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Mineralocorticoid receptor antagonists and reno-protection: What's the evidence & where do they fit? A guide for non-specialists

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Abstract

The role of aldosterone has yet to be well appreciated in chronic kidney disease (CKD). Two variables define CKD: an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 and a spot urine albumin-creatinine ratio of >30 mg/g. Both are needed for an accurate diagnosis. The presence of CKD at this level is associated with an elevated risk of cardiovascular death and a greater risk of CKD progression to kidney failure and subsequent dialysis. This paper presents an overview of aldosterone's importance in CKD and its contribution to the inflammatory processes involved in CKD development. Data on outcomes, both surrogate and hard, related to outcomes on CKD progression will also be discussed in the context of mineralocorticoid blockade. Based on recent epidemiological data as well as data examining markers of diabetic kidney disease progression, it is clear that use of both renin-angiotensin system inhibitors and aldosterone receptor antagonists have a significant role in altering the natural history of kidney disease progression itself, as well as reducing the risk of cardiovascular events that generally accompany long-standing kidney disease. This paper will discuss these issues and the management of consequent hyperkalaemia when both steroidal and non-steroidal mineralocorticoid receptor antagonists are used in detail.

KEYWORDS
diabetes, evaluation, kidney, nephropathy

1 | INTRODUCTION

First, it is essential to define the most common causes of kidney failure worldwide and how they are classified to understand when mineralocorticoid receptor antagonists (MRAs) should be used. Chronic kidney disease (CKD) is defined by Kidney Disease: Improving Global Outcomes (KDIGO) as an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 and a spot urine albumin-creatinine ratio (UACR) of >30 mg/g[1] (Figure 1). The presence of CKD at this level is associated with an elevated risk of cardiovascular death and a greater risk of CKD progression to kidney failure and subsequent dialysis.[1] CKD is asymptomatic until the late stages of the disease, i.e. losing at least 75%-80% of kidney function (eGFR <25 ml/min/1.73 m^2). The primary symptoms at that time are tiredness and lack of energy, primarily because of anaemia and electrolyte abnormalities such as

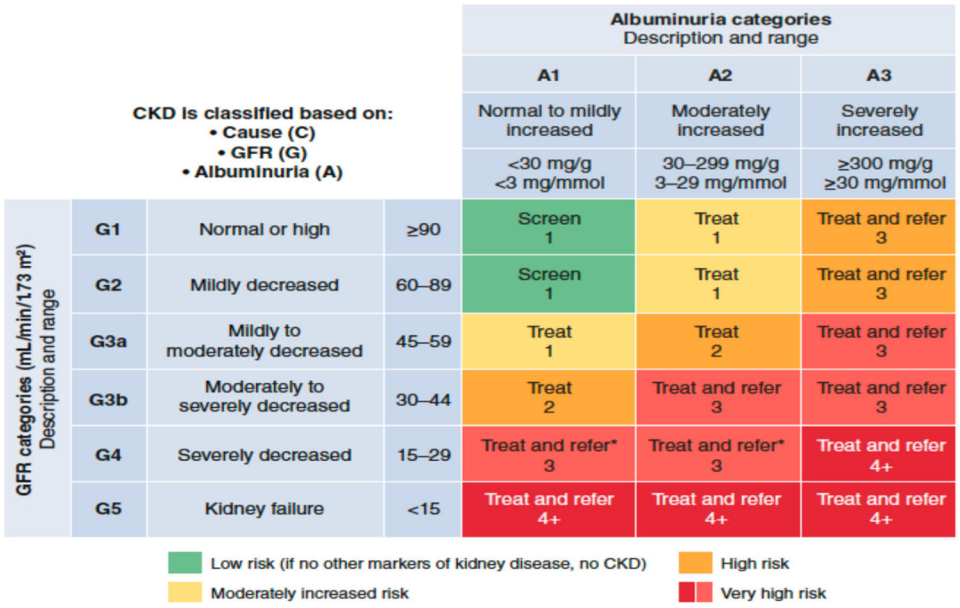


FIGURE 1 Kidney Disease: Improving Global Outcomes (KDIGO) Heat Map. The colours indicate the level of risk, with red being the highest and green the lowest. The heat map also defines when the practitioner should treat and refer the patient for help. CKD, chronic kidney disease; GFR, glomerular filtration rate.

elevated potassium levels and lower bicarbonate levels with associated acidosis.

Worldwide, the two most common causes of CKD are diabetes and poorly controlled hypertension, which have been present for many years, in that order.[2] Together, they account for about 72% of kidney failure worldwide. This is important as there is 12 fold increase in cardiovascular risk and almost five fold higher risk of all cause mortality when the eGFR is <45/ml/min/1.73 m^2.[1] Hence, it is critical to identify CKD early and prevent progression. In addition, the data are very clear that >300 mg/day of albuminuria is not only evidence of kidney disease but also elevated CV risk, and the relationship is linear as levels increase.[3,4] There are two critical things to remember when measuring albuminuria: first, small amounts of albuminuria >30 mg/g are a risk marker for heart failure,[5] and second, new guidelines from the American Diabetes Association, as well as recent trial data, suggest a >30% sustained decrease in albuminuria is needed to slow CKD progression.

