Nonsteroidal MRAs for Patients With Cardiovascular-Kidney-Metabolic Syndrome

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INTRODUCTION

Cardio-kidney-metabolic (CKM) risk factors including obesity, type 2 diabetes (T2D), and chronic kidney disease (CKD) contribute to heightened risk for development of cardiovascular disease (CVD), including heart failure (HF), atrial fibrillation, stroke, coronary artery disease, and peripheral arterial disease.[1] Recognition of the interplay between cardiometabolic risk and the progression of cardiorenal disease (included within CKM syndrome) has focused attention on strategies to optimize management of patients with CKM syndrome.

Epidemiologic data suggest that nearly three-fourths of the US population have CKM risk factors (CKM stage 1-2) including excess or dysfunctional adiposity, hypertension, metabolic syndrome, diabetes, or CKD, and approximately 1 in 8 have advanced disease (CKM stage 3-4) including subclinical or established CVD (atherosclerotic CVD or HF).[2] Advanced CKM disease is more common in the presence of adverse social determinants of health, underscoring that risk is not evenly distributed and may be impacted by sociodemographic factors.[1,2] Given the high burden of health care utilization in this population, the economic consequences are substantial.[3]

Key takeaways

- CKM syndrome refers to the interplay between cardiometabolic risk factors including obesity, T2D, CKD, and CVD.
- Data from outcomes trials suggest that treatment with finerenone, a nonsteroidal mineralocorticoid receptor antagonist (nsMRA), may improve cardiorenal outcomes across a broad range of CKM conditions both alone and in combination with a sodium-glucose cotransporter 2 inhibitor (SGLT2i).
- Finerenone is indicated to reduce the risk of adverse kidney and cardiovascular (CV) outcomes in patients with CKD and T2D, and to reduce the risk of adverse CV outcomes in patients with HF and left ventricular ejection fraction (LVEF) ≥40% (see Table 5 for complete information).
- Primary care clinicians (PCCs) play an essential role in early recognition of CKM syndrome and can facilitate early initiation of disease-modifying therapy when indicated.
- Multidisciplinary coordination with cardiology/nephrology/endocrinology specialists for CKM care can reduce care fragmentation and further enhance patient outcomes.

Recognition of a shared pathophysiology of CKM disease centered on the systemic consequences of excess or dysfunctional adipose tissue contributing to maladaptive adipokine signaling highlights an opportunity to prevent disease progression through early intervention.[4] Use of SGLT2is is established as an effective strategy for prevention of incident CKD and CVD in patients with T2D at high CV risk as well as prevention of disease progression in established CKD and HF with and without diabetes.[5-7] Accordingly, these drugs are now prioritized by consensus guidelines for treatment of eligible patients across the CKM spectrum. More recently, data have emerged to highlight the potential for additional modification of cardiometabolic risk with the use of nsMRAs.[8,9]

MINERALOCORTICOID RECEPTOR ACTIVATION AND CKM SYNDROME

A key shared mechanism in the progression of CKM syndrome is activation of the renin-angiotensin-aldosterone system (RAAS), which plays a central role in the regulation of blood pressure and fluid homeostasis.[10] Aldosterone, a key downstream effector of this system, acts primarily through binding of the mineralocorticoid receptor (MR), a nuclear receptor that is expressed in multiple tissues including the kidney, heart, and fibroblasts. Enhanced MR expression and activation leading to increased pro-inflammatory and profibrotic signaling are common in the setting of cardiometabolic risk states.[10] MR overactivation is now understood to be a key factor in driving systemic inflammation, plasma volume expansion, and cardiac hypertrophy and fibrosis as well as the development and progression of CKD and HF.[10,11] Accordingly, blockade of the MR with mineralocorticoid receptor antagonists (MRAs) has been an increasingly attractive therapeutic target for the management of CKM-related disease.[12]

Steroidal MRAs (sMRAs) including spironolactone and eplerenone have long been utilized in clinical practice for the management of hypertension (particularly resistant hypertension) and heart failure with reduced ejection fraction (HFrEF), where ample data support efficacy in prevention of morbidity and mortality across the spectrum of disease severity.[13,14] Utilization of these agents in clinical practice, however, remains suboptimal, in part due to concerns for hyperkalemia as well as the potential for off-target, anti-androgen side effects (particularly with spironolactone).[15] Data for use of sMRAs in patients with HF and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) have been mixed.[7,16,17]

