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Differentiation between emerging non-steroidal and established steroidal mineralocorticoid receptor antagonists: head-to-head comparisons of pharmacological and clinical characteristics

Jonatan Barrera-Chimal , Peter Kolkhof, Ixchel Lima-Posada , Alexandre Joachim , Patrick Rossignol, Frederic Jaisser

Abstract

Introduction: Mineralocorticoid receptor (MR) antagonists (MRAs) provide cardiorenal protection. However steroidal MRAs might induce hyperkalemia and sex hormone-related adverse effects. Several novel non-steroidal MRAs are being developed that are highly selective for the MR and may have an improved safety profile.

Areas covered: This narrative review summarizes data from head-to-head comparisons of emerging non-steroidal MRAs with older steroidal MRAs, including pharmacological characteristics, pharmacokinetic properties, clinical outcomes, and safety, and highlights similarities and differences between emerging agents and established steroidal MRAs.

Expert opinion: Head-to-head comparisons in phase 2 trials suggest that the new non-steroidal MRAs exhibit at least equivalent efficacy to steroidal MRAs but may have a better safety profile in patients with heart failure and/or kidney disease. When also taking into account data from recent phase 3 placebo-controlled trials, these novel non-steroidal MRAs have the potential to provide a cardiorenal benefit above that of current optimized standard-of-care treatment in a high-risk population with reduced renal function, with a low risk of hyperkalemia. To optimize therapy, further research is needed to clarify the molecular differences in the mode of action of non-steroidal MRAs versus steroidal MRA, and biomarkers that are predictive of MRA response need to be identified and validated.

Keywords: AZD9977, cardiorenal disease, chronic kidney disease, esaxerenone, finerenone, heart failure, hypertension, KBP-5074, non-steroidal mineralocorticoid receptor antagonists

Article highlights

- Mineralocorticoid receptor (MR) antagonists (MRAs) provide cardiorenal protection. However steroidal MRAs might induce hyperkalemia and sex hormone-related adverse effects.
- Novel non-steroidal MRAs are being developed that are highly selective for the MR and may have an improved safety profile.
- The physiochemical properties of these compounds provide potential advantages compared with steroidal MRAs with respect to organ protective effects and a reduced risk of severe hyperkalemia.
- Non-steroidal MRAs differ from each other with respect to tissue distribution, structural properties, MR binding modes, and the ability to modulate co-regulator recruitment to target genes involved in cardiac and renal tissue damage.
- Non-steroidal MRAs exhibit at least equivalent efficacy to steroidal MRAs but may have a better safety profile in patients with heart failure and/or kidney disease.
- Non-steroidal MRAs have the potential to provide cardiorenal benefit above that of current standard-of-care treatment in high-risk patients with reduced renal function, with a low risk of hyperkalemia.

1. Introduction

The mineralocorticoid receptor (MR) is expressed in various cells and tissues, including the kidney, heart, vasculature and immune cells amongst others, and is involved in fluid and electrolyte balance, haemodynamic homeostasis, and tissue injury [1,2]. Overactivation of the MR promotes inflammation, oxidative stress and fibrosis, and is implicated in the pathophysiology of renal and cardiovascular diseases [3-5]. MR antagonists (MRAs) can provide cardiorenal protection, including beneficial effects in hypertension, heart failure and chronic kidney disease (CKD) [3,6]. Notably, first generation (spironolactone) and second generation (eplerenone) steroidal MRAs reduce the risk of death in patients with heart failure with a reduced ejection fraction (HFrEF) [7-9].

However, adverse effects are a concern. Spironolactone binds to other steroid hormone receptors in addition to the MR, resulting in antiandrogenic and progestogenic adverse effects [10]. In addition, both spironolactone and eplerenone can cause hyperkalemia [11,12]. A meta-analysis of placebo-controlled trials in patients after myocardial infarction or with chronic heart failure found hyperkalemia was reported in 17.5% of patients on spironolactone (versus 7.5% on placebo) and 5.0% of eplerenone recipients (versus 2.6% on placebo) [12]. Although it does not reduce the clinical benefit of eplerenone [13], hyperkalemia may lead to MRA discontinuation, especially if these drugs are administered in combination with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) to patients with reduced renal function [14,15]. This is particularly a concern in the routine clinical practice setting, where an unselected heart failure population is treated, in contrast to clinical trial populations in which patients with advanced CKD are generally excluded [16].

Concerns over the safety profiles of steroidal MRAs stimulated interest in the development of MRAs that are highly selective for the MR and have a reduced risk of hyperkalemia and other adverse effects. Several new (non-steroidal) MRAs are currently in development. Indications being evaluated include hypertension, heart failure plus CKD and/or diabetes mellitus, and diabetic kidney disease [2]. To date, clinical data have been published for apararenone, AZD9977, esaxerenone, finerenone, and KBP-5074.

Head-to-head phase 3 comparisons of these emerging drugs with established steroidal MRAs are generally only possible in those indications for which spironolactone and/or eplerenone are approved (such as hypertension and heart failure). The newer MRAs are also being evaluated in disorders for

which spironolactone and/or eplerenone are not indicated (such as CKD in patients with type 2 diabetes); in those studies, the new MRA or placebo are added to optimized current standard-of-care therapy for that particular indication (see Expert Opinion section).

The aim of this narrative review is to provide an overview of data from head-to-head comparisons of MRAs, including pharmacological characteristics, pharmacokinetic properties, clinical outcomes, and safety profiles, in order to highlight similarities and differences between emerging agents and established MRAs (spironolactone and eplerenone). Head-to-head studies directly comparing newer MRAs have not yet been undertaken.

Relevant studies were identified based on a search of the PubMed database up to 21 July 2021 using the search terms: mineralocorticoid receptor antagonist, spironolactone, eplerenone, apararenone, AZD-9977, esaxerenone, finerenone, and KBP-5074. Papers were searched to identify head-to-head comparisons between these drugs. The ClinicalTrials.gov database (https://clinicaltrials.gov) was also searched.

2. Pharmacological characteristics

2.1 Receptor affinity, potency, and specificity

Both spironolactone (first generation, steroidal MRA) and eplerenone (second generation, steroidal MRA) provide natriuretic and cardiovascular and renal benefits [7,17]. Due to its non-specific binding to various steroid receptors, spironolactone can be associated with antiandrogenic and progestogenic adverse effects in addition to those associated with the MR blockade. Eplerenone is up to 40-fold less potent than spironolactone at the MR, but it displays much greater selectivity for the MR over other steroid hormone receptors, which reduces the risk of sex hormone-related adverse effects [18].

Newer, non-steroidal, MRAs generally exhibit both high affinity for the MR and good selectivity for the MR over other steroid receptors (**Table 1**) [19-30]]. Like eplerenone, the receptor selectivity of AZD-9977, esaxerenone, finerenone, and KBP-5074 is better than seen with spironolactone. However, with the exception of AZD9977, the potency of these new agents at the MR is greater than that of eplerenone. Finerenone has similar potency to spironolactone, while esaxerenone and KBP-5074 show greater potency than spironolactone. Apararenone has less inhibitory potential at the MR

compared with spironolactone, but is much weaker than spironolactone at the androgen, progesterone and glucocorticoid receptors (**Table 1**).

Even though non-steroidal MRAs bind to the same MR ligand-binding domain as steroidal MRAs, there appear to be some differences in the molecular mechanisms of action. Spironolactone and eplerenone are passive MR antagonists that quickly dissociate from the receptor. Spironolactone is able to promote co-factor (SRC-1) recruitment to an MR-dependent promoter but to a much lesser extent than aldosterone [31]. In contrast, finerenone is a “bulky” passive antagonist, binding of which results in an unstable receptor–ligand complex that is not able to recruit co-regulators [31]. Finerenone is a full MR antagonist with a mixed mechanism of antagonism involving impairment of several steps in the MR signalling pathway [31]. AZD9977 is a partial MR antagonist and agonist *in vitro* but, compared with eplerenone, it has a different pattern of interaction with the MR ligand-binding domain and a different pattern of recruitment of co-factor peptides [Bamberg et al. 2018]. Esaxerenone acts as a full antagonist and binds to the ligand-binding domain in a unique manner involving large side-chain rearrangements [25]. The binding modes for KBP-5074 and apararenone have not been reported.

