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Themed Issue: Emerging Fields for Therapeutic Targeting of the Aldosterone-Mineralocorticoid Receptor Signaling Pathway

THEMED ISSUE REVIEW

Novel non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease

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Mineralocorticoid receptor antagonists (MRAs) are key agents in guideline-oriented drug therapy for cardiovascular diseases such as chronic heart failure with reduced ejection fraction and resistant hypertension. Currently available steroidal MRAs are efficacious in reducing morbidity and mortality; however, they can be associated with intolerable side effects including hyperkalaemia in everyday clinical practice. Recently, a new class of non-steroidal MRAs (including esaxerenone, AZD9977, apararenone, KBP-5074 and finerenone) have been developed with an improved benefit–risk profile and a novel indication for finerenone for diabetic kidney disease. To better understand the non-steroidal MRAs, this review provides information on the molecular pharmacology as well as relevant current preclinical and clinical data on cardiorenal outcomes. A comparative review of all compounds in the class is discussed with regard to clinical efficacy and safety as well as a perspective outlining their future use in clinical practice.

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KEYWORDS
aldosterone, antagonist, cardiovascular disease, diabetic kidney disease, mineralocorticoid receptor, nonsteroidal

Abbreviations: BNP, pro-B-type natriuretic peptide; CKD, chronic kidney disease; DOCA, deoxycorticosterone acetate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LBD, ligand-binding domain; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; T2D, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

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1 | INTRODUCTION

The mineralocorticoid receptor (MR) and their antagonists (MRAs) have been important components of guideline-oriented drug therapy for cardiovascular diseases such as chronic heart failure with reduced ejection fraction (HFrEF) or resistant hypertension for many years (Carey et al., 2018; Ponikowski et al., 2016; Williams et al., 2018). In the past, these were exclusively MRAs with steroid-based chemical structures and proven clinical efficacy, namely, **spironolactone** and **eplerenone**. However, these drugs can have serious unwanted side effects in everyday clinical practice that limit their use (Agarwal et al., 2021). The focus here is on hyperkalaemia induced by steroidal MRAs, primarily seen in patients with impaired kidney function or concomitant therapy with renin–angiotensin system (RAAS) blockers, such as **ACE** inhibitors (ACEi) or **angiotensin type 1 receptor** blockers (ARBs) (Agarwal et al., 2021).

The limited risk–benefit profile of steroidal MRAs has recently led to the development of a new group of MRAs, the non-steroidal MRAs. These compounds were developed with the aim to improve the side-effect profile of currently available steroidal MRAs while maintaining clinical efficacy. They have so far demonstrated significant risk reduction in cardiovascular diseases as well as slowing kidney disease progression. This has led to the expansion of their clinical use in cardiorenal disease (Agarwal et al., 2021).

This review provides general information on the molecular pharmacology of MRAs and gives a brief overview of MRAs of both classes. Additionally, we comprehensively present data from all non-steroidal MRAs currently in development or in clinical use and discuss their preclinical and clinical efficacy/safety profiles.

2 | MOLECULAR BIOLOGY/ PHARMACOLOGY OF THE MR AND CARDIORENAL DISEASE

The MR (**NR3C2**) belongs to the group of nuclear hormone receptors that function as ligand-activated transcription factors (Alexander et al., 2015; McKenna & O'Malley, 2010). In 1987, the MR was cloned, and the high-affinity agonist ligands, **aldosterone**, **cortisol** and **corticosterone** were identified (Arriza et al., 1987). The MR consists of three functional domains: N-terminal domain; DNA-binding domain (DBD); and C-terminal ligand-binding domain (LBD) (Arriza et al., 1987). After ligand binding to the MR-LBD, a conformational change of the LBD is induced leading to chaperone release, nuclear translocation, DNA-binding, coregulator recruitment and transcriptional regulation of MR target genes (Galigniana et al., 2004). This process takes place under strict ligand-dependent control and involves a ligand-specific conformational change of the LBD, which induces the ligand-specific recruitment of a distinct set of MR coactivators.