Since sMRAs resemble naturally occurring steroid hormones, they may bind and block other steroid hormone receptors, including those for testosterone and progesterone; this anti-androgen effect may contribute to the risk for side effects including gynecomastia, diminished libido, and erectile dysfunction.[18] By contrast, nsMRAs lack a steroidal ring, contributing to a distinct molecular structure that limits cross-reactivity with other steroid hormone receptors, allowing for potent and highly selective blockade of the MR.[18] Although hyperkalemia remains a concern with all MRAs, a more balanced tissue distribution between heart and kidney for nonsteroidal in comparison with steroidal MRAs may provide a more favorable safety profile, particularly in patients with CKD.[10] Key differences between sMRAs and nsMRAs are summarized in **TABLE 1**.[10,19-21]

Two large, randomized trials of patients with diabetes and CKD (FIDELIO-DKD and FIGARO-DKD) have shown that treatment with finerenone lowers the incidence of HF and CKD progression despite heightened risk for hyperkalemia.[22,23] In FIDELIO-DKD, finerenone resulted in an 18% lower risk of CKD progression or death from renal causes vs placebo, and in FIGARO-DKD, the incidence of hospitalization for HF was 29% lower with finerenone vs placebo.[22,23] More recently, among 6001 patients with symptomatic HFmrEF/HFpEF enrolled in the FINEARTS-HF trial, treatment with finerenone was associated with lower rates of the composite of total worsening HF events and CV death vs placebo.[8] Notably, these effects were observed as early as 1

TABLE 1. Pharmacologic characteristics of steroidal and nonsteroidal MRAs.[10,19-21]

Characteristic	sMRAs		nsMRA
	Spironolactone	Eplerenone	Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency to MR	Highly potent	Somewhat potent	Highly potent
Selectivity to MR	Somewhat selective	Selective	Highly selective
Central nervous system penetration	Some penetration	Some penetration	None
Sexual side effects	Gynecomastia, decreased libido, breast and nipple pain	Few reports of gynecomastia and abnormal vaginal bleeding	None
Half-life	>20 hours[a]	4-6 hours[a]	2-3 hours[b]
Active metabolites	Present	None	None
Effect on blood pressure lowering	Significant	Moderate	Mild

[a]In patients with HF.
[b]In healthy volunteers.

month following initiation of finerenone treatment and were robust in patients treated and not treated with an SGLT2i at baseline, suggesting additive treatment benefits.[24] Subanalyses of FINEARTS-HF also noted potential improvement in CV and HF event-free survival up to 3.1 years, reduction in the risk of new-onset diabetes, and preserved efficacy and safety across LVEF categories.[25-27] Additionally, benefits observed in FINEARTS-HF were not affected by baseline atrial fibrillation status.[28] In a pooled analysis of these trials representing a broad spectrum of patients with CKM disease, treatment with finerenone did not influence CV mortality but was associated with lower rates of all-cause mortality, HF hospitalization, and composite kidney outcomes.[29] Another pooled analysis of these trials suggested that finerenone reduces the risk of new-onset atrial fibrillation or atrial flutter.[30] Collectively, these data suggest potential for use of nsMRAs with or without SGLT2is for treatment of patients with CKM syndrome.

In the CONFIDENCE trial, participants with CKD, albuminuria, and T2D already receiving a RAAS inhibitor were randomized to finerenone alone, empagliflozin alone, or the combination.[9] At 180 days, combination therapy produced a ~30% greater reduction in urine albumin-to-creatinine ratio (UACR) than either monotherapy, without a concerning signal of safety. Results were consistent in patients treated and not treated with glucagon-like peptide-1 (GLP-1) receptor agonists.[9] Additionally, the CONFIDENCE trial established UACR as a mediating biomarker that can be used as a marker of CKD progression, as it is associated with kidney failure.[9,31] These data suggested that combination therapy was associated with greater albuminuria reductions. Furthermore, a subanalysis of CONFIDENCE suggested that the benefits of combination therapy with finerenone and empagliflozin are preserved across a spectrum of predicted kidney disease risk.[32]