2.2 Tissue distribution

Both spironolactone and eplerenone are found in higher concentrations in the kidney compared with the heart in rodent models [24]. In contrast, finerenone [27], and possibly also esaxerenone [26], are distributed at similar concentrations within cardiac and renal tissues in rodents.

2.3 Pharmacokinetics

Key pharmacokinetic characteristics for MRAs are summarized in **Table 2** [6,28,32-43]. Given the nature and purpose of pharmacokinetic studies, these were not head-to-head comparative studies. Amongst the steroidal MRAs, spironolactone has multiple active metabolites with long elimination half-lives, whereas eplerenone has no active metabolites [6]. Metabolite profiles have not yet been reported for all emerging non-steroidal MRAs, but finerenone has been found to have no active metabolites [42]. The principal metabolite of apararenone has binding affinity for the MR which is one-fiftieth that of apararenone, suggesting that it does not contribute to efficacy [28]. Esaxerenone has a longer elimination half-life than other MRAs [37,38], apart from apararenone which has a notably long elimination half-life [28]. The half-life of AZD9977 increases with dose (unlike other MRAs), but the

reason for this is not yet clear [36]. Renal excretion of unchanged esaxerenone and finerenone is minimal [38,43], an important consideration for drugs that are intended for use in patients with chronic heart failure or diabetic renal disease who have reduced renal function. As a striking example, in patients with resistant hypertension and advanced CKD (estimated glomerular filtration rate [eGFR] 25–45 mL/min/1.73m^2) treated with spironolactone within a trial comparing the potassium binder patiromer with placebo, it was observed that 20 of 23 patients (87%) had detectable spironolactone metabolites at 1 week after the last spironolactone dose, 12 of 16 patients (75%) had detectable metabolites at 2 weeks after the last spironolactone dose, and 4 of 11 patients (36%) had detectable metabolites at 3 weeks [44].

Few pharmacokinetic data from patients treated with new MRAs have been published (**Table 2**). Exposure (area under the curve, AUC) to finerenone increased in people with moderate or severe renal impairment by 45–61%, but no consistent effect on maximum plasma concentration was seen [43]. Population pharmacokinetic analysis of patients with type 2 diabetes and CKD found similar increases in finerenone AUC with decreasing eGFR; however, dose-exposure analyses for urinary albumin-to-creatinine ratio (UACR) (efficacy marker) and eGFR and serum potassium (safety markers) indicated that finerenone 10 mg and 20 mg once daily were safe and efficacious at reducing albuminuria in this patient population, with the effects largely saturated at 20 mg [45]. Studies of esaxerenone showed that trough plasma levels increased dose-dependently in patients with hypertension and moderate renal impairment (irrespective of stratification by baseline eGFR) [46] or with type 2 diabetes and microalbuminuria [47].

3. Pharmacodynamic properties

Results of preclinical studies comparing the pharmacodynamic properties of emerging non-steroidal MRAs with steroidal MRAs are summarized in **Table 3** [19,21,23,26,27,48-52, 54]. No preclinical pharmacodynamic data were found for apararenone.

3.1 Effect on blood pressure

In animal models, esaxerenone and KBP-5074 showed dose-dependent antihypertensive effects, and they appeared to be at least as potent at lowering blood pressure as spironolactone and/or eplerenone [21,23,26,48] (**Table 3**). In contrast, finerenone lowered blood pressure only at the highest

dose evaluated (10 mg/kg), which was above the dose at which end-organ protective effects were already seen (1 mg/kg) [27].

3.2 Attenuation of cardiac and renal damage

In rodent models of non-diabetic cardiorenal disease, finerenone provided greater protection from heart and kidney damage than seen with eplerenone at equinatriuretic doses and, in contrast to eplerenone, provided protection at doses that did not reduce blood pressure [27,51,52] (**Table 3**). Finerenone reduced renal gene expression of inflammatory/remodelling markers in a dose-dependent manner (**Table 3**) [27].

In models of hypertension and non-diabetic cardiorenal damage, esaxerenone showed an antihypertensive effect, which was evident at a much lower dose than seen with spironolactone and eplerenone, and displayed renal and cardiac protective effects [21,26]. Esaxerenone also exhibited renoprotective effects in a murine model of hypertensive diabetic kidney disease; in this model it provided greater attenuation of organ damage than seen with spironolactone, while achieving a similar reduction in blood pressure to spironolactone [48].

In a rodent model of non-diabetic renal damage, KBP-5074 and eplerenone blunted the effect of aldosterone on serum potassium to a similar extent, while KBP-5074 was more effective than eplerenone at preventing an increase in UACR. The therapeutic index (calculated as the ratio of the concentration producing 50% maximal effect for increasing serum potassium to that for decreasing UACR) was greater for KBP-5074 than for eplerenone [50]. In models of hypertension and nephropathy, KBP-5074 reduced blood pressure to a greater extent than seen with eplerenone, and showed evidence of amelioration of kidney and heart damage [23].

In rodent models of CKD (non-diabetic and diabetic kidney disease), AZD9977 reduced albuminuria and improved renal histopathology to a similar extent to eplerenone, while (unlike eplerenone) not affecting urinary electrolyte excretion [19] (**Table 3**). An additional study in healthy rats found that AZD9977 affected urinary electrolyte excretion when fludrocortisone was used as the mineralocorticoid receptor agonist, but not when aldosterone was used, whereas eplerenone attenuated sodium retention induced by either mineralocorticoid [49].

A notable conclusion from the available data is that three of the novel non-steroidal MRAs, finerenone, esaxerenone and KBP-5074, have demonstrated greater efficacy against cardiac hypertrophy and remodelling compared with steroidal MRAs [23, 26, 27] (**Table 3**).

Differences in co-factor binding and ligand-mediated gene expression could provide the underlying molecular basis for the differences in cardiac and renal effects seen between steroidal and non-steroidal MRAs. For example, finerenone showed a different ligand-mediated cardiac gene expression profile to that seen with eplerenone in murine models, and this appeared to be mediated by selective MR co-factor modulation [51,52]. Finerenone was more effective than eplerenone at inhibiting the recruitment of transcriptional co-activators involved in the expression of genes associated with cardiac hypertrophy and fibrosis. AZD9977 was found to also have a distinct pattern of recruitment of co-factor peptides compared with eplerenone *in vitro* experiments [19]. Aldosterone elicits rapid, so called 'non-genomic' actions, which are mediated at least to some extent by a crosstalk between MRs and other receptor systems, including receptor tyrosine kinases such as epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR) [for a review see *Ruhs et al.* [53].

3.3 Obesity

In a mouse model of very high-fat diet-induced obesity, finerenone, but not spironolactone, improved insulin resistance and increased recruitment of interscapular brown adipose tissue [54] (**Table 3**).

3.4 Central nervous system

MRs are highly expressed in neurons in several regions of the central nervous system, including the hippocampus, certain nuclei of the hypothalamus, amygdala, nucleus tractus solitarius (NTS), cerebral cortex, and cerebellar Purkinje cells [55]. Although little is known about the function of MRs in the cerebral cortex and cerebellum, neurons of the NTS that co-express 11beta-HSD2 (which confers specificity to the MR for aldosterone), as well as those in the amygdala, seem to be involved in the regulation of sodium appetite [55]. MRs in the paraventricular nucleus (PVN) of the hypothalamus are involved in modulating blood pressure and renal function, by increasing sympathetic output to blood vessels, the heart and the kidneys [1]. Accordingly, long-term blood pressure modulation might be mediated, at least to some extent, by interfering with MRs in the PVN, as long as the respective MR antagonist passes the blood-brain barrier.

