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CKJ REVIEW

Clinical implications of mineralocorticoid receptor overactivation

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ABSTRACT

The mineralocorticoid receptor (MR) is a nuclear transcription factor that plays a critical role in regulating fluid, electrolytes, blood pressure, and hemodynamic stability. In conditions such as chronic kidney disease (CKD) and heart failure (HF), MR overactivation leads to increased salt and water retention, inflammatory and fibrotic gene expression, and organ injury. The MR is essential for transcriptional regulation and is implicated in metabolic, proinflammatory, and pro-fibrotic pathways. It is widely expressed in various cell types throughout the body, including the gastrointestinal tract, heart, brain, kidneys, immune cells, and vasculature. Animal studies suggest that MR activation induces oxidative stress in the kidneys and mediates renal inflammation and fibrosis. Immune cell-specific deletion of MR has shown protection against cardiac fibrosis, indicating the MR's role in pathological remodeling. In vascular smooth muscle cells, the MR regulates vascular tone and vasoconstriction.

Mineralocorticoid receptor antagonists (MRAs) can be categorized based on their chemical structure as either steroidal or nonsteroidal. Steroidal MRAs (sMRA), such as spironolactone and eplerenone, have demonstrated cardiovascular benefits but are limited by hyperkalemia, gynecomastia, and sexual dysfunction. Nonsteroidal MRAs (nsMRA) have shown promise in preclinical studies and clinical trials. They offer a promising alternative by effectively blocking MR without hormone-like effects, potentially improving cardiovascular and renal disease management.

Further education is necessary regarding the significance of MRA utilization in CKD and HF, balancing benefits with the risk of hyperkalemia. This risk could be mitigated by combining MRAs with potassium-binding agents. Studies are underway to explore the synergistic effects between nsMRAs and other agents, such as SGLT-2i inhibitors and Glucagon-like peptide-1 agonists, to optimize cardiorenal outcomes.

Overall, MR overactivation remains a significant therapeutic target, with nsMRAs showing promise as pivotal therapies in CKD and HF management. This review highlights the evolving landscape of MR-targeted therapies, their molecular mechanisms, and clinical implications in cardiorenal diseases.

Keywords: clinical implications, MR overactivation, nonsteroidal MRA, steroidal MRA

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INTRODUCTION

The mineralocorticoid receptor (MR) is a ligand-activated nuclear transcription factor present in various cell types throughout the body, including the kidney, heart, and the blood vessels supplying them [1]. The MR plays a crucial role in regulating fluid and electrolytes and, in turn, affects blood pressure and hemodynamic stability [2]. However, in conditions such as chronic kidney disease (CKD) and heart failure (HF), the MR is overactivated, inducing increased salt and water retention and the expression of genes involved in inflammatory and fibrotic pathways, causing organ injury [1].

MR nonligand activation refers to the activation of the MR by mechanisms other than its traditional ligands, which are aldosterone and cortisol. This can occur through various factors such as oxidative stress, protein–protein interactions with other cellular proteins, or changes in the cellular environment such as high blood sugar or sodium levels [3].

Since their discovery in the 1950s, the use of mineralocorticoid receptor antagonists (MRAs), despite having documented cardiovascular mortality benefits, has been limited by side effects such as hyperkalemia and breast complaints [4, 5]. In this review article, we aim to discuss the clinical implications of MR overactivation as well as provide an overview of the safety and efficacy of MRA use in CKD.

PATHOPHYSIOLOGY OF MR OVERACTIVATION

The MR belongs to steroid hormonal receptors, intracellular in nature, found typically in a transcriptionally inactive state in the cytoplasm [2]. On activation, these receptors undergo conformational changes, allowing translocation to the nucleus where they interact with cell-specific co-regulator proteins [2]. These proteins play a vital role in transcriptional regulation, epigenetics, and post-transcriptional modification. The MR, a ligand-activated nuclear transcription factor, is expressed in diverse cell types throughout the body, including the gastrointestinal tract, heart, brain, kidneys, immune cells, and vasculature [6]. The MR demonstrates similar affinities for various endogenous steroids such as progesterone, cortisol, and aldosterone.

Epithelial tissues expressing 11β-HSD2 convert cortisol into MR-inactive metabolites, cortisone, making aldosterone the primary ligand in these tissues [2, 7]. However, in other cell types lacking 11β-HSD2, such as macrophages and cardiomyocytes, cortisol may play a crucial role in regulating MR activity, which could be a therapeutic target not addressed by current renin–angiotensin–aldosterone system-modulating agents such as Angiotensin-converting enzyme inhibitors or Angiotensin II receptor blockers [2].

It is now acknowledged that mechanisms independent of aldosterone can activate the MR, and the MR's role in disease progression extends beyond its traditional impact on salt and fluid homeostasis. The MR is implicated in metabolic, proinflammatory, and pro-fibrotic pathways. MR activation in non-epithelial cells revealed a proinflammatory and pro-fibrotic effect, resulting in structural changes, including cardiac and vascular remodeling, endothelial dysfunction, proteinuria, and kidney injury [2, 8–11]. Conditions characterized by an increase in either aldosterone release, or reactive-oxygen species (ROS) production can lead to an excessive activation of extra-renal MRs or what is known as MR overactivation [12]. This overactivation contributes to the creation of a proinflammatory environment marked by the release of cytokines such as TNF-α, IL-1β, and IL-6, along with chemokines [12] (Fig. 1).

