from renal cause compared to placebo in FIDELIO-DKD.<sup>32</sup> In the FIGARO-DKD trial, finerenone reduced the risk for death from CVD, nonfatal myocardial infarction, nonfatal stroke, or hospitalizations from heart failure by 13%.<sup>33</sup> Such robust evidence is not available for steroidal MRAs, spironolactone, and eplerenone, and according to a recent meta-analysis, steroidal MRAs are associated with a higher incidence of adverse events such as hyperkalemia than finerenone when added to RAASi.<sup>37</sup> Furthermore, spironolactone can produce off-target endocrinal side effects such as gynecomastia.<sup>38</sup>

According to ADA Standards of Care in Diabetes, finerenone is indicated for the case patient K.A. to slow CKD progression. He had normal potassium and highly elevated UACR despite being on the maximum tolerated dose of RAASi. A ≥30% reduction in UACR is the goal since his UACR was ≥300 mg/g (≥30 mg/mmol).<sup>39</sup> Furthermore, for CVD risk management, finerenone, in addition to an SGLT2i, is indicated in patients with DKD to reduce the risk for progression to symp-

**FIGURE 2. Serum potassium monitoring during treatment with finerenone according to KDIGO guidelines<sup>5</sup>**

K <sup>+</sup> ≤ 4.8 mmol/L	K <sup>+</sup> 4.9-5.5 mmol/L	K <sup>+</sup> > 5.5 mmol/L
<ul style="list-style-type: none"> <li>• Initiate finerenone               <ul style="list-style-type: none"> <li>- 10 mg daily if eGFR 25-59 mL/min/1.73 m<sup>2</sup></li> <li>- 20 mg daily if eGFR ≥60 mL/min/1.73 m<sup>2</sup></li> </ul> </li> <li>• Monitor K<sup>+</sup> at 1 month after initiation and then every 4 months</li> <li>• Increase dose to 20 mg daily, if on 10 mg daily</li> <li>• Restart 10 mg daily if previously held for hyperkalemia and K<sup>+</sup> now ≤5.0 mmol/L</li> </ul>	<ul style="list-style-type: none"> <li>• Continue finerenone 10 mg or 20 mg</li> <li>• Monitor K<sup>+</sup> every 4 months</li> </ul>	<ul style="list-style-type: none"> <li>• Hold finerenone</li> <li>• Consider adjustments to diet or concomitant medications to mitigate hyperkalemia</li> <li>• Recheck K<sup>+</sup></li> <li>• Consider reinitiation if/when K<sup>+</sup> ≤5.0 mmol/L</li> </ul>

**Abbreviations:** K<sup>+</sup>, potassium; mmol/L, millimoles per liter.

tomatic heart failure (stage C).<sup>40</sup> As with blood pressure management practice, it would not be reasonable to wait until someone has advanced CKD or heart failure to be treated.

## MONITORING PHASE: RECOMMENDED FOLLOW-UP PLAN

### CASE:

#### Follow-up lab after 4 weeks:

K: 4.4 mmol/L

Serum creatinine: 1.8 mg/dL

eGFR<sup>a</sup>: 48 mL/min/1.73 m<sup>2</sup>

**Primary care professional decision:** Increase finerenone dose to 20 mg and follow up every 4 months<sup>b</sup>

**Follow-up after 4 months:** No symptoms or signs of heart failure or peripheral arterial disease

Blood pressure: 119/79 mm Hg HR: 69 Weight: 93 kg (205 lb)  
BMI: 34

Serum creatinine: 1.7 mg/dL

eGFR: 53 mL/min/1.73 m<sup>2</sup>

UACR: 200 mg/g (22.6 mg/mmol)<sup>c</sup> LDL: 65 mg/dL

Na: 140 mmol/L HbA1c: 7.5% K: 4.6 mmol/L

**Primary care professional decision:** Consider adding subcutaneous semaglutide (GLP-1 RA) 1.0 mg weekly

<sup>a</sup>30% initial reduction in eGFR is expected and acceptable.<sup>5</sup>