Data on the passage of MRs across the blood-brain barrier are available only for spironolactone (or canrenoate, the salt formulation of spironolactone's active metabolite canrenone), and for the novel MRAs esaxarenone and finerenone. Head-to-head comparisons have not been performed and direct comparison of data from the available studies is not possible due to differences in the animal species and methodologies used. A rough estimation can be deduced for each of the MRAs based on its relative distribution between brain tissue and blood, plasma, or other organs such as heart and kidneys. The data suggest that while spironolactone and its active metabolite canrenone pass the blood-brain-barrier to some extent in rats, dogs and rabbits, brain penetration in rats is low and very low/negligible for esaxerenone and finerenone, respectively [27, 56-59].

4. Clinical outcomes

4.1 Head-to-head comparisons of steroidal MRAs

Studies that compared the steroidal MRAs eplerenone and spironolactone are summarized in **Table 4** as background information [60-64]. Both drugs lower blood pressure, although the antihypertensive effect of spironolactone was greater than that of eplerenone in patients with mild-to-moderate essential hypertension [60]. In patients with hypertension associated with primary aldosteronism, two out of three studies found eplerenone and spironolactone had similar effects on blood pressure, while one found spironolactone had a greater antihypertensive effect [61-63].

4.2 Comparisons of non-steroidal MRAs with steroidal MRAs

Clinical studies comparing emerging non-steroidal MRAs with steroidal MRAs are summarized in **Table 5**. Relevant data have not yet been reported for KBP-5074.

4.2.1 Healthy volunteers

In a study evaluating urinary electrolyte excretion in healthy volunteers, which used the synthetic mineralocorticoid fludrocortisone, single doses of AZD9977 200 mg and eplerenone 100 mg attenuated fludrocortisone-induced sodium retention to a similar extent (and the combination of both drugs had an additive effect) (**Table 5**) [28,35,39,65-67]. This finding contradicted preclinical studies in rodent models that used aldosterone, which found that AZD9977 exerted similar organ-protective effects to eplerenone but unlike eplerenone had minimal effects on urinary electrolytes [19]. Additional

studies in rodents subsequently found that AZD9977 increased the urinary sodium/potassium ratio when fludrocortisone was used instead of aldosterone, suggesting that AZD9977 behaves differently depending on the agonist used (fludrocortisone versus aldosterone) [49].

In healthy volunteers, apararenone suppressed the reduction in urinary sodium:potassium ion ratio induced by fludrocortisone; the effect was less than that of eplerenone during the first 8 hours after dosing, but was greater than that of eplerenone from approximately 12 hours onwards [28] (**Table 5**).

4.2.2 Hypertension

Esaxerenone has been compared with eplerenone in the treatment of patients with essential hypertension [39,65]. These studies were performed in Japan, one of the countries where eplerenone is approved for the treatment of hypertension. The antihypertensive effect of esaxerenone 2.5 mg/day was non-inferior to that of eplerenone 50 mg/day after 12 weeks, while esaxerenone 5 mg/day produced significantly greater reductions in blood pressure than eplerenone (**Table 5**) [65]. The safety profiles were similar for both drugs.

4.2.3 Chronic heart failure plus chronic kidney disease

In patients with chronic HFrEF and moderate CKD (estimated glomerular filtration rate, eGFR, of 30–60 mL/min/1.73 m^2), finerenone 5 or 10 mg/day administered for 4 weeks was as effective as spironolactone (titrated from 25 to 50 mg/day; mean dose 37 mg/day) at reducing markers of haemodynamic stress, including serum BNP and N-terminal proBNP (NT-proBNP) levels and albuminuria (**Table 5**) [66]. Notably, finerenone was associated with smaller increases in mean serum potassium level, a lower incidence of hyperkalemia, smaller decreases in eGFR, and a lower incidence of worsening renal function compared with spironolactone. In addition, finerenone was associated with a smaller reduction in systolic blood pressure than seen with spironolactone.

4.2.4 Worsening chronic heart failure plus chronic kidney disease and/or diabetes mellitus

In a study evaluating finerenone in the high-risk population of patients with chronic HFrEF and CKD (eGFR 30–60 mL/min/1.73 m^2) and/or type 2 diabetes mellitus, patients received finerenone (2.5, 5, 7.5, 10 or 15 mg/day uptitrated to 5, 10, 15, 20 and 20 mg/day on day 30) or eplerenone (25 mg every other day, uptitrated to 25 mg/day on day 30 and 50 mg/day on day 60) for 3 months; uptitration took place if blood potassium was ≤5.0 mmol/L) [67].

The incidence of an exploratory composite clinical endpoint comprising death from any cause, cardiovascular hospitalization, and emergency presentation for worsening HF, was lower with finerenone (in all except the lowest dose group) compared with eplerenone, with the difference achieving nominal statistical significance in the finerenone 10→20 mg/day group (hazard ratio 0.56, 95% CI 0.35–0.9, p=0.02). The proportion of patients who experienced a reduction in NT-proBNP level of >30% after 3 months' treatment (primary endpoint) was similar in all finerenone dose groups and the eplerenone group (**Table 5**) [67]. Finerenone had a similar safety profile to eplerenone.

4.2.5 Renal endpoints

Head-to-head phase 3 studies specifically in renal disease have not been performed (as it is not an approved indication for eplerenone or spironolactone). However, some relevant data are available from the hypertension and heart failure phase 2 studies discussed in the previous sections; these data are summarized below. In addition, recent placebo-controlled studies with newer MRAs that have been conducted in renal indications are discussed in the Expert Opinion section.

In patients with essential hypertension, eGFR decreased during 12 weeks' treatment with esaxerenone 1.25–5 mg/day, while it decreased or remained stable with eplerenone 50–100 mg/day (**Table 5**) [39,65].

In patients with chronic HFrEF and moderate CKD, finerenone at doses of 2.5–10 mg/day for 4 weeks was associated with similar reductions in the urinary albumin:creatinine ratio to that seen with spironolactone 25–50 mg/day [66]. Smaller decreases in mean eGFR were seen with finerenone than with spironolactone, and the incidence of worsening renal function was lower with finerenone (**Table 5**).

In patients with worsening chronic HFrEF and CKD and/or type 2 diabetes, eGFR increased with low doses of finerenone and decreased with higher doses, but overall there were no significant differences in the changes in eGFR seen with finerenone 2.5–20 mg/day compared with eplerenone (at doses of 25 mg every other day to 50 mg/day) (**Table 5**) [67]. The incidence of renal adverse events requiring hospitalization was low with both finerenone and eplerenone during the 3-month study period.

See the Safety section for information on serum potassium levels during treatment with MRAs.

5. Safety

In head-to-head comparisons of steroidal MRAs, the overall rate of adverse events was similar with spironolactone and eplerenone (**Table 4**) [60,62]. However, gynecomastia was less common with eplerenone than with spironolactone [60-64].

Key safety data from comparisons between emerging non-steroidal MRAs and the older steroidal MRAs are summarized in **Table 5**. The overall incidence of adverse events was similar after a single dose of AZD9977 or eplerenone in healthy volunteers [35]. The overall incidence of adverse events with esaxerenone 2.5 or 5 mg/day was similar to that seen with eplerenone 50 mg/day in patients with essential hypertension. Finerenone was associated with a lower overall incidence of adverse events compared with spironolactone in patients with chronic HFrEF plus CKD [66], and with a similar incidence to eplerenone in patients with worsening chronic HFrEF plus CKD and/or diabetes mellitus [67]. In contrast to spironolactone, gynecomastia was not reported with non-steroidal MRAs.