Kidney

Evidence from animal models suggests that MR activation induces oxidative stress in the kidney and serves as a central mediator of renal inflammation and fibrosis [8, 13–16]. This is evidenced by DNA damage, increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, and ROS generation in the kidney [17]. MR function assessed in tissue-specific knockout or via overexpression of the MR reveals differences in MR function between epithelial and non-epithelial cells [2, 18]. Within renal epithelial cells, MR activation showed salt retention and fluid retention, while knockout models showed salt wasting in the setting of decreased epithelial sodium channel (ENaC) activity [18–20]. MR knockouts in myeloid and macrophage cells have shown a decrease in renal injury and, thus, proteinuria. Increased sodium reabsorption and potassium excretion in the aldosterone-sensitive distal nephron of the kidney result in increasing blood volume and blood pressure, leading to hypertension [21, 22]. Hypertension can cause damage to the kidneys, heart, and blood vessels and increase the risk of myocardial infarction, stroke, and HF. In addition, hypokalemia can lead to symptoms such as fatigue, weakness, cramps, constipation, palpitations, or numbness and can impair insulin secretion and glucose metabolism through the ATP-sensitive potassium (K_{ATP}) channel in islet cells, leading to hyperglycemia and diabetes [23, 24].

In rats with unilateral nephrectomy, aldosterone administration induces renal fibrosis characterized by increased expression of TGF-β, collagen, and connective tissue growth factor, leading to medullary and cortical fibrosis [25]. Also, aldosterone affects plasminogen activator inhibitor-1 production, contributing to glomerulosclerosis [26]. In renal fibroblasts expressing MRs, aldosterone stimulates extracellular signal-regulated kinase (ERK)1/2 phosphorylation and mRNA levels of collagens I, III, and IV, promoting collagen synthesis [27]. Additionally, aldosterone activates c-Jun, N-terminal kinase, and activator protein 1 in fibroblasts, inducing fibronectin synthesis, growth-factor receptor activation, and phosphoinositide 3-kinase/mitogen-activated protein kinase (PI3K/MAPK) signaling, promoting fibroblast proliferation and kidney fibrosis [28, 29].

Heart

The first indication of MR activation promoting cardiac fibrosis dates back to 1958 when the administration of a mineralocorticoid agent resulted in cardiac necrosis and subsequent fibrotic scarring in dogs [30]. Furthermore, studies on immune cell MR activity revealed that macrophage-specific deletion of MR in mice protected against deoxycorticosterone/salt-induced cardiac fibrosis [31]. This has been further verified with the knockout of the MR in cardiomyocytes and T cells in mice that showed improvement of post-MI ventricular remodeling [32]. Reduction in cardiac remodeling, fibrosis, and contractility dysfunction has been linked to MR knockouts in cardiomyocytes [33–35]. Thus, MR antagonism in cardiomyocytes and myeloid cells may be associated with a decrease in inflammatory and fibrotic processes, pathological remodeling, and organ dysfunction [31, 36–38].

Vessels

The MR expressed in vascular smooth muscle cells plays a vital role in regulating vascular tone and, thus, vasoconstriction [39, 40]. Deletion of the MR in vascular smooth muscle cells reduces ROS production, which prevents sulfenic modification on