<sup>b</sup>Serum potassium should be monitored 4 weeks after a dose adjustment and throughout treatment.<sup>41</sup>

<sup>c</sup>30% reduction in UACR is considered “renoprotective” by the ADA, the Food and Drug Administration, and the European Medicines Agency.<sup>39,42</sup>

Regular reassessment for risk factors (every 3 to 6 months) is a critical part of the holistic approach to improving outcomes in people with diabetes and CKD.<sup>39</sup> Furthermore, the KDIGO Heatmap shows the recommended frequency of kidney function monitoring by PCPs.<sup>5,6,23</sup> UACR and eGFR should be reassessed at regular intervals according to the KDIGO Heatmap to evaluate treatment response and anticipate the progression of CKD or any adverse events.<sup>5,6,23</sup> Several therapeutic interventions, including RAASi<sup>28,29</sup> and SGLT2is,<sup>43,44</sup> reduce glomerular hyperfiltration by affecting glomerular blood flow, inducing a transient

lowering of eGFR that usually does not exceed 30% in the absence of volume depletion. Similar conditions can occur after starting an nsMRA and should not be interpreted as acute kidney injury that requires medication cessation.

The dose-adjustment guideline for finerenone based on hyperkalemia risk was provided in the latest KDIGO guidelines (FIGURE 2).<sup>5</sup> In this case example, the potassium level is below 4.8 mmol/L after 1 month from finerenone initiation; dose intensification to 20 mg is needed to achieve the ADA target of decreasing albuminuria by 30% in patients with baseline UACR >300 mg/g.<sup>39</sup> Finerenone can reduce UACR within 3 months in a dose-dependent manner, with a significant reduction in UACR reaching 38%.<sup>13</sup> Diuretic or SGLT2i use is associated with lower hyperkalemia risk, and the currently available potassium binder and dietary modification might mitigate the hyperkalemia risk, facilitating the use of a 20-mg concentration of finerenone.<sup>45</sup> As with ACE inhibitors or ARBs, the target treatment dose of finerenone is the maximum tolerated label dose.

### CASE COMMENT:

Although patient K.A.'s KDIGO risk category improved after 4 months, it is justifiable to add a GLP-1 RA as K.A.'s glycemic and body weight control worsened during the last 4 months (FIGURE 1). The use of GLP-1 RAs in populations with T2D enhances glycemic control, reduces body weight, mitigates CVD risk, and, most recently, has been shown to slow CKD progression.<sup>46,47</sup> Adding a GLP-1 RA will fulfill the 4 pillars of DKD management and is expected to offer relevant additional benefits in CKM survival.<sup>10,48</sup>

## MULTIDISCIPLINARY CARE PHASE

It is important for PCPs to be familiar with guideline-directed medical therapies for conditions like CKM syndrome and to know when and how to use them.<sup>25</sup> However, involving an interdisciplinary care team may be necessary when any combination of 2 or more conditions of CKD, diabetes, and subclinical/clinical CVD are present. The team should include PCPs, certified diabetes care and education specialists, and subspecialists such as nephrologists, endocrinologists, and cardiolo-

gists. CKM syndrome coordinators are proposed to implement value-based care in comparison to volume-based care, which targets referrals of high-risk patients to subspecialists.<sup>3</sup> CKM syndrome coordinators can improve collaboration between the team and help with patient navigation across primary care and multiple specialists.<sup>3</sup>

## CONCLUSION

PCPs play a crucial role as frontline clinicians, treating the patient comprehensively across multiple conditions such as CKM syndrome. PCPs should be aware of the potential role of finerenone across the different management phases of CKM syndrome. The synergistic benefits of the 4-pillar approach using RAASis, SGLT2is, GLP-1 RAs, and nsMRA, in addition to a collaborative care model, are recommended to provide the best care for patients with CKM syndrome. ●

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