5.1 Hyperkalemia

In head-to-head comparisons of steroidal MRAs in hypertension or acute decompensated heart failure, hyperkalemia occurred with both spironolactone and eplerenone, and there was no clear difference in risk based on the available studies (**Table 4**) [62,64].

In the phase 3 trial of esaxerenone in hypertension (ESAX-HTN) (n=1001), hyperkalemia occurred at a slightly higher rate with esaxerenone compared with eplerenone (0.6–0.9% versus 0%) [65]. The patient population enrolled in this trial was relatively low risk for hyperkalemia because of overall preserved renal function and a low level of renin-angiotensin system (RAS)-acting medication at baseline; only 51.5% of patients had received prior antihypertensive therapy (specific medications not reported), the mean eGFR was 78.7 mL/min/1.73 m^2, and only 15.6% of patients had diabetes 65].

In contrast, the phase 2 trials of finerenone enrolled patient populations that were at high risk of developing hyperkalemia. In the trial in patients with chronic HFrEF and CKD (ARTS), 95% of the 392 patients were receiving concomitant RAS-acting drugs, the mean eGFR at baseline was 47.0 mL/min/1.73 m^2, and 34% of patients had diabetes [66]. Similarly, in the trial in patients with HFrEF and diabetes and/or CKD (ARTS-HF), 78.1% of the 1055 patients were receiving concomitant RAS-acting agents, mean eGFR was 53 mL/min/1.73 m^2, and 64.2% had diabetes [67]. In these studies, mean increases in serum potassium level were lower with finerenone compared with both

spironolactone and eplerenone, while the incidence of hyperkalemia with finerenone was lower than that seen with spironolactone and similar to that seen with eplerenone. This was seen in the context of similar efficacy outcomes with finerenone versus the steroidal MRAs with respect to albuminuria and NT-proBNP, and a lower incidence of worsening renal function with finerenone compared with spironolactone [66,67]. Overall, this suggests that finerenone may have a better safety profile with respect to hyperkalemia risk compared with steroidal MRAs while providing a similar level of efficacy.

6. Conclusion

The development of novel non-steroidal compounds represents a paradigm change for MRAs [68,69]. Although the second-generation MRA eplerenone is more selective for the MR than first-generation spironolactone, it is nonetheless still associated with hyperkalemia. The latest generation of non-steroidal MRAs is being developed with the intention of improving safety while maintaining efficacy. The physiochemical properties of these compounds appear to provide potential advantages compared with the older steroidal MRAs, particularly with respect to organ protective effects and a reduced risk of severe hyperkalemia. There may also be relevant differences in characteristics between the newer agents themselves, for example with respect to tissue distribution, structural properties, MR binding modes, and the ability to recruit co-regulators that transcribe genes involved in cardiac and renal tissue damage. Preclinical studies with various non-steroidal MRAs have demonstrated anti-inflammatory and antifibrotic renal and cardiac protective effects in rodent models, with several showing more potent effects than seen with steroidal MRAs.

To date, most available head-to-head clinical studies have involved esaxerenone or finerenone. In patients with essential hypertension, esaxerenone exhibited at least equivalent antihypertensive activity to eplerenone and was generally well tolerated. In patients with HFrEF and CKD, finerenone was as efficacious as spironolactone at reducing albuminuria and cardiac biomarkers, and was associated with smaller increases in serum potassium level and a lower risk of worsening renal function. In a high-risk population with worsening HFrEF and either CKD and/or diabetes, finerenone was able to provide a >30% reduction in NT-proBNP in a similar proportion of patients to eplerenone, with a similar tolerability profile. Overall, the available data from head-to-head comparisons in phase 2

trials suggest that the new non-steroidal MRAs exhibit at least equivalent efficacy to steroidal MRAs but may have a better safety profile in patients with heart failure and/or kidney disease.

7. Expert Opinion

The results of head-to head comparisons between new MRAs and steroidal MRAs covered in this review are encouraging. They suggest that the newer, non-steroidal, MRAs may offer advantages over steroidal MRAs for certain patient groups. It is important to consider these findings within the broader context of the full body of clinical trial data available for these agents, and some key points are highlighted below.

An important consideration is that these novel non-steroidal MRAs have the potential to make dual renin-angiotensin-aldosterone system (RAAS) blockade more efficacious and safer across a broad at-risk cardiorenal population, including diabetic patients. Previous attempts at dual blockade, such as adding aliskiren to an ACEi/ARB [70] or combing an ACEi plus an ARB [71,72] did not improve efficacy compared with single RAS blockade, and in some cases substantially increased the risk of hyperkalemia [70,71]. In contrast, recent large-scale placebo-controlled studies evaluating the addition of non-steroidal MRAs to RAS inhibitor therapy have provided encouraging results.

FIDELIO-DKD, which involved more than 5000 patients with type 2 diabetes and CKD (mean eGFR 44 mL/min/1.73 m^2), found that adding finerenone to optimal RAS blockade with either an ACEi or ARB (maximum approved dose without unacceptable adverse effects), reduced the risk of CKD progression and cardiovascular events [73,74]. The incidence of the primary outcome (a composite of kidney failure, sustained decrease in eGFR of ≥40%, or death from renal causes) occurred in 17.8% of the finerenone group compared with 21.1% of the placebo group (hazard ratio 0.82, 95% CI 0.73–0.93), while the incidence of the key secondary outcome (composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure) occurred in 13.0% versus 14.8% (hazard ratio 0.86, 95% CI 0.75–0.99) [73]. Adverse events occurred at a similar rate in both groups, and although hyperkalemia was more frequent with finerenone than with placebo, it led to treatment discontinuation in only 2.3% of patients. The cardiovascular benefits of finerenone were seen in patients with or without a history of pre-existing cardiovascular disease [74]. In the FIGARO-DKD trial, the primary composite outcome (time to first occurrence of cardiovascular

death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure) occurred in 12.4% of the finerenone group compared with 14.2% of the placebo group (hazard ratio, 0.87; 95% CI 0.76-0.98) in patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria, or stage 1 or 2 CKD with severely elevated albuminuria [75]. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone than placebo (1.2 % and 0.4%) [75].

The ESAX-DN trial, which involved 455 patients with type 2 diabetes and microalbuminuria (UACR 45 to <300 mg/g creatinine), found that adding esaxerenone to RAS inhibitor therapy provided additional benefit with respect to proteinuria [40]. The proportion of patients achieving UACR remission (defined as <30 mg/g creatinine and ≥30% reduction from baseline on two consecutive occasions; primary endpoint) was 22% in the esaxarenone group versus 4% with placebo (p<0.001). Hyperkalemia was more common with esaxerenone than with placebo, leading to treatment discontinuation in 4% of esaxerenone recipients versus 0.4% in the placebo group. Additional data come from a 24-week study of apararenone in patients with stage-2 diabetic nephropathy [76]. Apararenone 2.5, 5 and 10 mg reduced UACR significantly compared with placebo (to 62.9%, 50.8% and 46.5% of baseline values, respectively, versus 113.7% with placebo; all p<0.001), and the effect was seen irrespective of concomitant ACEi/ARB use. Serum potassium levels increased during the first 12–16 weeks of apararenone treatment (to a median 0.1–0.3 mmol/L) and then stabilized or declined.

Separately, the BLOCK-CKD study found that KBP-5074 was effective at reducing blood pressure in patients with advanced (stage 3b/4) CKD and uncontrolled hypertension (n=162), and carried a low risk of hyperkalemia [77]. Participants were receiving ≥2 antihypertensive drugs (diuretic, RAAS blockers, calcium-channel blockers) at baseline. After 84 days, placebo-subtracted reductions in systolic blood pressure were -7.0 mmHg with KBP-5074 0.25 mg (p=0.0399) and –10.2 mmHg with KBP-5074 0.5 mg (p=0.0026). No hyperkalemia ≥6.0 mmol/L occurred. The incidence of hyperkalemia 5.6–<6.0 mmol/L was slightly higher with KBP-5074 2.5 and 5.0 mg (11.8% and 16.7%) than with placebo (8.8%), but there was no difference in the rate of drug discontinuation due to hyperkalemia (0% and 3.7% versus 3.5%).