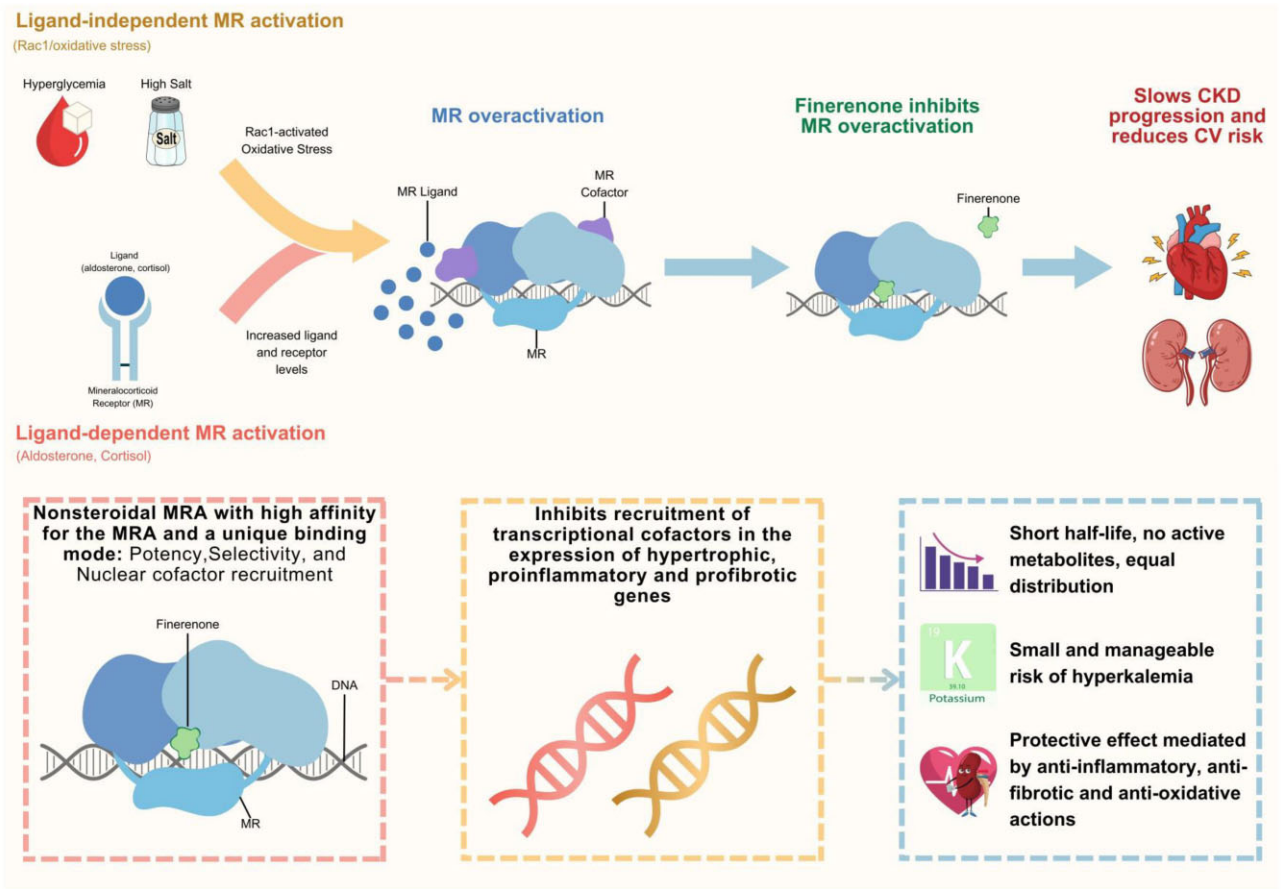

Figure 1. Pathophysiology of MR overactivation.

the endothelin-B receptor, impairing its signaling and inactivating endothelial nitric oxide synthase [39]. MR activation in isolated smooth muscle cells promotes the activation of NADPH oxidase, causing various detrimental effects, including vascular calcification, fibrosis, stiffness, and inflammation by increasing cellular expression of several genes (collagen I and III, alkaline phosphatase, parathyroid hormone receptor-2, and bone morphogenetic protein-2) [41, 42].

THERAPEUTIC TARGETING OF MR OVERACTIVATION

Steroidal MRA (sMRA)

Steroidal MRAs represent a critical therapeutic option in managing conditions associated with MR overactivation. These compounds, which include well-known drugs such as spironolactone and eplerenone, function by antagonizing the effects of aldosterone, thereby mitigating the pathological activation of MR. However, the clinical utility of sMRAs has been tempered by their side-effect profiles, limiting their use in broader patient populations (Table 1) [43, 44].

Spironolactone introduced 27 years before cloning the MR, was the first sMRA launched [4]. Spironolactone was initially released as a potassium-sparing diuretic to counteract potassium loss induced by loop diuretics with a blood pressure-controlling capability [4]. The second sMRA, eplerenone, was discovered decades later during the period when the role of aldosterone and MR in anti-fibrosis and cardiac remodeling was being explored [4]. Eplerenone exhibits greater selectivity than spironolactone but has ~40-fold lower *in vitro* affinity for the MR than spironolactone [45].

Compelling evidence supporting the therapeutic efficacy of sMRAs in patients with chronic heart failure with reduced ejection fraction (HFrEF) is derived from the RALES [46], EPHESUS [47], and EMPASIS-HF [48] trials. The RALES trial showed that spironolactone reduced mortality by 30% (relative risk 0.70, 95% CI 0.60–0.82, $P < .001$) in patients with severe HF. Similarly, EPHESUS trial indicated a 15% mortality reduction (relative risk 0.85, 95% CI 0.75–0.96, $P = .008$) with eplerenone in patients with acute myocardial infarction complicated by left ventricular dysfunction. The EMPHASIS-HF trial further supported these findings, showing a 37% reduction (hazard ratio 0.63, 95% CI 0.54–0.74, $P < .001$) in the primary composite outcome of cardiovascular death or heart failure hospitalization with eplerenone in patients with systolic heart failure and mild symptoms.

However, the REMINDER [49] trial, which assessed eplerenone administration during the acute phase of ST-elevation myocardial infarction in patients without evidence of HF, and the ALBATROSS [50] trial, which investigated a single intravenous bolus of potassium followed by oral spironolactone for 6 months in patients with acute MI, did not demonstrate a clear benefit of early sMRA use when added to standard care for patients admitted with MI.