Extrapolating from the results of the DELIVER trial of dapagliflozin and the FINEARTS-HF trial, one analysis projected that the treatment of HFmrEF/HFpEF with the combination of an SGLT2i and finerenone would lead to significant improvements in event-free survival over the lifetime, adding a projected 3.6 years of life free from CV death or worsening HF events for an average 65-year-old with HFmrEF/HFpEF.[33] A trial-level analysis of multiple CKM trials suggested that CKM multimorbidity is substantial, increases over time, and is associated with adverse events, confirming the need for timely identification and intervention.[34] Key data from recent clinical trials of finerenone and notable subanalyses from phase 3 studies of CKD in T2D and from HF with LVEF ≥40%, which are important conditions within CKM syndrome, are summarized in **TABLE 2** and **TABLE 3**.

In addition to CKD associated with T2D and HF with LVEF ≥40%, finerenone may extend options for patients with CKD associated with type 1 diabetes (T1D) according to a recently published study.[35,36] CKD in T1D represents a major unmet need, as up to 40% of patients with T1D develop CKD.[35] Furthermore, up to 40% of adults >30 years who were eventually diagnosed with T1D were originally diagnosed and treated as T2D, highlighting that PCCs do not have to definitively rule out T1D.[36] Historically, disease-modifying options have been more limited in T1D than in T2D. Results from the FINE-ONE randomized trial in patients with T1D and CKD indicate that finerenone significantly reduced UACR over 6 months by 25% compared to placebo.[37]

Trials of other MRAs in CKM syndrome are also informative (**TABLE 2**).[16,38,39] In the TOPCAT randomized, double-blind trial, which enrolled patients with symptomatic HF and LVEF ≥45%, there was no difference between spironolactone and placebo in the primary composite outcome of death from CV causes, aborted cardiac arrest, or HF hospitalization, but hyperkalemia was increased with spironolactone.[16] However, spironolactone significantly reduced the incidence of hospitalization for HF by 17% compared to placebo.[16] In the BARACK-D randomized, open, blinded endpoint trial, older adults with stage 3b CKD who received spironolactone did not have improved CV outcomes compared to placebo, and spironolactone was frequently discontinued due to safety concerns.[38] An investigational nsMRA, balcinrenone, was combined with dapagliflozin in adults with estimated glomerular filtration rate (eGFR) 25 to <60 mL/min/1.73 m^2, UACR >100 to ≤5000 mg/g, and serum potassium 3.5 to 5.0 mmol/L in the MIRO-CKD phase 2b randomized controlled trial.[39] The combination of balcinrenone and dapagliflozin reduced UACR up to 32.8% compared with dapagliflozin alone after 12 weeks.[39]

GUIDELINE-DIRECTED MANAGEMENT OF CKM SYNDROME

Patients with early manifestations of CKM syndrome are commonly encountered in primary care, making this the optimal setting for early intervention to prevent disease progression. PCCs can adopt a practical screening mindset that includes evaluating for silent organ injury before symptoms drive care, which means routine kidney surveillance (eGFR and UACR) in high-risk patients, proactive assessment for HF risk and early HF (symptoms, volume status, and consideration of natriuretic peptide–based risk assessment), and periodic review of CVD risk factors, including blood pressure, lipids, smoking, and weight trajectory.[5-7,40] When abnormal findings emerge, PCCs can address CKM conditions early by implementing interventions and coordinating multidisciplinary care. Of note, the recently published 2026 American Heart Association/American College of Cardiology

TABLE 2. Notable clinical trials of MRAs in CKM syndrome.