These studies indicate that non-steroidal MR antagonists have the potential to provide a cardiorenal benefit above that of current optimized standard-of-care treatment in a high-risk population with reduced renal function, with a low risk of hyperkalemia. These findings also highlight the potential

benefit of these non-steroidal compounds compared to steroidal MRAs with respect to the overall benefit/risk balance of treatment. The results of these studies will help clarify the role of the novel MRAs in different groups of patients at cardiorenal risk.

Several other issues related to the use of MRAs warrant consideration. To optimize therapeutic benefit, it is important to be able to better stratify patients. To do this, biomarkers that are predictive of MRA response need to be identified and validated. One possible approach is proteomic analysis, which has been used to identify various plasma protein biomarkers associated with pleiotropic effects induced by spironolactone [78]. Another approach is latent class analysis, which has been used to identify clinical subgroups of heart failure patients with different prognoses and potentially different clinical responses to treatment with eplerenone [79]. Additional studies using similar approaches could be used to help predict which patients are most likely to benefit from novel MRAs.

Another issue is the question of sex-related differences. The presence of sex-associated differences in disease manifestations, risk factors and outcomes in cardiac and renal pathologies has been observed in preclinical studies. Conflicting results are sometimes observed in clinical trials, and it is possible that some might be due to a lack of consideration of potential sex-related differences when designing studies. In many studies, women are under-represented and consequently there is a paucity of clinical data in women. Increasing the representation of women in clinical studies, as well as modifying study designs to take account of male/female differences in pathophysiology would facilitate the gathering of data that would be valuable for establishing the optimal use of MRAs in women as well as men.

Further research is needed to clarify the molecular differences in the mode of action of non-steroidal MRAs versus steroidal MRAs, to help address the many questions remaining unanswered in this area.

Given that basic studies show that MR activation in specific cell types contributes to cardiac and renal injury, it is possible that in the future, MR antagonists specifically targeting certain cell types might be developed [80], which could represent a next generation of highly targeted MRAs.

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Table 1. Pharmacological characteristics of mineralocorticoid receptor antagonists: receptor affinity and tissue distribution [19-30]

	Spironolactone	**Eplerenone**	**Apararenone**	**AZD9977**	**Esaxerenone (CS-3150)**	**Finerenone (BAY 94-8862)**	**KBP-5074**
Generation	First	Second	Third				
Class	Steroidal		Nonsteroidal				
Receptor binding							
Binding mode	Partial agonist	Partial agonist	Unknown	Partial agonist	Full antagonist with large side-chain rearrangements	Bulky antagonist and inverse agonist	Unknown
Affinity for MR Affinity for GR/AR/PR	++ +	+ ↓↓	+ ↓↓	+ ↓↓	++ ↓↓	++ ↓↓	++ ↓↓
MR IC_{50} (nM)	10[a] - 36[c] 66[b] 24[d] 14.3[e]	- 370[b] 713[c] 970[b] 990[d] 268[e]	280[a]	- 370[b] - - - -	- - 9.4[c] 3.7[b] - -	- - - - 18[d] -	- - - - - 2.7[e]
GR IC_{50} (nM)	- 764[C] 2600[b] 2410[d] 1950[e]	- 3060[C] 36,000[b] 21,980[d] >10,000[e]	-	- - - - -	- >10,000[c] >5000[b] - -	- - - >10,000[d] -	- - - - 2410[e]

AR IC_{50} (nM)	- 133[C] 640[b] 77[d] 30.7[e]	- >100,000[c] 42,000[b] 21,240[d] 2090[e]	-	- - - - -	- >10,000[c] >5000[b] - -	- - - >10,000[d] -	- - - - No activity[e]
PR EC_{50} (nM)	- 1200[C] 180[b] 740[d] 906[e]	- >100,000[c] 7400[b] 31,210[d] >10,000[e]	-	- - - - -	- >10,000[c] >5000[b] - -	- - - >10,000[d] -	- - - - 122[e]
GR, AR, PR IC_{50} (nM)[f]	0.05–6050[a]	-	>100,000[a]	-	-	-	-
Tissue distribution (kidney/heart)[g]	>6-fold higher in kidney > heart	3-fold higher in kidney > heart		-	Equal distribution	Equal distribution	-

Data are from direct comparative studies unless indicated otherwise. It should be noted that each study compared a single newer MRA versus spironolactone and/or eplerenone; no studies compared newer MRAs with each other. IC_{50} values from different studies cannot be compared due to differences in assay methodology and agonist concentrations.
a Method not reported.
b Transcriptional activity reporter gene assay.
c Radioligand binding assay.
d The same functional cell-based steroid hormone receptor transactivation assay was used to evaluate finerenone [Bärfacker et al 2012, Pitt et al. 2012] and spironolactone and eplerenone [Fagart et al. 2010] in separate studies.
e Beta-lactamase reporter technology.
f Reported as a pooled range for all three receptors.
g Evaluated in rats.
EC_{50} = half-maximal effective concentration; IC_{50} = half-maximal inhibitory concentration; AR = androgen receptor; GR = glucocorticoid receptor; MR = mineralocorticoid receptor; PR = progesterone receptor.

Table 2. Pharmacokinetic properties of mineralocorticoid receptor antagonists

Parameter / Disease state	**Spironolactone [**6,32,33]	**Eplerenone [**6,34]	**Apararenone** [28]	**AZD9977** [35,36]	**Esaxerenone [**37-40]	**Finerenone** [41-43]
T_{max}	1-2 h[a]	1-2 h[b]	4.0 h[b]	0.5–0.8 h[b]	1.5–4.0 h[b]	0.5–0.75 h[b]
Elimination half-life	1.3-1.4 h for parent drug >12 h for active metabolites	3-6 h	275–285 h for parent drug >1100 h for active metabolite	2–10 h Increases with dose	20–30 h	2–3h[d]
Metabolites	Multiple active metabolites	No active metabolites	Metabolite with low activity (MR binding affinity one-fiftieth of that of apararenone)	n/a	n/a	No active metabolites
Excretion	<1% unchanged drug recovered in urine; 10–15% of dose excreted in urine in form of metabolites	66% of dose excreted via urine; <3% unchanged drug recovered from urine	<14% of dose excreted in urine[c]	24–37% of dose excreted in urine; 20% of dose excreted unchanged in urine	38.5% of dose excreted in urine; <2% unchanged drug excreted in urine	80% of dose excreted via urine; <1% unchanged drug excreted in urine
Mild/moderate/severe renal impairment (CL_{CR} 50-80 / 30 to <50 / <30 mL/min)	-	Non-significant increase in AUC as renal function decreased	-	-	-	Exposure (AUC) increased with moderate/severe (but not mild) renal impairment; no consistent effect on

						C_{max}
Hypertension + moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2)	-	-	-	-	Trough plasma levels increased dose-dependently, regardless of baseline eGFR	-
T2DM + microalbuminuria (UACR ≥45 to <300 mg/g creatinine); eGFR ≥30 mL/min/1.73 m^2	-	-	-	-	Trough plasma levels increased dose-dependently	-

Data are from separate studies performed for each compound. Values are for healthy volunteers unless indicated otherwise. No pharmacokinetic data for KBP-5074 in humans were found.
a Fed state.
b Fasting state.
c Not specified further.
d Value for clinically relevant doses of 10 or 20 mg.
AUC = area under the plasma concentration curve; C_{max} = maximum plasma concentration; eGFR = estimated glomerular filtration rate; h = hours; MD = multiple dose; MR = mineralocorticoid receptor; n/a = not available; SD = single-dose; T2DM= type 2 diabetes mellitus; T_{max} = time to maximum concentration; UACR = urinary albumin-creatinine ratio.