Table 1: Summary of RCTs on steroidal MRA in cardiovascular and renal disease.

Trial	Drug name	Aim of the study	Study results	Side effect
RALES	Spironolactone	To determine the effect on mortality and morbidity in patients with severe heart failure	37% reduction in mortality and hospitalizations	gynecomastia, impotence/hyperkalemia
ALBATROSS	Spironolactone	Investigate the clinical effects of a rapid and prolonged MRA regimen initiated early after the onset of any type of MI	The study failed to show the benefit of early MRA use in addition to standard therapy in patients admitted for MI	not specified
TOPCAT	Spironolactone	To assess the effectiveness in patients with HFpEF	No significant difference in primary outcomes	hyperkalemia, increased serum creatinine
EPHESUS	Eplerenone	To evaluate the efficacy of eplerenone post-AMI in patients with HF and systolic LV dysfunction	Reduced overall mortality and CV mortality or hospitalization	hyperkalemia
EMPHASIS-HF	Eplerenone	To assess the effect on cardiovascular outcomes in patients with mildly symptomatic LV systolic dysfunction	Significant improvements in all-causes mortality, CV mortality, all-cause hospitalization, and HF hospitalization	hyperkalemia
REMINDER	Eplerenone	Assess the impact of early eplerenone treatment on cardiovascular outcomes in patients with acute STEMI without known heart failure	Improved outcomes when added to standard therapy within 24 hours of MI symptoms without HF or low ejection fraction	non-significant
ALCHEMIST	Spironolactone	To compare spironolactone to placebo in time to onset of the first incident of the composite endpoint of nonfatal MI, ACS, hospitalization for HF, nonfatal stroke, or CV death	No reduction of the primary composite endpoint but a potential reduction in the risk of HF hospitalization	——
SPIRRIT-HFpEF	Spironolactone	To determine whether treatment with Spironolactone combined with usual care improves outcomes in HFpEF patients	ongoing	——
SPIRIT-HF	Spironolactone	To compare Spironolactone to Placebo in reducing the rate of the composite endpoint of recurrent heart failure hospitalizations and cardiovascular death in symptomatic HF patients	ongoing	——
ACHIEVE	Spironolactone	To determine whether spironolactone reduces death or hospitalization for HF and is well tolerated in patients that require dialysis	ongoing	——

AMI: acute myocardial infarction, HFpEF: heart failure with preserved ejection fraction, LV: left ventricle, MI: myocardial infarction, STEMI: ST-elevation myocardial infarction.

Despite spironolactone not showing a significant benefit in the primary composite endpoint of the TOPCAT [51]trial, subsequent analyses revealed notable regional variation in event rates and drug adherence, leading to different treatment effects and a significant reduction in HF hospitalization as well as in primary outcome in North/South American group (HR 0.82, 95% CI 0.69–0.98, $P = .026$) [51, 52]. Two ongoing studies that are currently recruiting, SPIRRIT-HFpEF [53] and SPIRIT-HF [54], are exploring the effects of spironolactone in HF patients. The SPIRRIT-HFpEF [53] trial is a registry-based prospective randomized clinical trial involving patients from the Swedish Heart Failure Registry and the USA, focusing on cardiovascular death or time to HF hospitalization. The SPIRIT-HF [54] study, funded by the German Centre for Cardiovascular Research, is investigating spironolactone's impact on recurrent HF hospitalization and cardiovascular death in symptomatic patients with HF and mid-range or preserved ejection fraction across several European countries.

There are two large studies in end-stage kidney disease (ESKD) patients will clarify safety and efficacy of spironolactone use in this patient population. The ALdosterone antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST, NCT01848639), which has concluded and aims to measure a primary composite endpoint of time to onset of the first

Table 2: Summary of RCTs on nonsteroidal MRA in cardiovascular and renal disease.

Trial	Drug name	Aim of the study	Study results	Main side effect
BLOCK-CKD	Ocedurenone (KBP-5074)	Assess the efficacy and safety of Ocedurenone in patients with moderate-to-severe CKD with uncontrolled or resistant hypertension	Significant reduction of SBP in patients with CKD and uncontrolled hypertension	hyperkalemia
ESAX-HTN	Esaxerenone (CS-3150)	Evaluate antihypertensive effect and safety of Esaxerenone compared to Eplerenone in patients with essential hypertension	Esaxerenone 5 mg/day showed superior antihypertensive activity to Eplerenone 50 mg/day	hyperkalemia
ESAX-DN	Esaxerenone (CS-3150)	Evaluate efficacy and safety of different doses of Esaxerenone compared to placebo in T2D patients with microalbuminuria	Higher UACR remission rate and significant reduction in UACR	hyperkalemia
FIDELIO-DKD	Finerenone	Assess Finerenone efficacy and safety in reducing the progression of kidney disease, as measured by the composite endpoint of time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death	Reduced risk of CKD progression and CV events in patients with T2D and CKD	hyperkalemia
FIGARO-DKD	Finerenone	Composite of death from CV causes, nonfatal MI, nonfatal stroke, or HF hospitalization	Improved CV outcomes in patients with T2D and CKD	hyperkalemia
MIRACLE	Balcinrenone (AZD9977)	Evaluate the efficacy and safety of balcinrenone in combination with dapagliflozin on UACR	No significant reduction in UACR in patients treated with balcinrenone plus dapagliflozin compared with dapagliflozin plus placebo	dose-dependent hyperkalemia
FINEARTS-HF	Finerenone	Evaluate efficacy and safety in reducing CV death and HF events in patients with preserved ejection fraction ≥40%	Significantly reduced the composite of cardiovascular death and total (first and recurrent) heart failure events compared to placebo	hyperkalemia