Study	Condition	Evidence focus	Design	Population	Key findings
FIDELIO-DKD Trial[22]	T2D + CKD	Composite kidney outcome in patients with T2D + CKD	RCT; finerenone + placebo	Stage 1 or stage 2 CKD with albuminuria and T2D	Reduced kidney failure, sustained decrease ≥40% in eGFR, or reduced death from renal causes (HR, 0.82; 95% CI: 0.73, 0.93; *P* =.001)
FIGARO-DKD Trial[23]	T2D + CKD	Composite CV outcome in patients with T2D + CKD	RCT; finerenone vs placebo	Stage 1 or stage 2 CKD with albuminuria and T2D	Reduced CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF (HR, 0.87; 95% CI: 0.76, 0.98; *P* =.03)
FINEARTS-HF Trial[8]	HF	HFmrEF/HFpEF clinical outcomes	RCT; finerenone vs placebo	Symptomatic HF, LVEF ≥40%	Reduced total worsening HF events and death from CV causes with finerenone (RR, 0.84; 95% CI: 0.74, 0.95; *P* =.007)
CONFIDENCE Trial[9]	T2D + CKD	Combination therapy in T2D + CKD	RCT; finerenone, empagliflozin, or finerenone + empagliflozin	CKD with albuminuria and T2D	Combination therapy reduced UACR by 29% compared to finerenone alone (mean ratio 0.71; 95% CI: 0.61, 0.81; *P* <.001) and empagliflozin alone (mean ratio 0.68; 95% CI: 0.59, 0.79; *P* <.001)
FINE-ONE Trial[36]	T1D + CKD	Reduction in UACR	RCT; finerenone vs placebo	T1D and CKD	Finerenone significantly reduced UACR over 6 months by 25% (HR, 0.75; 95% CI: 0.65, 0.87; *P* =.0001)
TOPCAT Trial[16]	HF	Composite CV outcome in patients with HFpEF	RCT; spironolactone vs placebo	Symptomatic HF and LVEF ≥45%	No significant difference in primary composite outcome; increased risk of hyperkalemia with spironolactone; reduction in hospitalization for HF with spironolactone (HR, 0.83; 95% CI: 0.69, 0.99; *P* =.04)
BARACK-D Trial[38]	CKD	Composite CV outcome in older adults with CKD	Prospective, randomized, open, blinded endpoint trial; spironolactone vs usual care	Older adults (mean age 74.8 years) with stage 3b CKD	No significant difference in CV outcomes; increased risk of hyperkalemia with spironolactone and frequent discontinuation of spironolactone due to safety concerns
MIRO-CKD Trial[39]	CKD	Reduction in UACR	RCT dose-finding phase 2b trial; balcinrenone + dapagliflozin vs dapagliflozin	Adults with CKD (eGFR 25 to <60 mL/min/1.73 m^2, UACR >100 to ≤5000 mg/g, and serum potassium 3.5 to 5.0 mmol/L)	Reduction in UACR of 22.8% with balcinrenone 15 mg (*P* =.0038) and reduction of 32.8% with balcinrenone 40 mg (*P* =.0001) after 12 weeks

Abbreviations: CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial; RR, rate ratio.

Multisociety Guideline for CKM Syndrome endorses the use of nsMRA (finerenone) for treatment of patients with HFpEF, T2D, CKD, and albuminuria.[41] Readers are referred to the full guideline publication for specific recommendations (https://www.ahajournals.org/doi/10.1161/CIR.0000000000001453).

CASE STUDY

An overweight 62-year-old man with T2D, CKD, hypertension, and HFpEF presents to the primary care clinic for a follow-up visit following a recent hospitalization for management of worsening HF.

Measurements and laboratory values from recent hospitalization:

- Body mass index 26 kg/m^2
- Waist-to-height ratio 0.55 (normal <0.5)
- Blood pressure 135/86 mmHg
- Heart rate 75 bpm
- Exam: No jugular venous distension, clear lungs to auscultation, normal cardiac exam without murmur or gallop, no peripheral edema
- LVEF 55% (by echocardiography)
- Glycated hemoglobin (HbA1c) 8.5%
- Potassium 4.8 mEq/L
- eGFR 35 mg/mL/1.73 m^2 (Kidney Disease: Improving Global Outcomes Stage 3b CKD)
- NT-proBNP 1000 pg/mL
- Urine albumin:creatinine ratio: 100 mg/g

Medications:

- Empagliflozin 25 mg once daily
- Metformin 1000 mg twice daily
- Losartan 100 mg daily
- Hydrochlorothiazide 25 mg daily

What additional therapies should be considered for this patient?