Table 3 Pharmacodynamic properties of non-steroidal mineralocorticoid receptor antagonists (compared with steroidal mineralocorticoid receptor antagonists)

	AZD9977	Esaxerenone	Finerenone	KBP-5074
Blood pressure	-	**DOCA/high-salt rat model (high-aldosterone HT) (2 wks):** ESA 3 mg/kg had a greater antihypertensive effect than SPI 30 mg/kg or EPL 30 mg/kg (SBP increased by 14 mmHg with ESA versus 60 mmHg with SPI, 72 mmHg with EPL and 68 mmHg in untreated rats) [21]. **DSS high-salt rat model (low-aldosterone HT) (13 wks):** ESA had dose-dependent antihypertensive (SBP) effect; effect on BP of ESA 0.5 mg/kg similar to that of SPI 100 mg/kg and EPL 100 mg/kg [26]. No hyperkalemia >5.5mEq/L seen, but mean serum potassium was higher with ESA 0.5–2 mg/kg (5.2–5.4 mEq/L) and EPL 100 mg/kg (5.2 mEq/L) vs untreated animals (4.7 mEq/L). **HS-treated T2D mouse model**	**DOCA/high-salt rat model (10 wks):** FIN reduced SBP only at the highest investigated dose of 10 mg/kg (and not at 0.1 or 1 mg/kg), whereas EPL 30 and 100 mg/kg both had a significant hypotensive effect. [27].	**DSS high-salt rat model (41 days):** KBP (0.3–10 mg/kg) prevented increases in SBP (attenuated by 9–22%); the effect was greater than seen with EPL 120 mg/kg (~8%) [23]. **SHRSP high-salt rat model (33 days):** KBP (5–50 mg/kg) prevented elevation of SBP (attenuated by 12–20%) whereas EPL had no effect [23].

		(DKD with HT) (8 wks): ESA 1 mg/kg reduced BP to a similar extent to SPI 20 mg/kg [48]		
Renal effects				
Electrolytes	**Low-salt rat model (acute elevation of endogenous aldosterone) (single dose):** AZD did not affect urinary Na^+/K^+ ratio, whereas EPL increased the ratio (by increasing Na^+ excretion) [19]. **Uni-nephrectomized db/db mouse model (4 wks):** Chronic administration of AZD or EPL both increased the urine Na^+/K^+ ratio (EPL increased Na^+ excretion; no increase in K^+ in either group) [19]. **Healthy rats (single dose):** When administered with aldosterone and salt, both AZD (2–120 mg/kg) and EPL (1–100 mg/kg) increased the urine Na^+/K^+ ratio dose-	**Adrenalectomized rat model (20 hours):** After 5 hours, ESA 0.3–3 mg/kg provided similar inhibition of aldosterone-induced decrease in urinary Na^+/K^+ ratio to that seen with SPI or EPL at 3–30 mg/kg. ESA had a longer duration of effect: at 3 hours, ESA, SPI and EPL inhibited the reduction in Na^+/K^+ ratio by 38% vs 57% vs 46%; at 20 hours, ESA had an inhibition value of 56%, whereas SPI and EPL had no effect [21].	-	**Uni-nephrectomized aldosterone/high-salt rat model (4 wks):** KBP and EPL blunted aldosterone-induced reduction in serum K^+; significant increases in K^+ seen with KBP 5 mg/kg (but not 0.5 or 1.5 mg/kg) and EPL 450 mg/kg (but not 15 or 50 mg/kg). Urinary Na^+/K^+ ratio increased with KBP 1.5 and 5 mg/kg and with EPL 450 mg/kg **[50].**

	dependently. When administered with the synthetic mineralocorticoid fludrocortisone, EPL (1–30 mg/kg), but not AZD (3–100 mg/kg), caused a dose-dependent increase in urine Na^+/K^+ ratio [49].			
Inflammation/Fibrosis / Remodelling/Albuminuria	**Uni-nephrectomized aldosterone/high-salt rat model (4 wks):** AZD dose-dependently reduced albuminuria and improved renal histopathology to a similar extent to EPL. Reduction in mean renal pathology score seen with AZD 30 and 100 mg/kg/day and with EPL 10 and 30 mg/kg/day [19]. **Uni-nephrectomized db/db (obese diabetic) mouse model (4 wks):** AZD reduced urinary albumin excretion and prevented further progression of	**DSS high-salt rat model (7 wks):** ESA inhibited proteinuria and renal hypertrophy, and ameliorated renal histopathological changes (e.g. fibrosis), to a greater extent than SPI or EPL. Inhibition of increased urinary protein was seen with ESA 0.5–2 mg/kg (but not 0.25 mg/kg); EPL 10 and 100 mg/kg (but not 30 mg/kg) also had an inhibitory effect, but SPI (10–100 mg/kg) did not [26]. **HS-treated T2D mouse model (DKD with HT) (8 wks):** ESA 1 mg/kg attenuated albuminuria, renal fibrosis, inflammation, and markers of oxidative stress to a	**DOCA/high-salt rat model (10 wks):** Dose-dependent protection from functional and structural renal damage, reduction in proteinuria, and reduction in renal expression of proinflammatory and profibrotic biomarker genes with FIN 0.1–10 mg/kg. Protection at dosages that did not reduce SBP. At equinatriuretic doses, FIN 10 mg/kg provided greater protection than EPL 100 mg/kg. Proteinuria significantly lower with FIN 10 mg/kg vs EPL 100 mg/kg [27]. FIN dose-dependently reduced the induction of important pro-inflammatory/remodelling marker genes, including PAI-1, MCP-1,	**DSS high-salt rat model (41 days):** KBP 1–10 mg/kg reduced urinary albumin excretion by 35–57% (no change with 0.3 mg/kg); albumin excretion increased with EPL 120 mg/kg. KBP dose-dependently reduced kidney-body weight ratio (reflecting fibrosis/inflammation) and showed a trend towards reduced kidney injury (not seen with EPL) [23] **SHRSP high-salt rat model (29 days):** KBP 5–50 mg/kg reduced urinary albumin excretion by 51–63%; a reduction was seen with EPL (39%) only on day 29 and not at earlier timepoints. KBP and EPL reduced kidney-body weight ratio to

	nephropathy to a similar extent to EPL [19].	greater extent than seen with SPI 20 mg/kg (while reducing BP to a similar extent as SPI) [48].	OPN and MMP-2, with FIN 1 mg/kg having similar inhibitory efficacy to EPL 100 mg/kg [27].	a similar extent. KBP reduced renal small artery cross-sectional area more than seen with EPL [23]. **Uni-nephrectomized aldosterone/high-salt rat model (4 wks):** KBP 0.5, 1.5 and 5 mg/kg and EPL 50 and 450 mg/kg (but not 15 mg/kg) prevented increase in UACR. Therapeutic index (ratio of EC_{50} for increasing serum K+ to EC_{50} for decreasing UACR) was 39-fold better for KBP vs EPL (24.5 vs 0.62) **[50].**
Cardiac effects				
Inflammation/Fibrosis / Remodelling	-	**DSS high-salt rat model (7 wks):** ESA inhibited LV hypertrophy/reduced LV weight (as did SPI and EPL). However, EPL and SPI showed only partial efficacy at doses up to 100 mg/kg whereas ESA (0.25, 0.5, 1, 2 mg/kg) dose-dependently reduced LV weight with a clearly higher maximal efficacy. ESA 1 and 2 mg/kg (but not SPI 10–100 mg/kg or EPL 1—100 mg/kg) inhibited	**DOCA/high-salt rat model (10 wks):** Dose-dependent reduction in pro-BNP and protection from structural heart damage with FIN 1 and 10 mg/kg. Protection at dosages that did not reduce SBP. Heart:body weight ratio reduced with FIN 1 and 10 mg/kg vs PL but relative heart weight did not differ vs PL with EPL 30 or 100 mg/kg [27]. At equinatriuretic doses, FIN provided greater protection than	**DSS high-salt rat model:** KBP 1, 3 and 10 mg/kg (but not EPL 100 mg/kg) reduced heart:body weight ratio. Both KBP and EPL reduced LV wall thickness [23]. **SHRSP high-salt rat model:** KBP and EPL both reduced heart:body weight ratio; neither KBP nor EPL reduced heart small artery cross-sectional area [23].