The MR can interact with more than 20 coregulator proteins that modify MR-target gene expression (Fuller et al., 2017). In general, these proteins can be divided into coactivators, which activate gene transcription by different mechanisms such as chromatin remodelling or histone modification, or corepressors with histone deacetylase activity (Fuller et al., 2017). Depending on the composition of these MR coregulator multiprotein complexes, MR-target gene transcription is then induced or repressed. The configuration of these complexes depends on the chemical ligand structure and on cell/organ-specific expression of the MR and its coregulators. Taken together, these processes, also known as selective MR modulation, allow for highly gene-, cell- and organ-specific gene regulation by the MR depending on the bound agonist or antagonist ligands.

Ligand-activated MR is an important regulator of electrolyte and water homeostasis. The MR is expressed in renal epithelial cells where aldosterone binding induces the expression of **epithelial sodium channels**, **serum–glucocorticoid-regulated kinase 1** and **sodium–potassium ATPases** inducing water and sodium reabsorption (Berger et al., 2000). During the last 20 years, additional multifaceted functions of the MR have been identified that are important in the pathogenesis of cardiovascular and renal disease. The MR is expressed in almost all cardiac cells including cardiomyocytes, cardiac fibroblasts, endothelial and vascular smooth muscle cells. By using cell type-specific murine deletion models, MR was shown to induce cardiomyocyte hypertrophy and apoptosis, oxidative stress and cardiac fibrosis and negatively affects vascular function and BP after agonist ligand activation (Fraccarollo et al., 2011; Lother et al., 2011; McCurley et al., 2012; Rickard et al., 2014). In the aggregate, ligand-activated MR promotes cardiac damage and worsens cardiac function in ischaemic and nonischaemic injury models.

In the kidney, MR is expressed in endothelium and vascular smooth muscle cells, as well as in podocytes and mesangial cells, in addition to its expression in epithelial cells of the distal nephron (Bertocchio et al., 2011). Ligand-activated renal MR drives chronic kidney disease (CKD) by promoting glomerulosclerosis, renal fibrosis, proteinuria and a decline in GFR (Bertocchio et al., 2011; Epstein, 2015; Yao et al., 2019). MR plays a crucial role in the development of diabetic nephropathy by inducing renal fibrosis, mesangial expansion, tubulointerstitial damage and inflammation (Han et al., 2006; Lee et al., 2020; Leroy et al., 2009). In recent years, increasing evidence demonstrates the importance of the MR activation in cells of the innate and adaptive immune system. Moreover, MR activation in different cell types (including dendritic cells, monocytes, macrophages or T-cells) is significantly involved in the pathogenesis of cardiorenal disease (Barbaro et al., 2017; Ferreira et al., 2021).

Taken together, these data support that the MR is a key pathogenetic regulator of cardiorenal disease under certain conditions. Due to its broad expression profile in disease-relevant cell types, as well as its molecular mode of action, pharmacological blockade of the MR allows a highly specific therapeutic intervention for these diseases.

3 | STEROIDAL MRAs—AN OVERVIEW

Currently, two steroidal MRAs are in clinical use (Figure 1) The first one, **spironolactone**, was discovered in 1957 as a steroidal MRA derived from the chemical structure of **progesterone** followed by