To appreciate changes in kidney function and alterations in cardiorenal risk, one must be familiar with the KDIGO heat map (Figure 1).[6] Over the past few decades, the decline in kidney function has been relatively stable; the United States Renal Data System (USRDS) 2023 showed that 14.0% of US adults had low eGFR <60 ml/min/1.73 m^2, albuminuria >30 mg/g, or both.[7] Using the KDIGO risk classification, 10.5% had moderate-risk disease, 2.4% had high-risk disease and 1.1% had very high-risk disease. During this period, CKD prevalence was highest in Black individuals (18.8%) and lowest in Hispanic individuals (12.0%) (Figure 2).[7]

Treating those with CKD requires using maximally tolerated doses of a renin-angiotensin system blocker, as used in all outcome trials testing the efficacy and an inhibitor of the sodium-glucose cotransporter 2 (SGLT2).[8,9] Recent analyses of outcome studies in people with kidney disease from diabetes indicate that the use of four 'pillars of therapy' may provide maximum slowing of CKD progression. These pillars include the aforementioned agents as well as the addition of a non-steroidal MRA and a glucagon-like 1 peptide receptor agonist.[8] This article will concentrate on the data affected by MRAs.

Before examining the effects of MRAs, it is crucial to understand where aldosterone is produced and its role in cardiorenal disease. Most people think it is produced only by the adrenal glands. This is not true; other body areas, such as fatty tissue, produce aldosterone at lower levels. Thus, obesity is a state of relative hyperaldosteronism at low levels.[10–12] Note that substantial weight loss reduces these levels.

MRAs block the receptor for the hormone aldosterone, which your body makes. Aldosterone causes your kidneys to hold on to salt and water, raising your blood pressure. It is one way your body naturally adjusts blood pressure in your blood vessels.

The effects of MR stimulation on the kidney beyond sodium and potassium homeostasis have now been the focus of data derived from the Chronic Renal Insufficiency in Cohort (CRIC) study. This long-term study evaluated the association between serum aldosterone concentrations and kidney disease progression among 3680 participants.[13] The primary outcome of CRIC was CKD progression (defined as the composite of a 50% decline in eGFR or end-stage kidney disease), whichever occurred first over a median follow-up of 9.6 years. They found that higher aldosterone concentrations were associated with lower eGFR, lower serum potassium, higher urinary potassium and greater protein excretion. Over 38% (n = 1412) of the 3680 patients developed CKD progression. The main finding by the authors was that 11% of the group had an increased risk of CKD progression for each doubling of serum aldosterone value. Moreover, individuals with the highest quartile of serum aldosterone had a 45% increased risk of CKD progression. These data support the concept that higher serum aldosterone levels among individuals with CKD are independently