Hospitalization for management of worsening HF is a sentinel event and identifies patients at high risk for recurrent HF exacerbation and death. This early post-discharge

Table 3. Notable subanalyses of clinical trials of finerenone in CKM conditions.

Study	Condition	Evidence focus	Design	Population	Key findings
FINEARTS-HF Time to Benefit Analysis[24]	HF	Time to significant benefit of finerenone in HF	Prespecified analysis	Symptomatic HF, LVEF ≥40%	First statistical significance observed within 1 month of therapy initiation and sustained until final follow-up
FINEARTS-HF Long-Term Benefits[25]	HF	Estimated long-term benefit of finerenone in HF	Prespecified analysis	Symptomatic HF, LVEF ≥40%	Projected mean event-free survival gains: 2.0 years (age 65), 3.1 years (age 55) free from CV death or worsening HF events
FINEARTS-HF Across the EF Spectrum[26]	HF	Finerenone efficacy in HF across LVEF	Prespecified analysis	Symptomatic HF, LVEF ≥40%	Finerenone reduced CV death and total HF events consistently across LVEF categories (LVEF <50%: RR, 0.84 [95% CI: 0.68, 1.03]; LVEF ≥50% to <60%: RR, 0.80 [9% CI: 0.66, 0.97]; and LVEF ≥60%: RR, 0.94 [95% CI: 0.70, 1.25]; $P_{interaction}$ =.70)
FINEARTS-HF New-Onset Diabetes Analysis[27]	HF	New onset of diabetes	Prespecified analysis	Symptomatic HF, LVEF ≥40%	Risk of new-onset diabetes reduced by 24% with finerenone (HR, 0.76; 95% CI: 0.59, 0.97)
FINEARTS-HF New-Onset AF Analysis[28]	HF	New onset of AF or AFL	Prespecified analysis	Symptomatic HF, LVEF ≥40%	Benefit of finerenone on CV and HF not modified by baseline AF status; new onset AF was nonsignificantly reduced with finerenone (subdistribution HR, 0.77; 95% CI: 0.57, 1.04; *P* =.05)
FINE-HEART Pooled Analysis[30]	HF	New onset of AF or AFL	Pooled analysis of FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF	Cross trial T2D + CKD; symptomatic HF, LVEF ≥40%	During 2.9 years of median follow-up, finerenone reduced the risk of new-onset AF/AFL by 17% (HR, 0.83; 95% CI: 0.71, 0.97, *P* =.019)
Lifetime Benefits of Comprehensive Medical Therapy[33]	HF	Combination SGLT2i + finerenone therapy in HF	Cross-trial analysis of DELIVER, FINEARTS-HF, and PARAGON-HF	Cross trial HFmrEF/HFpEF	Combined use of SGLT2i and finerenone estimated to reduce risk of CV death or first HF worsening event by 31% (HR, 0.69; 95% CI: 0.59, 0.81)
CONFIDENCE Kidney Risk Subanalysis[32]	T2D + CKD	Combination therapy in T2D + CKD across spectrum of kidney risk	Prespecified analysis	CKD with albuminuria and T2D	Relative efficacy and safety of simultaneous finerenone and empagliflozin combination therapy were consistent across a wide spectrum of predicted kidney disease risk
FINE-HEART Pooled Analysis[29]	CKM	CV, kidney, and mortality outcomes	Cross-trial analysis of FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF	Cross trial T2D + CKD; symptomatic HF, LVEF ≥40%	Over 2.9 years of follow-up, finerenone reduced the risk of CV death (HR, 0.89; 95% CI: 0.78, 1.01; *P* =.076), death from any cause (HR, 0.91; 95% CI: 0.84, 0.99; *P* =.027), hospitalization from HF (HR, 0.83; 95% CI: 0.75, 0.92; *P* <.001), and the composite kidney outcome (HR, 0.80; 95% CI: 0.72, 0.90; *P* <.001)
CKM Trial-Level Analysis[34]	CKM	Progression and overlap of CKM conditions	Trial-level analysis of I-PRESERVE, TOPCAT, PARAGON-HF, DELIVER, and FINEARTS-HF trials	Cross trial HFmrEF or HFpEF	CKM multimorbidity was substantial, increased over time, and was associated with adverse outcomes

Abbreviation: AFL, atrial flutter.