MI: myocardial infarction, SBP: systolic blood pressure.

incident of nonfatal MI, acute coronary syndrome (ACS), hospitalization for HF, nonfatal stroke, or cardiovascular (CV) death [55]. The preliminary results presented at the American Society of Nephrology Kidney Week 2023 show no reduction of the primary composite endpoint but a potential reduction in the risk of HF hospitalization [56]. The other major trial with spironolactone in ESKD patients that is still ongoing is the aldosterone bloCkade for Health Improvement EValuation in End-stage renal disease trial (ACHIEVE, NCT03020303) with a primary endpoint of CV death or hypertensive HF (HHF) [57].

Side-effect profile and barriers to implementation of sMRA

Both steroidal MRAs carry the risk of potentially life-threatening hyperkalemia, particularly in patients with worsening kidney function when combined with other renin–angiotensin system blockers. However, Spironolactone has additional sexual side effects, including impotence and gynecomastia, due to its unselective binding to androgen and progesterone receptors. The underutilization of steroidal MRAs in patients with HFrEF, despite the proven mortality benefit, may be attributed to a lack of widespread educational initiatives and concerns regarding the perceived risk of hyperkalemia [58, 59].

Nonsteroidal MRA (nsMRA)

Nonsteroidal MRAs are a promising therapeutic option in managing conditions with MR overactivation. They offer a new mechanism of action that effectively blocks the MR without the hormone-like effects of sMRAs, which can cause adverse side effects. This breakthrough has opened up new possibilities in treating cardiovascular and renal diseases where MR overactivation is a major factor (Table 2) [44].

PF-3882845, discovered by Pfizer, and KBP-5074 (Ocedurenone) are nsMRAs that showed promise in preclinical studies. PF-3882845 demonstrated a superior therapeutic index compared to eplerenone in a preclinical CKD model [60]. Although phase I trials were conducted, further development was terminated in 2012 [61]. KBP-5074, closely related to PF-3882845, exhibited a 39-fold improved therapeutic index over eplerenone and is being investigated for treatment-resistant hypertension in CKD [62]. The BLOCK-CKD study, a phase II study, demonstrated its efficacy in reducing blood pressure with a lower risk of hyperkalemia [63]. Should these results be reproducible in a larger Phase III trial, KBP-5074 could add additional treatment options for resistant hypertension in people with advanced CKD.

AZD9977, a nsMR ligand, was discontinued in phase I due to safety and efficacy reasons in 2015 [64]. However, a recent phase II trial, MIRACLE (NCT04595370), explores balcinrenone (AZD9977) in combination with dapagliflozin in patients with HF and CKD and the effect of the combination in different doses of AZD9977 on urinary albumin-to-creatinine ratio after 12 weeks. The trial showed no significant reduction in urinary albumin-to-creatinine ratio (UACR) in patients treated with balcinrenone plus dapagliflozin compared with dapagliflozin plus placebo, with reduced estimated glomerular filtration rate (eGFR) in highest dose group [65].

Apararenone (MT-3995) showed weaker inhibitory potential on androgen-, progesterone-, and glucocorticoid receptors compared to spironolactone [66]. Clinical studies in patients with diabetic nephropathy (DN) demonstrated efficacy in reducing UACR, especially in those concomitantly receiving renin–angiotensin system (RAS) blockers [67]. While the antihypertensive effect was modest in patients with normal baseline blood pressure, a notable reduction in systolic blood pressure was observed in those with elevated baseline blood pressure [67]. However, despite promising results, Mitsubishi Tanabe decided to discontinue the development of apararenone [68].

Esaxerenone (CS-3150) exhibits a high binding affinity for the human MR surpassing both spironolactone and eplerenone [69]. The drug demonstrates selectivity for the MR over other steroid hormone receptors and has shown antihypertensive and cardiorenal protective effects in preclinical animal models [69]. A pivotal Phase III trial (ESAX-HTN, NCT02890173) in Japanese patients with essential hypertension demonstrated that esaxerenone is an effective antihypertensive, non-inferior to eplerenone, with superior blood pressure reductions at a 5 mg/day dosage [70]. Additionally, the ESAX-DN trial explored esaxerenone's efficacy and safety in type 2 diabetes (T2D) patients with microalbuminuria, showing positive outcomes but with a higher incidence of hyperkalemia compared to the placebo (4% vs 0.4% of patients, respectively) [71].