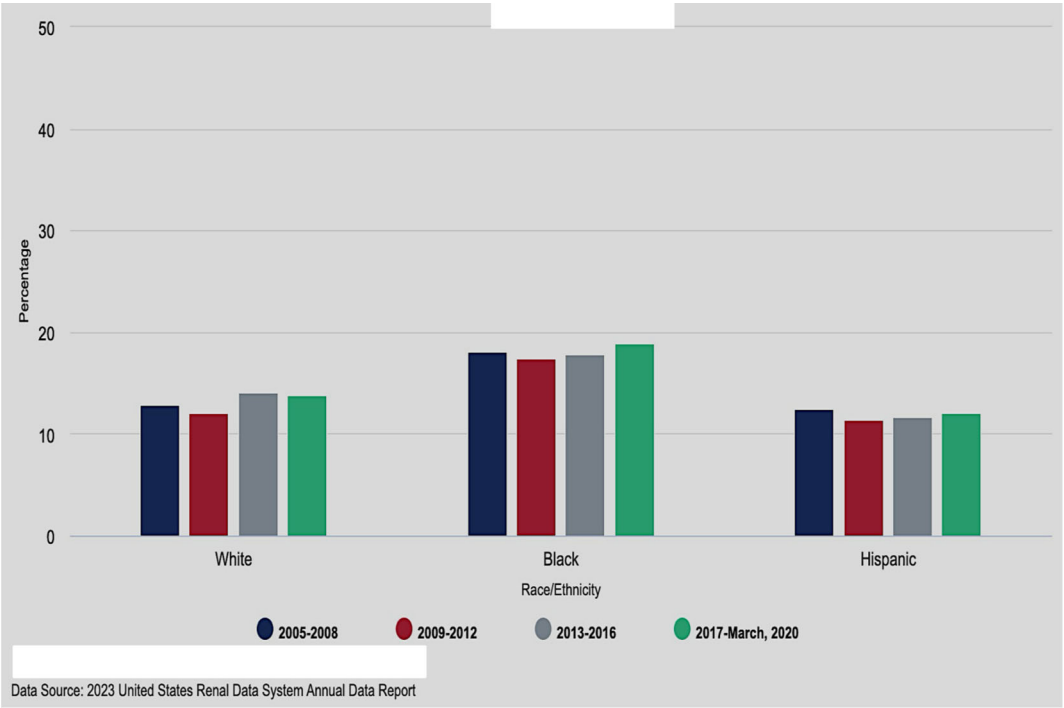


FIGURE 2 Prevalence of CKD in United States Adults 2023 by different Race and Year. Adapted from the United States Renal Data Service 2024.

associated with increased risk for kidney disease progression, irrespective of concomitant diabetes.

While there are abundant animal data on aldosterone in both the heart and the kidney, in humans, the bulk of the data on aldosterone receptor antagonists are in heart failure rather than kidney failure.[14] Studies in kidney disease are limited to albuminuria reduction as the hyperkalaemia magnitude precludes an outcome study.[15]

2 | ROLE IN NEPHROPATHY (WITH AND WITHOUT DIABETES)

Aldosterone contributes to the pathogenesis of CKD in various disease states. Persistent activation of the MR by aldosterone in renal cells can cause glomerulosclerosis, proteinuria and a chronic, accelerated decline in GFR.[16–18] Inhibition of aldosterone with a non-steroidal MRA is proven to slow decline in kidney function and albuminuria, as well as heart failure hospitalization.[19] This is not true for spironolactone, which was only shown to reduce albuminuria and mortality in patients with heart failure with reduced ejection fraction in the Randomized Aldactone Evaluation Study (RALES).[20]

Diabetic kidney disease occurs in about 40% of patients with type 2 diabetes mellitus.[21] The MR is expressed in all kidney cells, but those with diabetes have increased MR expression in their renal leukocytes compared with healthy controls.[22] Activation of the MR in the immune cells has been shown to contribute to the pathogenesis of cardiovascular and renal disease.[23]

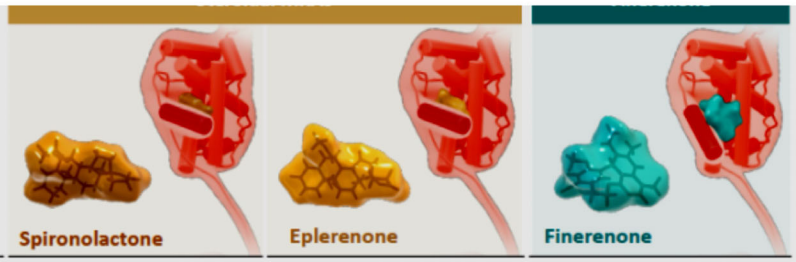
Inhibition of the renin-angiotensin system with angiotensin-converting enzyme inhibitors and aldosterone receptor blockers can slow but not halt the progression of diabetic kidney disease.[24] Aldosterone 'escape' or 'breakthrough' is unfortunately common in patients treated long-term with renin-angiotensin system blockers.[25,26] This breakthrough is associated with an accelerated decline in eGFR and increased albuminuria in patients with diabetic kidney disease. This highlights another area where adding MRA therapy can improve outcomes.

MRAs effectively treat CKD, even in patients without diabetes. A systematic review showed a significant decrease in proteinuria when MRAs were added to renin-angiotensin system blockers, regardless of diabetes status.[27] However, hyperkalaemia is a major limiting factor.

3 | STEROIDAL AND NON-STEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONISTS

Steroid hormone receptors comprise a subfamily of nuclear receptors that act as intracellular receptors and nuclear transcription factors. This subfamily consists of the androgen receptor, glucocorticoid receptor (GR), MR, progesterone receptor and oestrogen receptors.[28] The GR is activated by cortisol, whereas the MR is promiscuous, with the same binding affinity for aldosterone and cortisol.[29] MRs mediate fluid, electrolyte and haemodynamic homeostasis, as well as tissue repair.[28,29] GR modulation impacts energy homeostasis, stress responses and inflammation.[28] Because MRs and GRs are often

(A)



	Spironolactone	Eplerenone	Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	-
Sexual side effects	++	(+)	-
Half-life	> 20 hours	4-6 hours	2-3 hours
Active metabolites	++	-	-
Effect on BP	+++	++	+

(B)