		plasma BNP elevation; mean BNP level with ESA 1 and 2 mg/kg was 153.9 and 140.9 ng/mL vs 246.5 ng/mL in untreated animals, while BNP levels were >200 ng/mL with SPI and EPL [26].	EPL. FIN 1 mg/kg reduced proBNP to similar extent as EPL 100 mg/kg [27]. **Post-MI chronic HF rat model (8 wks):** FIN 1 mg/kg, but not EPL 100 mg/kg, improved LV function and reduced plasma pro-BNP level [27]. **Transverse aortic constriction (TAC) mouse model:** FIN 10 mg/kg attenuated pressure-overload induced cardiac hypertrophy to a greater extent than EPL 200 mg/kg. Mean increase in LV mass with FIN 28.4 mg vs 38.4 mg with EPL vs 39.3 mg in vehicle-treated mice). TAC-induced increase in myocyte size inhibited by both FIN and EPL vs vehicle-treated mice (mean cross-sectional area 296.1 and 332.1 vs 369.1 square micrometers). FIN induced a distinct cardiac gene expression profile (e.g. *Tnnt2* expression reduced with FIN but not EPL; FIN reduced *BNP* expression less than	

			seen with EPL) [51]. **Isoproterenol-induced cardiac fibrosis mouse model (2 wks):** At equinatriuretic doses, FIN 10 mg/kg had superior cardiac antifibrotic and anti-inflammatory effects, and provided greater improvement in global longitudinal peak strain, than EPL 200 mg/kg. Cardiac fibrosis and macrophage infiltration were blocked only by FIN and not EPL. FIN but not EPL inhibited profibrotic cardiac *TNX* gene expression [52].	
Obesity	-	**-**	**Mouse model of very high-fat diet-induced obesity:** FIN but not SPI improved insulin resistance, as shown by a significant reduction in the homeostasis model assessment of insulin resistance (HOMA) index. FIN but not SPI increased recruitment of interscapular brown adipose tissue [54].	**-**

All studies used male animals.
AZD = AZD9977; BP = blood pressure; DKD = diabetic kidney disease; DOCA/salt = deoxycorticosterone acetate-/salt-challenge model of cardiorenal damage; DSS = Dahl salt-sensitive; EPL = eplerenone; ESA = esaxerenone; FIN = finerenone; HS = high-salt; HT = hypertension; KBP = KBP-5074; LV = left ventricular; MI = myocardial infarction; PL = placebo; pro-BNP = prohormone of brain natriuretic hormone; SBP = systolic blood pressure; SHRSP = stroke-prone spontaneous hypertensive rat; SPI = spironolactone; T2D = type 2 diabetes; TNX = tenascin-X; Tnnt2 = troponin T type 2; UACR=urinary albumin-to-creatinine ratio; wks = weeks.

Table 4 Comparison of clinical effects between the steroidal mineralocorticoid receptor antagonists eplerenone and spironolactone

Clinical condition **Study design / duration /** **N / Sex ratio** **[Reference]**	**Treatment groups**	**Blood pressure**	**Cardiac effects:** **B-type natriuretic peptide; composite clinical endpoint**	**Renal effects:** **Protein/albumin excretion**	**Adverse effects**
Hypertension (mild to moderate) R, DB / 8 wks / N=417 / M:F 58%:42% [60]	EPL 50, 100 or 400 mg od EPL 25, 50 or 200 mg bd SPI 50 mg bd PL	EPL 50–400 mg daily reduced mean SBP and DBP (PEP) vs PL (p<0.05). SPI acted as a positive control (EPL 100 mg reduced BP by 75% vs SPI 100 mg).	–	–	Overall incidence of AEs similar for EPL vs PL and EPL vs SPI. Serum K level increased with EPL 400 mg od, and 25, 50 and 200 mg bd, and with SPI (all p<0.05 vs PL). No gynecomastia with EPL. Incidence of impotence similar for EPL vs PL.
Hypertension with primary aldosteronism					
R, OL-BE / 24 wks / N=34 / M:F 8:9 (EPL) and 7:10 (SPI) [61]	EPL 25–100 mg bd SPI 25–200 mg bd Dose titrated up if BP <140/90 mmHg not	PEP: Similar percentage of patients achieved BP <140/90 mmHg at week 16 with	–	–	Similar risk of mild hyperkalemia with EPL vs SPI (3 cases with EPL 150 mg daily vs 2

	achieved	EPL (82.4%) and SPI (76.5%) (p=1.00).			cases with SPI 400 mg daily). No gynecomastia with EPL. Two cases of painful gynecomastia with SPI 400 mg; resolved after switching to EPL 150 mg, with continued BP control.
R, DB / 16 wks / N=141 / M:F 96:45 [62]	EPL 100–300 mg od SPI 75–225 mg od Dose titrated up if DBP ≤90 mmHg not achieved	PEP: Smaller mean decrease in DBP with EPL vs SPI (–5.6 vs –12.5 mmHg; difference –6.9 mmHg, p<0.001).	–	–	Overall incidence of AE similar with EPL vs SPI. Male gynecomastia (4.5% vs 21.2%, p=0.033) and female mastodynia (4.5% vs 21.1%, p=0.026) less common with EPL vs SPI. Hyperkalemia occurred in 1 EPL vs 7 SPI recipients.
R, OL / 12 mon / N=54 / M:F 24/30 [63]	EPL 25–100 mg daily SPI 12.5–100 mg daily	No significant difference in effect on BP with EPL vs SPI (–	–	No significant difference in effect on urinary albumin	Gynecomastia seen in spironolactone group (n=2) but not EPL

		28/–16 vs –30/–19 mmHg).		excretion with EPL vs SPI (–3.8 vs –4.4 mg/g creatinine).	group. No patients had serum K >5.0 mEq/L in either group.
Heart failure (acute decompensated) OB / 594±317 days / N=838 / M:F 492:305 [64]	EPL 34±15 mg SPI 27±8 mg	No significant difference in effect on SBP with EPL vs SPI (+12±24 vs +16±26 mmHg).	No significant difference in effect on serum BNP with EPL vs SPI (–55±58 vs –163±644 pg/mL, p=0.372). PEP: No significant difference in risk of composite of cardiovascular death or hospitalization (hazard ratio 1.1016, 95% CI 0.567–1.764).	–	Gynecomastia/breast pain seen with SPI (4%) but not EPL (p=0.018). Prevalence of severe hyperkalemia >6 mEq/L did not differ between EPL and SPI (6% vs 8%, p=0.549).

bd = twice daily; BNP = brain natriuretic peptide; BP = blood pressure; DB = double-blind; DBP = diastolic blood pressure; EPL = eplerenone; F = female; OB = observational; od = once daily; OL = open-label; OL-BE = open-label, blinded-endpoint; M = male; mon = months; PEP = primary endpoint; PL = placebo; R = randomized; SBP = systolic blood pressure; SPI = spironolactone; wks = weeks.