Finerenone, a potent antagonist at the human MR, demonstrates high selectivity (at least 500-fold) for the MR compared to spironolactone and eplerenone [72]. In non-diabetic kidney disease models, finerenone reduces proteinuria, and tubulointerstitial fibrosis [73]. It demonstrates anti-fibrotic efficacy in heart and kidneys, providing vascular benefits and improving endothelial dysfunction [74]. The drug exhibits blood pressure-independent effects and is associated with less kidney hypertrophy compared to eplerenone [75].

Clinical trials, including FIDELIO-DKD [76] and FIGARO-DKD [77], show finerenone's efficacy in reducing kidney failure, CV death, and morbidity in CKD patients with T2D [76, 77]. The primary outcome measured in the FIDELIO-DKD trial was a composite endpoint of the time to first occurrence of kidney failure, defined as either the initiation of chronic dialysis over 90 days or renal transplantation (ESKD) or a persistent decline in eGFR <15 ml/min/1.73 m^2 sustained for a minimum of 4 weeks. This primary endpoint was achieved as specified in the trial with an 18% reduction in the group on finerenone compared to those on placebo (HR: 0.82, 95% CI, 0.73–0.93, $P = .001$).76 Similarly, a 14% reduction in secondary composite CV outcome was seen in patients on finerenone compared to those on placebo (HR 0.86, 95% CI, 0.75–0.99, $P = .03$) [76]. The incidence of hyperkalemia-related discontinuation was higher in the finerenone group compared to the placebo group (2.3% and 0.9%, respectively) but markedly lower than the group on spironolactone on top of RAS blockade in CKD [78]. Thus, the FIDELIO-DKD trial showed that finerenone, when combined with optimized RAS blockade therapy, slows DKD progression and plays a role in CV event prevention, offering an effective treatment modality to patients with DKD.

Whereas the primary outcome measure in FIGARO-DKD involves a composite outcome of time to first occurrence of CV mortality and morbidity, as evaluated by the composite endpoint of time to first occurrence of CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF [77]. The key prespecified secondary endpoint is a composite evaluation of the time to first occurrence of kidney failure, a sustained decrease of eGFR $\geq$40% from baseline over at least 4 weeks, or renal death [77]. The primary composite CV outcome was reduced by 13% (HR 0.87, 95% CI, 0.76–0.98, $P = .03$), with the benefit driven primarily by a lower incidence of hospitalized HF (HR 0.71; 95% CI, 0.56–0.90), while the secondary composite kidney outcome was reduced non-significantly by 13% (HR 0.87, 95% CI, 0.76–1.01). Hence, FIGARO-DKD showed the association of finerenone with a lower risk of CV morbidity and mortality, particularly in terms of a lower incidence of hospitalized HF in patients with DKD (stage 2–4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria).

Additionally, FINEARTS-HF79, a recently published clinical trial evaluating finerenone's efficacy and safety in patients with HF and preserved or mildly reduced ejection fraction, showed that finerenone resulted in a significant decrease in composite of HF events and CV related deaths compared to placebo [79]. The primary outcome was a composite of total worsening HF events and death from CV causes. While the secondary outcomes included total worsening HF events, change from baseline in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), improvement in the New York Heart Association (NYHA) functional class, a kidney composite outcome, death from cardiovascular causes, and death from any cause. The study showed that finerenone was associated with a significantly lower rate of the primary outcome compared to placebo (rate ratio (RR) $= 0.84$, 95% CI, 0.74–0.95, $P = .007$) as well as the secondary outcome, namely worsening HF events or death from cardiovascular causes (RR 0.82, 95% CI, 0.71–0.94, $P = .006$). It also led to a moderate benefit in patient-reported health status (KCCQ total symptom score) (Difference 1.6, 95% CI, 0.8–2.3, $P < .001$) but did not significantly improve the NYHA functional class or the risk of the kidney composite outcome (OR $= 1.01$, 95%CI, 0.88–1.15, HR, 1.33, 95%CI, 0.94–1.89, respectively). However, one should keep in mind that the $>$50% of the patients had an eGFR >60 ml/min/1.73 m^2 with a median UACR <20 mg/g making this population not the ideal target to detect a benefit in kidney composite outcomes. Moreover, all the prespecified subgroups were underpowered, so the results of the subgroup analysis should be interpreted with caution [79].

Moreover, the FINE-ONE clinical trial80 (NCT05901831), a Phase III randomized and placebo-controlled study that is ongoing and actively recruiting, aims to evaluate the efficacy and safety of finerenone in patients with type 1 diabetes and CKD. The primary outcome is the relative change in UACR from baseline over 6 months. Secondary outcomes include the incidences of treatment-emergent adverse events, treatment-emergent serious adverse events, and hyperkalemia. The study aims to enroll ~220 adults with type 1 diabetes, UACR between 200 and 5000 mg/g, and eGFR between 25 and 90 ml/min/1.73 m^2. Participants will be randomized to receive either finerenone or a placebo in addition to standard care (ACE inhibitors or Angiotensin II receptor blockers). The primary efficacy analysis will assess the geometric mean ratio of the change in log UACR from baseline over 6 months between the finerenone and placebo groups. Safety will be evaluated by monitoring the number of

participants experiencing treatment-emergent and treatment-emergent serious adverse events, and hyperkalemia [80].