TABLE 4. The stages of CKM syndrome.[1]

Stage and description	Characteristics
Stage 0 No risk factors	• Focus on primordial prevention and preserving cardiovascular health
Stage 1 Excess/dysfunctional adipose tissue	• Overweight/obesity • Abdominal obesity • Impaired glucose tolerance
Stage 2 Metabolic risk factors and CKD	• Hypertension o Nonmetabolic etiologies of hypertension • Metabolic syndrome • Moderate- to high-risk CKD o Nonmetabolic etiologies of CKD • Type 2 diabetes • Hypertriglyceridemia
Stage 3 Subclinical CVD in CKM syndrome[a]	• Subclinical atherosclerotic CVD • Subclinical HF
Stage 4 Clinical CVD in CKM syndrome	• HF • Peripheral arterial diseas • Stroke • Atrial fibrillation • Coronary heart disease

[a]Risk equivalents of subclinical CVD in CKM Stage 3: very high-risk CKD, high predicted risk for CVD using risk calculator.

visit is an opportunity to reduce the risk of recurrent HF. This patient has T2D, CKD (based on a reduced eGFR and high albuminuria), elevated BMI, high waist-to-height ratio, uncontrolled blood pressure, and HFpEF consistent with a broad range of cardiometabolic risks typical of Stage 4 CKM syndrome (CKM stages are summarized in **TABLE 4**). Targets for optimization include agents that will reduce risk of CKD progression, lower blood pressure, and lower overall cardiometabolic risk. Improvement in glycemic control is certainly important given evidence of diabetic kidney disease and the tight linkage between intensive control of blood glucose and microvascular outcomes; however, tight glycemic control alone has not been associated with improvement in CV outcomes, so additional interventions are needed for CV risk reduction.

The patient is already managed with an SGLT2i, which has been shown to reduce risk of recurrent HF in patients with HF, including those recently hospitalized for HF management.[42,43] Data from the FINEARTS-HF trial suggest that the addition of an nsMRA, finerenone, in this setting may further reduce risk of recurrent HF, and the benefits appear to be amplified in the early post-discharge interval.[26] The patient also has a secondary indication for finerenone based on the underlying diagnosis of diabetes and CKD, where data from FIGARO-CKD and FIDELIO-CKD suggest CV benefits. While use of an sMRA in this context may be considered as an alternative if finerenone is not accessible, it remains unclear whether the balance of safety and efficacy is consistent across the class; while data supporting use of sMRAs is robust in HFrEF, data supporting sMRA efficacy for HFpEF have been mixed, including a recently presented study that was terminated prematurely and was accordingly underpowered for the primary efficacy assessment.[44] Additionally, the safety profile of sMRAs in patients with advanced CKD is a concern.[16,43] Other attractive targets for intervention include blood pressure, which remains elevated above guideline-recommended targets (<130/80 mmHg), and central adiposity. Screening for sleep apnea, an important and treatable cause of secondary hypertension, should be considered, particularly if the patient has suggestive symptoms of snoring or daytime somnolence. Use of an angiotensin receptor-neprilysin inhibitor (ARNI) in place of losartan is a consideration given the possibility for greater reduction in blood pressure, though data supporting greater efficacy of ARNI compared with angiotensin II receptor blockers in patients with HFpEF is less compelling when LVEF is in the normal or supranormal range.[45] An alternative in this case is to use a GLP-1 or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist such as semaglutide or tirzepatide, since it might allow for simultaneous reduction in blood glucose, weight, and blood pressure with benefits for functional capacity and quality of life; however, data regarding the impact of this strategy on long-term CV outcomes in HFpEF are limited.[46-48] Practical guidance for use of finerenone, including strategies for dosing and laboratory surveillance, is outlined in **TABLE 5**.[49-51]