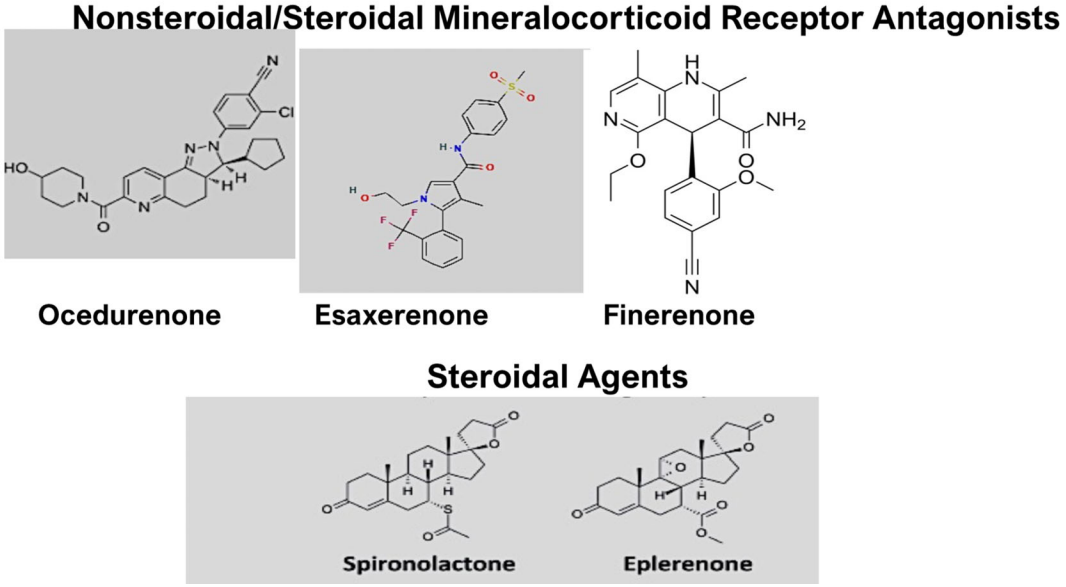


FIGURE 3 (A) Comparison of mineralocorticoid receptor antagonist (MRA) inhibitors: steroidal and non-steroidal comparison of MRA inhibitors: steroidal and non-steroidal. There are differences in half-life among the non-steroidal MRAs and some other properties, but they are similar in how they interact with the receptor with bulky shape. (B) Different chemical structures of non-steroidal mineralocorticoid inhibitors that are approved in the world. BP, blood pressure; CNS, central nervous system.

expressed in the same tissues and cells, regulating their functional interactions is critical to maintaining homeostatic balance.

Interestingly, progesterone also acts as an endogenous MRA because it can compete with aldosterone for MR binding with similar affinity. Overactive or persistent activation of the MR has been implicated in the pathogenesis of hypertension, heart failure, and CKD. In contrast, blockade of the receptor with a MRA is part of an effective strategy to treat and possibly prevent these problems.[30] However, many patients who would benefit from treatment with an MRA are not prescribed one.

MR activation by aldosterone contributes to hypertension. Ligand-activated MR in the renal epithelial cells of the distal tubule and collecting duct induces sodium and water reabsorption and potassium excretion, increasing extracellular volume and blood pressure.[31] Primary aldosteronism from excess adrenal aldosterone production is the most common secondary cause of hypertension and can be

treated with MRAs. Unfortunately, primary aldosteronism is widely underdiagnosed.[32,33]

Beyond primary aldosteronism, other medical conditions such as obesity and diabetes can also result in elevated aldosterone levels, contributing to hypertension, cardiovascular disease and kidney disease.[34] This knowledge supports using MRAs in treating these conditions, irrespective of elevated blood pressure.

Steroid MRAs have been consistently beneficial in patients with CKD by decreasing albuminuria and improving blood pressure; there are no outcome data, however, on slowing the decline in eGFR. All studies with steroidal MRAs show an increased risk of adverse events, particularly hyperkalaemia and, in some cases, significant decreases in eGFR. In all studies, hyperkalaemia frequently led to premature discontinuation of therapy.

4 | UNDERSTANDING STEROIDAL VERSUS NON-STEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONISTS

There are clear, apparent differences between the steroidal and non-steroidal MRAs (Figure 3A). These are not only structural but also in terms of action and durability. Steroidal MRAs were initially developed in the late 1950s, and spironolactone was the active prototype.[35] However, spironolactone is a prodrug metabolized into several other biologically active metabolites, including canrenone and 7-α-thiomethyl spironolactone.[36] These active metabolites have long half-lives and can accumulate. This is evident in a clinical setting, where spironolactone metabolites were measured in patients with an eGFR of 25-45 ml/min/1.73 m^2. In this study, 38% of patients had detectable urinary levels of metabolites up to 3 weeks after stopping treatment.[35] In addition, steroidal MRAs do not have the same anti-inflammatory ability as non-steroidal agents when eplerenone is compared with finerenone.[35]

Non-steroidal MRAs are a new class of agents distinguished from steroidal MRAs by numerous factors (Figure 3A, B). They were developed to deliver similar benefits as steroidal agents without the high hyperkalaemia risk. The first non-steroidal MRA approved for use by the FDA was finerenone. The differences in their chemical structures are shown in Figure 3(A,B).