Similarly, the FIND-CKD trial, an ongoing and actively recruiting Phase III randomized controlled trial, aims to investigate the efficacy and safety of finerenone compared to placebo in slowing the progression of kidney disease in patients with CKD but without diabetes. The primary outcome is the mean annual rate of change in the eGFR from baseline to month 32. The secondary outcomes include a combined cardiorenal composite outcome comprising time to kidney failure, a sustained ≥57% decrease in eGFR, hospitalization for HF, or cardiovascular death; a kidney composite outcome comprising the onset of kidney failure or a sustained ≥57% decrease in eGFR from baseline; a cardiovascular composite endpoint comprising hospitalization for HF or death from cardiovascular-related causes. The trial will also assess the safety and tolerability of finerenone, with a particular focus on hyperkalemia as an adverse event of special interest.

Finerenone received FDA approval on 9 July 2021, for reducing the risk of sustained eGFR decline, ESKD, cardiovascular death, nonfatal MI, and hospitalization for HF in CKD patients associated with T2D [80]. Notably, available sMRAs are not indicated for this purpose.

CLINICAL IMPLICATIONS

Hyperkalemia

Hyperkalemia remains a significant challenge, particularly with MRA use. In the FINE-HEART pooled analysis, comparing finerenone with a placebo, it was found that 12.8% of patients taking finerenone experienced hyperkalemia, in contrast to 6.2% of those on the placebo, highlighting the importance of vigilant monitoring [81].

When finerenone was compared with spironolactone and eplerenone regarding the occurrence of serious hyperkalemia, distinct differences were observed. Within the FINE-HEART pooled analysis, the rate of finerenone discontinuation due to hyperkalemia was 1.3%. This is in comparison to spironolactone, which had a slightly higher discontinuation rate of 2% in the RALES study [46], and eplerenone, which had a lower rate of 1.1% in the EMPHASIS-HF study [48]. Additionally, the frequency of hospitalization due to hyperkalemia was 0.8% for those on finerenone. On the other hand, eplerenone showed a smaller percentage of 0.3%, and the rate for spironolactone was not provided [81, 46, 48].

Interestingly, patients on finerenone had a lower risk of hypokalemia compared to placebo in the FINE-HEART study (4.8% vs 10.1%, respectively) [81].

Prescription of MRAs

Healthcare providers can enhance the prescription rates of MRAs, by integrating these strategies into clinical practice, ultimately leading to better management of conditions associated with MR overactivation:

Education and awareness: providers maybe unfamiliar with this novel class of medications (nsMRA), its appropriate clinical use and adverse side effects making it difficult for them to assess the benefit-risk profile and thus prescribing the medication. Thus, educating physicians through continuing medical education programs, workshops, and seminars about the benefits and guidelines for MRA use is crucial.

Electronic health records: implementing electronic health record-embedded clinical decision support tools can prompt physicians to consider MRAs during patient encounters. These tools have been shown to increase MRA prescriptions by providing timely alerts and reminders about guideline-directed medical therapies.

Multidisciplinary team approaches: involving a team of healthcare professionals, including pharmacists and nurses, can improve the initiation and maintenance of MRA therapy. These teams can help monitor patients for side effects such as hyperkalemia and adjust dosages as needed, thus addressing one of the main barriers to MRA use. In clinical practice, physicians often reduce the dose of RAS inhibitors when serum [K^+] rises above 5.0 mmol/l, which makes it harder for them to prescribe another medication that carries a risk of hyperkalemia, such as spironolactone or finerenone. Thus, providing clinicians with a serum potassium monitoring schedule and a potassium management algorithm while on several hyperkalemia-inducing medications can help promote MRA usage. An algorithm similar to the one suggested by FIDELIO-DKD can be used as a reference point to develop a more extensive and intricate algorithm applicable to all the pillars of DKD (Fig. 2).

Patient education: educating patients about the importance of MRAs in managing their condition can improve adherence to prescribed therapies. Patients who understand the benefits and potential side effects are more likely to continue with their treatment plans.

Medication cost: the cost of the medications might be an issue for some patients on the basis of their insurance status making providers wary of prescribing the medications if the costs are high or unclear on the basis of the payer. Thus, advocacy with policymakers, payers, and pharmaceutical companies is needed to lower costs.

FUTURE PERSPECTIVES

Further education is warranted concerning the significance of MRA utilization in individuals with CKD and HF, despite the potential risk of hyperkalemia. Combining nsMRAs with potassium-binding agents may offer a pathway for high-dose MRA therapy with reduced hyperkalemia risk, a concept already under investigation with sMRAs and patiromer [78]. Results from the DIAMOND trial suggest that co-administration of patiromer is associated with a smaller increase in serum potassium, lower hyperkalemia rates, and less frequent reduction in MRA dose below target [82].