Table 5 Comparison of clinical effects between emerging non-steroidal MRAs and older steroidal MRAs

Clinical condition **Study design / duration /** **N / Sex ratio** **[Reference]**	**Treatment groups**	**Blood pressure**	**Cardiovascular effects:** **B-type (brain) natriuretic protein; composite clinical endpoint**	**Renal effects: protein/albumin excretion; electrolytes; eGFR**	**Adverse effects**
Healthy volunteers					
AZD9977 R, CO / Single dose / N=23 / Male [35]	FLU AZD 200 mg + FLU EPL 100 mg + FLU AZD 200 mg + EPL 100 mg + FLU	–	–	PEP: In the presence of FLU, AZD 200 mg had similar effect to EPL 100 mg on urinary Na^+/K^+ ratio (by increasing Na^+ excretion). Coadministration of AZD + EPL had an additive effect.	Frequency of AEs similar across groups.
Apararenone R, DB, PC, AC/ Single dose / N=36 / Male [28]	APA 160, 640 mg EPL 200 mg PL	-	-	PEP: After FLU challenge, APA 640 mg (but not 160 mg) and EPL 200 mg increased Na^+/K^+ ratio significantly vs PL. EPL effect peaked at 8 h;	Incidence of AEs: APA 160 mg 33.3%, APA 640 mg 33.3%, EPL 11.1%, PL 16.7%.

				APA effect increased from 8–12 h onwards. EPL had greater effect than APA 160 mg for 0–24 h; APA 160 and 640 mg had greater effect than EPL for 24–48 h.	
Essential hypertension					
Esaxerenone R, DB-PC, OL-AC / 12 wks[a] / N=423 / M:F 295:128 [39]	ESA 1.25, 2.5, 5 mg od EPL 50→100 mg od (escalated after 2–4 weeks) PL	PEP: Dose-response reduction in SBP/DBP of –10.7/–5.0, –14.3/–7.6 and –20.6/–10.4 mmHg with ESA 1.25, 2.5, 5 mg ($p<0.05$, $p<0.001$, $p<0.001$ vs PL). Reduction of –17.4/–8.5 mmHg with EPL.	–	Mean change in creatinine-adjusted eGFR –2.31 to –6.36 mL/min/1.73 m^2 with ESA vs –2.11 mL/min/1.73 m^2 with EPL.	Incidence of AEs similar between groups (ESA 30.1–40.5%, EPL 36.9%, PL 46.0%).
Esaxerenone (ESAX-HTN) R, DB / 12 wks[a] / N=998 / M:F 721:277 [65]	ESA 2.5, 5 mg od EPL 50 mg od	PEP: ESA 2.5 mg non-inferior to EPL 50 mg for reduction in SBP/DBP (between-group difference –1.6/–0.7 mmHg). ESA 5 mg	–	eGFR decreased slightly in both ESA groups vs remained stable in EPL group.	Incidence of AEs similar between groups: ESA 2.5 mg, 38.4%; ESA 5 mg, 44.1%, EPL 50 mg, 37.0%.

		superior to EPL 50 mg (difference –4.8/–2.3 mmHg, both p<0.0001). Percentage achieving BP <140/90 mmHg: 31.5% and 41.2% with ESA 2.5 and 5 mg vs 27.5% with EPL 50 mg.			Incidence of hyperkalemia (two consecutive levels ≥5.5 or one ≥6.0 mEq/L): ESA 2.5 kg, 0.9%; ESA 5 mg, 0.6%; EPL 50 mg, 0%.
Heart failure[b] + chronic kidney disease[c]					
Finerenone (ARTS) R, DB-PC[d], OL-AC / 4 wks / N=392 / M:F 312:80 [66]	FIN 2.5, 5, 10 mg od, 5 mg bd SPI 25→50 mg od (uptitrated day 15[e]; mean dose 37 mg/day) Both added to evidence-based therapy for HF	Smaller reduction in mean SBP with all doses of FIN vs SPI (–1.9 to –4.2 mmHg vs –10.1 mmHg, p=0.0023–0.0255). Changes with FIN similar to PL (–3.1 mmHg).	Similar reductions in median levels of BNP and NT-proBNP with FIN 10 mg od/5 mg bd vs SPI (–31.0/–35.0 vs –47.0 pg/mL, and –193.65/–106.40 vs –170.30 pg/mL, respectively).	Similar reduction in mean UACR with all FIN doses and SPI (geometric mean ratio versus baseline 0.69–0.86 vs 0.61). Smaller decrease in mean eGFR with FIN vs SPI (–0.85 to –2.69 vs –6.7 mL/min/1.73 m^2, p=0.0001–0.0133).	Lower overall incidence of AEs with all FIN doses vs SPI (47.0–53.7% vs 79.4%). PEP: Smaller increase in mean serum K with FIN vs SPI (0.04–0.30 vs 0.45 mmol/L, p<0.0001–0.0107). Lower incidence of hyperkalemia with FIN vs SPI (5.3% vs 12.7%, p=0.048). Lower incidence of worsening renal

					function with FIN vs SPI (1.5–10.4% vs 38.1%).
Worsening heart failure[f] + chronic kidney disease and/or diabetes mellitus[g]					
Finerenone (ARTS-HF) R, DB / 90 days / N=1055 / M:F 816:239 [67]	FIN 2.5→5, 5→10, 7.5→15, 10→20, 15→20 mg od (uptitrated day 30)[h] EPL 25 mg qad→25 mg od→50 mg od (uptitrated on days 30 and 60)[h]; mean dose 38.6 mg/day Both added to evidence-based therapy for HF	Mean SBP decreased by <3 mmHg in all groups.	PEP: No significant difference in proportions achieving a decrease in NT-proBNP of >30% from baseline with any FIN dose (30.9–38.8%) vs EPL (37.2%). Exploratory: Incidence of composite endpoint (death from any cause, cardiovascular hospitalization, emergency presentation for worsening HF) lower in all FIN groups (except 2.5→5 mg) vs EPL; nominal significance	No significant difference for change in eGFR with FIN vs EPL. Mean eGFR increased with the two lowest FIN doses (+ 1.317 and +0.431 mL/min/1.73 m^2) and decreased with the three higher FIN doses (–0.146 to –2.440 mL/min/1.73 m^2) and with EPL (–1.085 mL/min/1.73 m^2).	Similar overall incidence of AEs with all FIN doses (62.9–78.5%) and EPL (76.9%). Mean change in serum K smaller with all FIN doses (+0.119–0.202 mmol/L) vs EPL (+0.262 mmol/L). Similar incidence of hyperkalemia ≥5.6 mmol/L with FIN (3.6–6.3%) vs EPL (4.7%). Renal AEs leading to hospitalization occurred in 1 patient each with FIN 2.5→5, 7.5→15, and 15→20 mg vs 2

			achieved for FIN 10→20 mg (HR 0.56, p=0.02).		with EPL.

a Preceded by a 4-week washout period to remove effects of previous antihypertensive treatments.
b Chronic heart failure with reduced ejection fraction.
c Moderate chronic kidney disease (eGFR 30–60 mL/min/1.73 m^2).
d Results not reported here.
e SPI titrated up provided serum potassium remained ≤4.8mmol/L.
f Worsening chronic heart failure with reduced ejection fraction, requiring hospitalization and intravenous diuretics.
g Patients with type 2 diabetes mellitus had an eGFR of >30 mL/min/1.73 m^2; those without diabetes had an eGFR of 30–60 mL/min/1.73 m^2.
h Both study drugs were titrated up provided serum potassium remained ≤5.0 mmol/L.
AE = adverse effect; APA = apararenone; bd = twice daily; BNP = B-type (brain) natriuretic peptide; CO = cross-over; DB = double-blind; DB-PC = double-blind placebo-controlled; eGFR = estimated glomerular filtration rate; EPL = eplerenone; ESA = esaxerenone; FIN = finerenone; FLU = fludrocortisone (synthetic mineralocorticoid); HF = heart failure; HR = hazard ratio; K = potassium; M:F = male:female; MRA = mineralocorticoid receptor antagonist; NT-proBNP = amino-terminal proBNP; od = once daily; OL-AC = open-label active comparator; PEP = primary endpoint; PL= placebo; qad = every other day; R = randomized; SBP = systolic blood pressure; UACR = urinary albumin:creatinine ratio.