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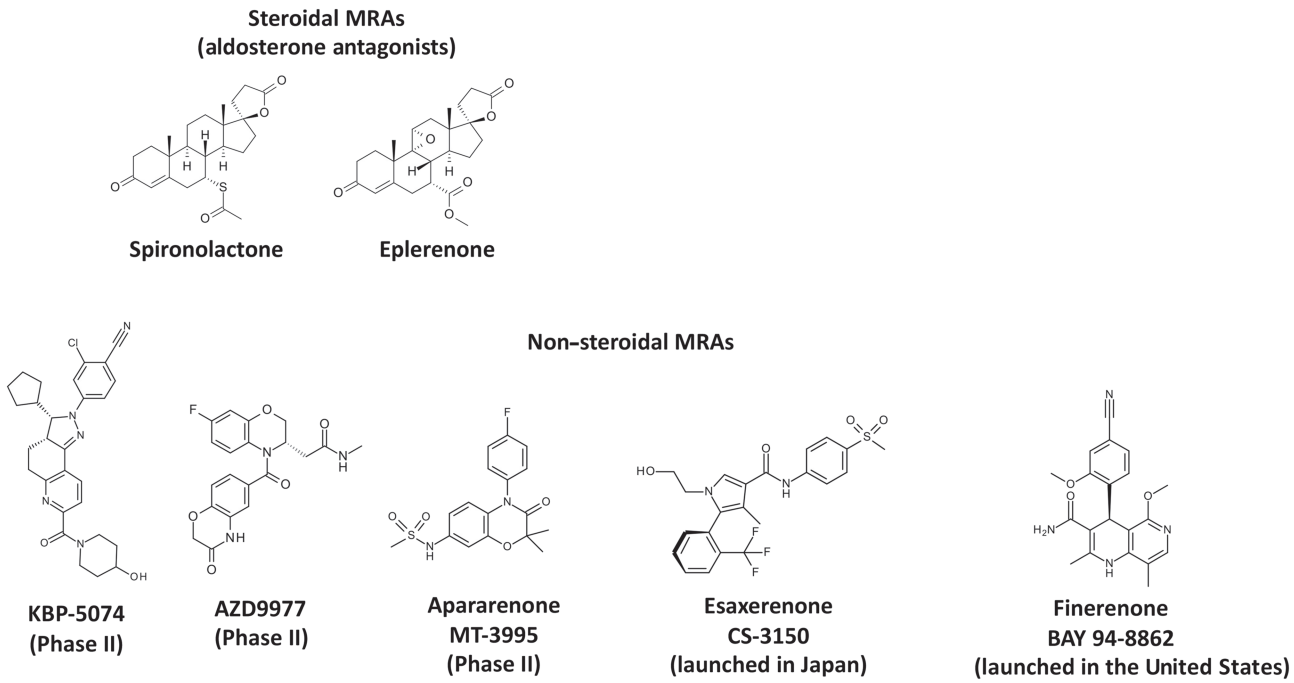

FIGURE 1 Overview over chemical structures of steroidal mineralocorticoid receptor antagonists (MRAs) and novel non-steroidal MRAs in clinical development or approved

eplerenone as the second steroidal MRA in 1987 (de Gasparo et al., 1987; Kagawa et al., 1957). Both substances have a similar binding mode to the MR-LBD, preventing the binding of agonist ligands. They are both called 'passive' MRAs, which means that these compounds are not able to stabilize the receptor conformation in such a way as to effectively bind transcriptional coregulators, especially corepressors (Kolkhof et al., 2017). This type of MR-LBD binding is essentially distinct from the binding of so-called 'bulky' antagonists (see non-steroidal MRAs) (Fagart et al., 2010) and may explain the distinct pharmacological differences between steroidal and non-steroidal MRAs.

In terms of their specific pharmacodynamic and pharmacokinetic profiles, major differences are observed between both steroidal MRAs (Figure 2). Spironolactone exhibits a higher affinity to the MR compared with eplerenone (MR IC_{50}: spironolactone: 24 nM and eplerenone: 990 nM) (Fagart et al., 2010) (Figure 2). In contrast, eplerenone shows a much higher MR selectivity, hence not associated with the spironolactone antiandrogenic and progestational side effects due to unspecific binding to androgen and progesterone receptors (Fagart et al., 2010) (Figure 2). Pharmacokinetically, eplerenone exhibits lower plasma protein binding and has a shorter plasma half-life compared with spironolactone, which is converted to its active metabolites, canrenone and 7α-thiomethylspironolactone (plasma half-life: eplerenone: 4–6 h and spironolactone: >12 h in healthy volunteers/>24 h in heart failure patients) (Kolkhof et al., 2017).