Ongoing trials and new data regarding the efficacy of SGLT2is and nsMRAs and their role in slowing down CKD progression and reducing CV risk seem to provide the optimal opportunity to use pillars of therapy in managing CKD after several years of therapeutic scarcity in this field. By combining RAS blockade with SGLT2i, MRA, and possibly Glucagon-like peptide-1 agonists, clinicians have the opportunity to target several key factors implicated in DKD progression, improving prognosis and slowing disease progression. Preclinical studies involving mouse models have demonstrated synergistic effects between finerenone and empagliflozin, particularly in reducing proteinuria and cardiac and renal fibrosis [83, 84]. Ongoing trials, such as the CONFIDENCE trial assessing finerenone in combination with empagliflozin, will provide further insights into potential synergies and therapeutic benefits in the context of HF and CKD [85].

In summary, physicians must receive education and apply evidence-based use of MRAs to maximize their benefits and minimize the side effects. As the clinical evidence evolves,

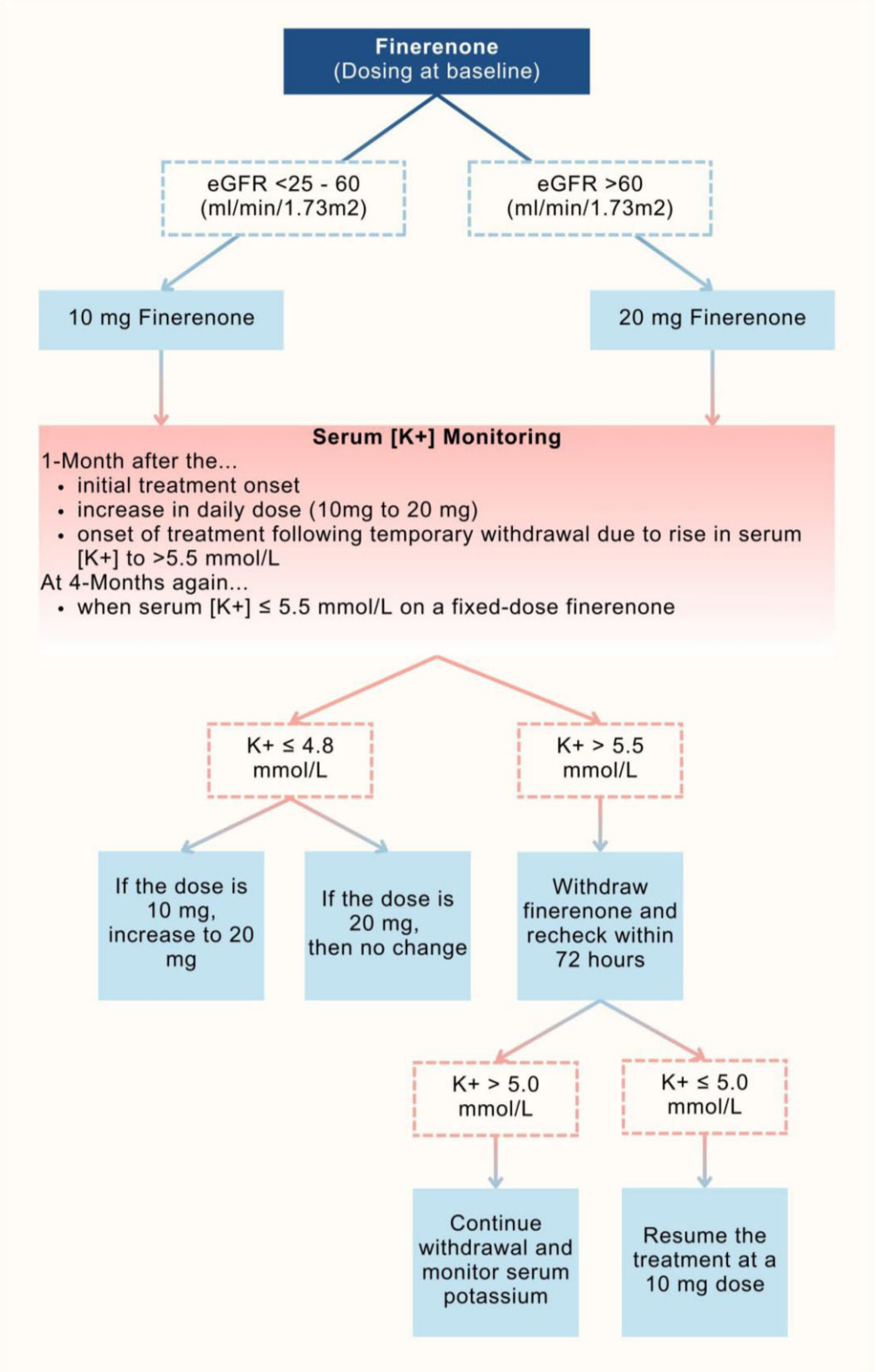

Fig.2 Proposed algorithm for finerenone dose adjustment based on serum potassium levels.

nsMRAs may emerge as a pivotal therapy across various cardiorenal disease scenarios.

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CONFLICT OF INTEREST STATEMENT

None declared.

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