One significant difference between the two classes is tissue-binding characteristics (Figure 3A). Non-steroidal MRAs have a unique binding mode that determines potency, selectivity and nuclear cofactor recruitment, while their physicochemical properties, including lipophilicity and polarity, to determine tissue penetration and distribution. These properties offer a novel MRA pharmacology with pronounced anti-fibrotic efficacy in animal models.

Non-steroidal MRAs were developed to retain the clinical efficacy of steroidal MRAs while reducing adverse effects, specifically hyperkalaemia.[28] The non-steroidal MRAs show fewer side effects, including less hyperkalaemia, because of their higher selectivity for the MR and unique binding method.[30] In addition, increased potency allows for lower dosages of the non-steroidal MRAs.[37]

MR mediates fluid, electrolyte, haemodynamic homeostasis and tissue repair.[32] GR modulation impacts energy homeostasis, stress responses and inflammation.[38] Because MRs and GRs are often expressed in the same tissues and cells, regulating their functional interactions is critical to maintaining homeostatic balance.[38] It is noteworthy that progesterone also acts as an endogenous MRA because it can compete with aldosterone for MR binding with similar affinity. This helps to explain the hormonal side effects associated with spironolactone, such as changes in menstruation and gynaecomastia.

While there are five different non-steroidal MRAs, only two are approved, one only in Japan, and a third, ocedurenone, is under active development. Esaxerenone in Japan was developed for hypertension, and finerenone was the first to be approved internationally for reduced cardiorenal events (Figure 3B). As a result, much of the data we have on non-steroidal MRA pharmacology comes from early studies of finerenone and, to a certain extent, esaxerenone.

Finerenone acts as a 'bulky antagonist', as do all non-steroidal agents, meaning that the binding of finerenone changes the conformation of the MR so that it can no longer assume the agonist position.[39,40] This is in stark contrast to spironolactone, which retains some aldosterone-like activity.[39] Finerenone, therefore, has differential downstream effects on MR blockade. Compared with the steroidal MRAs, finerenone is less lipophilic with an increased polarity that alters tissue distribution and tissue penetration (Figure 3A).[41] The greater polarity also reduces the likelihood of finerenone crossing the blood-brain barrier.[41]

Compared with spironolactone, finerenone delays the aldosterone-induced translocation of the MR from the cytoplasm into the nucleus, which exerts its effect on transcription.[39] Finerenone also reduces the binding of transcriptional cofactors to a greater extent than spironolactone.[39]

5 | NON-STEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONISTS

5.1 | Finerenone

The FDA approved finerenone in July 2021 to reduce the risk of kidney function decline, kidney failure, cardiovascular death, non-fatal heart attacks, and hospitalization for heart failure in adults with CKD from type 2 diabetes mellitus.[42] Approximately 2.2 million adults in the United States are estimated to meet at least one criterion to qualify for finerenone.[43]

Two phase 3 trials, multicentre, double-blind, placebo-controlled trials, involved patients with type 2 diabetes mellitus and CKD. In this study, CKD was defined as either (a) eGFR of 25-59 ml/min per 1.73 m^2 with a UACR of 30-299 mg/g and diabetic retinopathy, or (b) eGFR of 25-74 ml/min per 1.73 m^2 with a UACR of 300-4999 mg/g. In Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD), the primary efficacy outcome was time-to-event of a composite of kidney failure, sustained

≥40% decrease in eGFR from baseline, or renal deaths.[19] In contrast, the secondary efficacy outcomes were the time-to-event of a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure and a sustained ≥57% decrease in eGFR from baseline (equivalent to a doubling of the serum creatinine).[18] The primary and secondary efficacy outcomes were reversed in the Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes (FIGARO-DKD) trials to facilitate the FIDELITY pooled analysis.[18]

The FIDELITY pooled analysis examined 13 026 patients derived from both the FIDELIO and FIGARO trials who were followed for a median of 3 years.[18] Please note that a diagnosis other than Stage 1 heart failure was exclusionary in the FIDELIO trial. Compared with the placebo, the patients who received finerenone had a 23% risk reduction in the composite renal outcome (including a 20% risk reduction in progression to end-stage renal disease) and a 14% risk reduction in prespecified cardiovascular events.[44] A decrease in heart failure hospitalization and cardiovascular deaths primarily drove the reduction in cardiovascular events. Those treated with finerenone also had a modest decrease in mean ± SD systolic blood pressure (−3.2 ± 15.0 mmHg) compared with placebo (0.5 ± 14.6 mmHg). However, the patients' blood pressures were relatively well controlled at baseline, with a mean systolic blood pressure of 136.7 ± 14.2 mmHg. Patients with poorly controlled blood pressure may theoretically see a further reduction.