Results from the Randomized Aldactone Evaluation Study (RALES) in 1663 patients with HFrEF in the New York Heart Association classification (NYHA Stage III–IV) clearly demonstrated that spironolactone significantly reduces mortality and markedly lowers hospitalization rate for heart failure in these patients (Pitt et al., 1999). The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) then showed that eplerenone significantly reduced total and cardiovascular mortality, as well as hospitalization rate in 6642 patients with myocardial infarction (MI), left ventricular ejection fraction (LVEF) ≤40% and symptomatic heart failure (HF) (Pitt et al., 2003). In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS) in 2737 patients with LVEF ≤ 30% and NYHA Stage II, eplerenone treatment resulted in a substantial decline of all-cause and cardiovascular death, and hospitalization rate (Zannad et al., 2011). Consequently, the current European Society of Cardiology heart failure guidelines (Ponikowski et al., 2016) recommend steroidal MRAs as third-line therapy after ACEi and β-**adrenoceptor** blockers for the treatment of HFrEF. Despite the convincing results with steroidal MRAs in HFrEF, no significant reduction of the primary endpoint could be achieved with spironolactone in heart failure with preserved ejection fraction (HFpEF) in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure with Aldosterone Antagonist) (Pitt et al., 2014). However, because this study had limitations in study design and substantial regional variations in which benefit of spironolactone was documented in the Americas but not in Eastern Europe (Pfeffer et al., 2015), it is not yet possible to conclusively assess whether MRAs affect morbidity and/or mortality in HFpEF.

Data on steroidal MRAs and their effects in patients with CKD are limited. In 2014, a Cochrane review analysed data from 27 studies in 1549 patients and documented that spironolactone reduces proteinuria and systolic/diastolic BP in patients with CKD (Bolignano et al., 2014). Analyses of GFR showed only imprecise effects by

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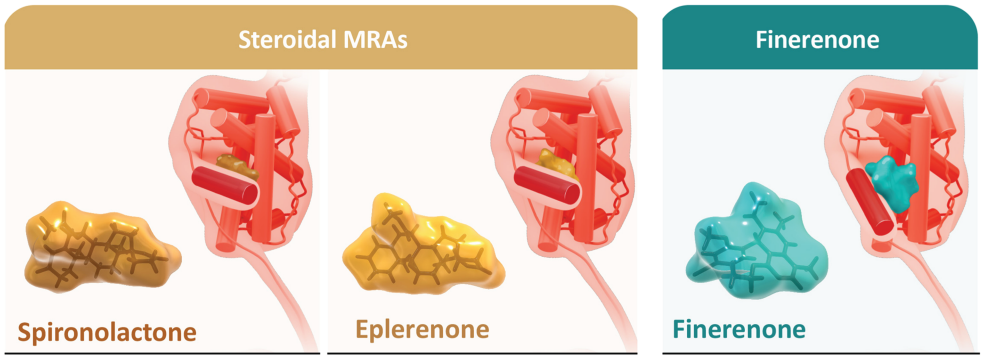

	Spironolactone	Eplerenone	Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (non-steroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	–
Sexual side effects	++	(+)	–
Half-life	>20 h**	4–6 h**	2–3 h*
Active metabolites	++	–	–
Effect on BP	+++	++	+