SUMMARY

CKM syndrome provides a clinically useful framework for understanding how metabolic risk, CKD, and CVD amplify each other, and why therapies with multidomain benefit can be especially valuable. Evolving therapies targeting the spectrum of cardiometabolic risk including SGLT2 inhibitors, nsMRAs, and GLP-1/GIP receptor agonists are emerging that may favorably modulate risk in patients with CKM across the risk spectrum, including patients with HF and mildly reduced or preserved ejection fraction. In particular, data regarding the use of finerenone from large, prospective clinical trials enrolling patients across the CKM spectrum (including those with HFpEF) suggest significant benefits with regard to CV risk reduction. While the use of sMRAs (spironolactone, eplerenone) may be preferred in patients with HFrEF, where the evidence base is strong, the weight of evidence may favor use of finerenone in patients with

TABLE 5. FDA-approved indications, dosing, and potassium monitoring for nonsteroidal and steroidal MRAs.

MRA	FDA-approved indications	Dosing	Potassium monitoring
Finerenone[48]	To reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, nonfatal myocardial infarction, and hospitalization for HF in adult patients with CKD associated with T2D To reduce the risk of CV death, hospitalization for HF, and urgent HF visits in adult patients with HF with LVEF ≥40	Starting dose: • 20 mg once daily if eGFR ≥60 mL/min/1.73 m^2 • 10 mg once daily if eGFR ≥25 to <60 mL/min/1.73 m^2 • Initiation not recommended if eGFR <25 mL/min/1.73 m^2 Target dose: • CKD associated with T2D: 20 mg daily • For patients with HF with LVEF ≥40%, the target dose is 20 mg if baseline eGFR is ≥25 to <60 mL/min/1.73 m^2 and 40 mg if baseline eGFR is ≥60 mL/min/1.73 m^2 Doses are increased, maintained, or decreased based on serum potassium monitoring	Measure serum potassium at baseline and 4 weeks after initiating treatment If serum potassium levels are >4.8 to 5.0 mEq/L, initiation may be considered with additional serum potassium monitoring within the first 4 weeks Measure serum potassium 4 weeks after a dose adjustment and periodically throughout treatment, and adjust dose if needed, according to drug labeling
Spironolactone[49]	Treatment of HF with reduced ejection fraction[a]	If serum potassium is ≤5.0 mEq/L and eGFR >50 mL/min/1.73 m^2, initiate 25 mg daily. Can increase to 50 mg daily or reduce to 25 mg every other day depending on response If eGFR is between 30 and 50 mL/min/1.73 m^2, consider initiating treatment at 25 mg every other day	Monitor potassium at baseline and approximately 1 month after initiation or dose changes and routinely throughout treatment
	Treatment of hypertension	Recommended initial dose is 25 to 100 mg daily, can be titrated at 2-week intervals	
	Treatment of edema associated with hepatic cirrhosis or nephrotic syndrome	In patients with cirrhosis, initiate in a hospital setting and titrate slowly Initial dose is 100 mg daily, but can range from 25 to 200 mg daily	
	Treatment of primary hyperaldosteronism	100 to 400 mg doses in preparation for surgery	
Eplerenone[50]	Improving survival of patients with symptomatic HFrEF after an acute myocardial infarction	Initiate at 25 mg once daily and titrate to the recommended dose of 50 mg once daily, preferably within 4 weeks Adjust dose based on serum potassium level	Monitor potassium at baseline and approximately 1 month after initiation or dose changes and routinely throughout treatment; adjust dose if needed, based on drug labeling
	Treatment of hypertension	50 mg once daily; if blood pressure response is inadequate, can increase to 50 mg twice daily after 1 month	

[a]Guidelines indicate that the use of spironolactone may be appropriate for HFpEF, provided that potassium is <5.0 mEq/L and eGFR is >30 mL/min/1.73 m^2.

HF and higher ejection fractions, particularly where there is an overlap with other cardiometabolic risk factors such as diabetes and CKD. The practical challenge now is implementation: reducing inertia through routine screening and identification, promptly initiating and maintaining effective therapies, and monitoring for adverse effects or disease worsening. PCCs play a key role in collaborating with cardiology, nephrology, and endocrinology specialists to implement comprehensive CKM care.●

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