A sub-analysis was performed on the FIDELIO-DKD population to determine the effect of finerenone when used together with a SGLT2 inhibitor.[45] Of the 5674 patients in the study, 259 (4.6%) were being treated with an SGLT2 inhibitor at baseline. The combination group had a significant benefit in further reducing heart failure hospitalizations and further protecting against hyperkalaemia (8.1% vs. 18.7%).

Regarding safety, rates of adverse events, including severe and adverse kidney events, were not statistically different. Hyperkalaemia-related adverse events did occur more frequently in the finerenone group compared with placebo (14% vs. 6.9%), but this infrequently led to treatment discontinuation (1.7% vs. 0.6%), and no events were fatal. There were no differences in other clinically significant side effects, including gynaecomastia, impotence and menstrual irregularities. One final fact is that while the inclusion criteria were serum potassium <4.8 mEq/L at screening, many patients at baseline had a serum potassium of 5.0 mEq/L and were admitted into the trial. Moreover, the FDA label for finerenone indicates it can be started up to a serum potassium level of 5.0 mEq/L.[46] In the trial, everyone was given general guidance about low-potassium diets initially and periodically. Among the highest-risk group for hyperkalaemia, i.e. those with eGFR <45 ml/min/1.73 m^2, 93/3908 (2.3%) people developed hyperkalaemia necessitating study termination versus 31/3900 (0.8%) in the placebo group.[44] In this very small subgroup of potassium >5.5 mEq/L, potassium binders such as sodium polystyrene sulphonate were used on a limited basis because of their tolerability. Newer, better-tolerated potassium binders had just become available during the last years of the trial. However, these newer agents, sodium zirconium cyclosilicate and patiromer, are tolerated well and allow the patient to continue cardiorenal protective therapy based on observational data. Data for each agent showing daily use for 1 year show both the efficacy and tolerability of these binders, which can serve as 'enablers' for evidence-based kidney-preserving therapy to be used.[47,48]

6 | OTHER NON-STEROIDAL AGENTS

6.1 | Ocedurenone (KBP-5074)

Ocedurenone is a novel non-steroidal MRA manufactured by KBP BioSciences that has a higher affinity and selectivity for the MR when compared with the steroidal MRAs (Figure 3B).[49] This agent is being developed for resistant hypertension and slowed kidney disease progression. Preclinical animal studies utilizing Dahl salt-sensitive rats and stroke-prone spontaneous hypertensive rats showed that ocedurenone performed better than eplerenone at lowering blood pressure, decreasing albuminuria and reducing renal injury.[49] In addition, ocedurenone showed no significant change in serum levels of creatinine or potassium. The safety of varying doses of ocedurenone was also confirmed in rat and canine models.

Based on the above data, a phase 2b clinical trial, BLOCK-CKD, was conducted.[50] This was a multicentre, randomized, double-blind, placebo-controlled study involving 162 patients with resistant or poorly controlled hypertension and advanced CKD (stage 3B-4). Patients were randomized to receive treatment with ocedurenone 0.25 mg, ocedurenone 0.5 mg, or placebo daily for 12 weeks. All patients were on stable doses of at least two background antihypertensive medications (non-potassium sparring diuretics, renin-angiotensin system blockers and calcium channel blockers) and had a resting, trough-seated systolic blood pressure of 140-179 mmHg before randomization. The primary efficacy endpoint, the baseline change in the seated systolic blood pressure, was met. The placebo-subtracted systolic blood pressure decreased by 7 mmHg in the ocedurenone 0.25 mg group ($p = .04$) and by 10.2 mmHg in the ocedurenone 0.5 mg group ($p = .0029$). In an exploratory analysis, the reduction in systolic blood pressure was comparable between patients taking less than two versus three antihypertensives at baseline.

The secondary efficacy outcomes showed a trend towards benefit for patients receiving ocedurenone, although neither the change in diastolic blood pressure nor the change in UACR was statistically significant. In total, 125 of the 162 participants (77.2%) had albuminuria at baseline, with a wide range of albuminuria present (UACR ranged from 31.2 to 7971 mg/g). Using the median UACR values, there was a trend towards UACR reduction in those treated with ocedurenone, but it was not statistically significant.

In terms of safety, potassium levels increased in all three groups studied. The incidence of hyperkalaemia (serum potassium ≥5.6 mmol/L) increased in all groups. Still, it was most frequent for the ocedurenone 5 mg group (13% of patients vs. 9.8% in the 2.5 mg group and 8.8% in the placebo group). There were no instances of

severe hyperkalaemia (serum potassium ≥6 mmol/L). No significant change in the eGFR was observed for either of the ocedurenone groups when compared with placebo.

A phase 3 trial of ocedurenone (CLARION) is currently in the recruitment stage (NCT04968184). This is a multicentre, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety and durability of ocedurenone in adults with Stage 3B/4 CKD and uncontrolled hypertension on two or more antihypertensive medications. This study is not estimated to be completed until early 2025.