FIGURE 2 Overview of binding mode of spironolactone, eplerenone and finerenone with proposed/hypothesized conformational change of helix 12 and summary of respective key pharmacodynamic and pharmacokinetic characteristics. For graphical representation of MR, the structure of human oestrogen receptor-α (**ERα**) was used as reference. DNA-binding and ligand-binding domains (PDB: 1HCQ and 1A52) (Schwabe et al., 1993; Tanenbaum et al., 1998) were assembled and coloured using Chimera v1.15 and Cinema 4D R21. *In healthy volunteers. **In heart failure patients

spironolactone (Bolignano et al., 2014). An updated version of the Cochrane analyses from 2020 confirmed the beneficial effects of steroidal MRAs on proteinuria, as well as on GFR in patients with mild to moderate CKD; however, the data were based on heterogeneous results in the individual studies (Chung et al., 2020). The antiproteinuric and beneficial actions on GFR by MRAs were confirmed in a recent meta-analysis, which included 2767 patients from 31 trials (Alexandrou et al., 2019). A consistent drawback in all trials of steroidal MRAs in CKD was an increased risk of hyperkalaemia, which in many cases can be therapy limiting (Alexandrou et al., 2019; Bolignano et al., 2014; Chung et al., 2020). In fact, Navaneethan et al. (2009) described a significant threefold increase in the risk of hyperkalaemia with the addition of spironolactone to ACEi and/or ARB. A recent meta-analysis by Currie et al. (2016) among seven smaller studies with steroidal MRAs in patients with CKD and diabetes mellitus revealed even a 4.3-fold higher relative risk of developing hyperkalaemia with steroidal MRAs on top of RAAS inhibition compared with RAAS inhibition alone. In an observational study, which included all Stockholm citizens initiating steroidal MRA therapy during 2007–2010 ($n = 13{,}726$ new users, 99.2% spironolactone), 18.5% experienced hyperkalaemia during the first year, 47% discontinued steroidal MRA therapy after hyperkalaemia and 76% were not reintroduced to therapy after discontinuation (Trevisan et al., 2018). Thus, hyperkalaemia was very common and frequently followed by therapy interruption, especially among participants with CKD. Furthermore, in late-stage CKD, MRAs have relative or absolute contraindications.

These data indicate that although the steroidal MRAs are clinically efficacious in patients with HFrEF, data in patients with CKD still appear to be incomplete and their use is limited by hyperkalaemia development.

4 | NOVEL NON-STEROIDAL MRAs

Considering the described benefit–safety profile of steroidal MRA, the development of new selective non-steroidal MRA has been intensively pursued with the aim to improve efficacy and reduce unwanted side effects, in particular hyperkalaemia (Kolkhof et al., 2021). Multiple novel compounds are currently in development at different stages or already in clinical use including **esaxerenone**, **AZD9977**, apararenone, KBP-5074 and **finerenone** (Figures 1 and 3).

4.1 | Esaxerenone

The non-steroidal MRA esaxerenone or CS-3150 (Daiichi Sankyo) has been recently approved in Japan for the treatment of arterial