6.2 | Esaxerenone

Esaxerenone, developed by Daiichi Sankyo, has a high oral bioavailability and a long half-life of approximately 30 h (Figure 3B).[51,52] In preclinical studies, esaxerenone showed higher selectivity for the MR than steroidal MRA. Unlike spironolactone and eplerenone, esaxerenone did not show any agonistic effect on the MR. In addition, esaxerenone blocked aldosterone-induced transcriptional activation of the MR with more potency than the steroidal MRAs.[51]

Based on positive outcomes from two phase 3 clinical trials, esaxerenone was first approved in Japan in January 2019 to treat hypertension.[53] The first, ESAX-HTN, was a phase 3 study that compared the effects of esaxerenone and eplerenone in 1001 hypertensive Japanese patients.[54] After a washout period, patients were randomized to receive esaxerenone 2.5 mg, 5 mg, or eplerenone 50 mg daily for 12 weeks. Blood pressure was assessed by calculating the mean of three sitting clinic blood pressures for the primary efficacy endpoint. At the end of the 12 weeks, there was a significant decrease in both systolic and diastolic blood pressures with esaxerenone 5 mg compared with eplerenone 50 mg daily. Systolic blood pressure decreased by −4.8 mmHg (95% CI −6.4 to −3.1, $p < .0001$), and diastolic blood pressure decreased by −2.2 mmHg (95% CI −3.3 to −1.3, $p < .0001$). While there was a trend towards greater systolic and diastolic blood pressure reduction in the esaxerenone 2.5 mg group compared with the eplerenone 50 mg group, they were not statistically different. A secondary efficacy endpoint using 24 h ambulatory blood pressure monitoring showed esaxerenone 2.5 mg had a more significant systolic blood pressure reduction than eplerenone [−2.6 (95% CI −4.6 to −2.6), $p < .01$] while esaxerenone 5 mg had greater systolic and diastolic blood pressure reduction than eplerenone [systolic blood pressure −6.5 (95% CI −8.4 to −4.5), $p < .0001$ and diastolic blood pressure −3.1 (95% CI −4.1 to −2.1), $p < .001$].

Regarding safety, the proportion of patients with two consecutive potassium levels of ≥5.5 mEq/L or one potassium level of ≥6.0 mEq/L was low, 0.9% in the esaxerenone 2.5 mg group, 0.6% in the esaxerenone 5 mg group and none in the eplerenone group.

The second trial, ESAX-DN, was a placebo-controlled phase 3 study that evaluated the effects of esaxerenone on 455 Japanese patients with hypertension, type 2 diabetes and diabetic kidney disease who were already being treated with a renin-angiotensin system blocker.[55] All patients had microalbuminuria (a UACR of 45-299 mg/g) and an eGFR ≥ of 30 ml/min per 1.73 m^2. The patients were randomized to receive a placebo or esaxerenone daily for 52 weeks. Those receiving esaxerenone were initiated at 1.25 mg daily, but the dose was increased to 2.5 mg based on serum potassium monitoring. The primary efficacy endpoint was the proportion of patients with resolution of microalbuminuria, defined as a UACR <30 mg/g and at least ≥30% reduction in UACR from baseline. At the end of the 52 weeks, significantly more patients in the esaxerenone group had resolution of their microalbuminuria, with the between-group difference being 18% (95% CI 12-25%, $p < .001$). Those in the esaxerenone group would also probably achieve remission sooner. The results did not differ in the prespecified subgroups based on baseline eGFR, UACR, blood pressure, or co-administration with dipeptidyl peptidase 4 or SGLT2 inhibitors.

Regarding safety, patients in the esaxerenone group had significant elevations in serum potassium and substantial reductions in eGFR compared with baseline.[55] The proportion of patients with two consecutive potassium levels of ≥5.5 mEq/L or one potassium level of ≥6.0 mEq/L was 9% (compared with 2% in the placebo group). This led to a higher discontinuation rate because of hyperkalaemia in the esaxerenone group (4% vs. 0.4% in the placebo group). The percentage reduction in eGFR compared with baseline was 11% in the esaxerenone group versus 1% in the placebo group. Still, the final eGFRs during a 4-week follow-up after the study were comparable.

7 | HYPERKALAEMIA RISK AND MANAGEMENT

MRAs can cause increased potassium levels by blocking the activation of the MR in the distal nephron, reducing potassium excretion.[29] In general, people at highest risk for hyperkalaemia from MRAs are those with an eGFR <45 ml/min/1.73 m^2 and a serum potassium level >4.5 mEq/L who are already receiving a diuretic appropriate for reduced kidney function.[56]

A meta-analysis showed a homogeneous 3.06-fold increased relative risk of hyperkalaemia (95% CI 1.26-7.41) when steroidal MRAs were added to a renin-angiotensin system blocker compared with the blocker alone.[57] Compared with placebo, each non-steroidal MRA was associated with a more significant increase in serum potassium level, independent of baseline renin-angiotensin system blocker use.[50,54,55,58] Thus, while all classes of MRAs will raise potassium, the question is one of magnitude and management.

For many reasons, non-steroidal MRAs are hypothesized to cause less hyperkalaemia than steroidal MRAs.[28] In a comparator study, there was far less hyperkalaemia with finerenone than with spironolactone (Figure 4).[59] In comparing the magnitude of potassium change in CKD between steroidal and non-steroidal MRAs, a comparative analysis was done between two separate studies, a subset of the FIDELITY pooled analysis cohort and the AMBER trial. Each database was composed of people with: (a) guideline-defined resistant hypertension, i.e. a maximally dosed renin-angiotensin system blocker, calcium channel blocker and thiazide-like diuretic, with BP >130/80; (b) presence of Stage 3b or 4 CKD; and (c) effects on these two

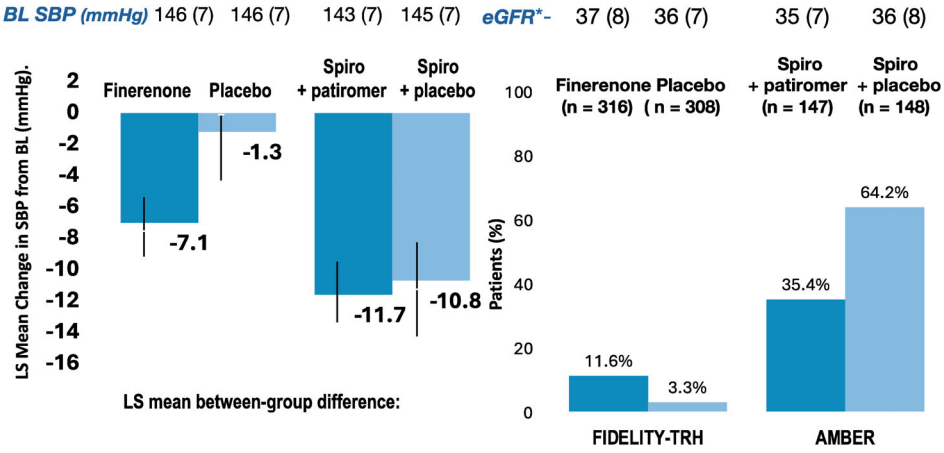


FIGURE 4 Comparison of spironolactone with finerenone in a subset of patients with true resistant hypertension with comparable eGFRs.[59] BL, baseline; eGFR, estimated glomerular filtration rate; LS, least squares; SBP, systolic blood pressure.

classes of agents' serum potassium within 3-4 months (Figure 4). It should be noted that the AMBER trial tested whether those needing guideline-recommended spironolactone to treat resistant hypertension could tolerate it if a potassium binder was concomitantly given, in this case, patiromer. Figure 4 shows that while finerenone was not as good an antihypertensive agent, it yielded a far lesser rise in potassium than spironolactone. There is over three times more hyperkalaemia with spironolactone, even with a binder, than with finerenone (Figure 4). This low level of hyperkalaemia risk is also evident with ocedurenone in the BLOCK-CKD trial.[50]

The approach to managing hyperkalaemia used in the finerenone trials is outlined in the Physicians' Desk Reference.[46] Serum potassium was measured at screening, and diuretic type and dose were evaluated to ensure an appropriate diuretic for kidney function. There was education about a low potassium diet, and as long as serum potassium was ≤5 mEq/L, a low dose of the non-steroidal agents started. Recheck potassium level in 1 month, and if still <5 mEq/L, increase to the highest dose and recheck in a month. If still in a safe range, continue. Other details are found in the Physicians' Desk Reference.

It should be known that hypokalaemia can be just as dangerous as hyperkalaemia. A review of over 911 000 people from a database showed that a U-shaped association was noted between serum potassium and mortality in all groups, with the lowest all-cause mortality in controls with potassium values between 4.0 and <5.0 mEq/L.[60] Higher mortality rates were noted in those aged ≥65 versus 50-64 years. Lastly, all-cause mortality was significantly elevated for every 0.1 mEq/L change in potassium between <4.0 and ≥5.0 mEq/L.

8 | CONCLUSIONS

There is a clear benefit to utilizing MRAs in patients with resistant hypertension, heart failure and CKD. Still, steroidal MRAs are underutilized in practice, primarily for fear of hyperkalaemia. This has led to a flurry of development of non-steroidal MRAs that have similar benefits with fewer side effects, specifically less risk of hyperkalaemia. One such agent, finerenone, is approved in patients with diabetic nephropathy, whereas no such steroidal agent has this indication. The development of non-steroidal MRAs will significantly expand the benefits the patient may receive with far less safety risk.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable for this article as no new data were created or analyzed in this study. All the data were acquired from already peer-reviewed published manuscripts.

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