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	Esaxerenone	AZD9977	Apararenone	KBP-5074	Finerenone	Spironolactone
MR IC_{50} (nM)	3.7[1]	370[6]	280[8]	2.7[10]	18[12]	24[12]
Pharmacological profile: • Agonism/antagonism • Cofactor recruitment	• Full antagonist[1] • No data	• Partial agonist[6] • 'Modulator'[6]	• Full antagonist[8] • No data	• Full antagonist[10] • No data	• Full antagonist[12] • Inverse agonist[13, 14]	• Full antagonist[12] • Partial agonist[13]
Active metabolites	• M1: weak antag., long half-lives[2]	• No data	• '1118174': weak antag., long half-lives	• No data	• No active metabolites[15]	• Main: 7α-TMS and canrenone: full antag., long half-lives[21]
Human half-life (healthy volunteers)	• 30 h[2]	• 4–9 h[6]	• 275–285 h[8] • 1126–1250 h for '1118174'[8]	• ~60 h[11]	• 2–3 h[15]	• 7α-TMS: 13.8h[21] and canrenone: 16.5h[21]
Renal excretion: • % of dose • % unchanged	• 38.5%[2] • 1.6%[2]	• 24–37%[7] • No data	• <14%[8] • No data	• No data • No data	• 79.6%[16] • <1%[15]	• Canrenone: ~5%[22, 23] • Unchanged spironolactone: 0%[22]
Clinical effects on BP: • Absolute SBP decrease • In direct comp. to sMRAs or nsMRAs (for spironolactone)	• Robust[3] • 2.5 mg·d^{-1}non-inf., 5 mg·d^{-1}superior to eplerenone[4]	• No data • No comp. data	• Robust[9] • No comp. data	• Robust[11] • No comp. data	• Modest[17, 18] • Less than spironolactone[19]	• Robust[24, 25, 26] • Higher than finerenone[18]
Clinical effects on serum K^+: • Mean change in serum K^+ (in DKD, CKD or rHT-CKD) • Discontinuation due to hyperkalaemia vs. placebo • In direct comp. to sMRAs or nsMRAs (for spironolactone) (HT or wCHF with CKD)	• Between 0.2 and 0.3 mM[5] (DKD) • 4% vs. 0.4%[5] • Higher than eplerenone[4] (HT)	• No patient data • No data • No data	• 0.14–0.25 mM[9] (DKD) • 2.7–4.1% vs. 0%[9] • No data	• 0.19–0.33 mM[11] (rHT-CKD) • 3.7% vs. 3.5%[11] • No data	• 0.18[20]–0.25[18] mM (DKD) • 2.3% vs. 0.9%[18], 1.2% vs. 0.4%[20] • Less than spironolactone[19] (wCHF with CKD)	• ~0.4 mM[24] (rHT-CKD) – 0.8 mM[27] (CKD) • 7% vs. 1%[24] • Higher than finerenone[19] (wCHF with CKD)

FIGURE 3 Pharmacodynamic and pharmacokinetic characteristics of non-steroidal mineralocorticoid receptor antagonists and spironolactone. [1]Arai, Homma, et al. (2015); [2]Yamada et al. (2019); [3]Ito et al. (2019); [4]Ito, Itoh, et al. (2020); [5]Ito, Kashihara, et al. (2020); [6]Bamberg et al. (2018); [7]Whittaker et al. (2020); [8]Nakamura and Kawaguchi (2021); [9]Wada et al. (2021); [10]Bakris, Yang, and Pitt (2020); [11]Bakris et al. (2021); [12]Pitt et al. (2012); [13]Amazit et al. (2015); [14]Grune et al. (2018); [15]Heinig et al. (2016); [16]Gerisch et al. (2018); [17]Bakris et al. (2015); [18]Bakris, Agarwal, et al. (2020); [19]Pitt et al. (2013); [20]Pitt et al. (2021); [21]Gardiner et al. (1989); [22]Karim et al. (1976); [23]Karim (1978); [24]Agarwal et al. (2019); [25]Weinberger et al. (2002); [26]Williams et al. (2015); [27]Bianchi et al. (2006). 7α-TMS, 7α-thiomethylspirono-lactone; CKD, chronic kidney disease; comp., comparison; DKD, diabetic kidney disease; HT, arterial hypertension; modest, ≤5-mmHg SBP change; nsMRA, non-steroidal MRA; rHT, uncontrolled/resistant hypertension; rHT-CKD, uncontrolled/resistant hypertension and chronic kidney disease; robust, ≥10-mmHg SBP change; SBP, systolic BP; sMRA, steroidal mineralocorticoid receptor antagonist; wCHF, worsening of chronic heart failure

hypertension. Esaxerenone is a high-affinity (IC_{50}: 3.7 nM) and highly selective MRA, with a more than 1000-fold higher selectivity for the MR compared with the glucocorticoid, progesterone or androgen receptor (Arai, Homma, et al., 2015) (Figure 3). The co-crystal structure of the MR-LBD with esaxerenone revealed a different binding mode compared with steroidal MRAs, where helix 12 of the LBD is prevented from going into agonist position, thus likely blocking the binding of coactivators (Takahashi et al., 2020). This binding mode may explain why esaxerenone lacks agonistic actions at the MR in the absence of aldosterone, as seen with steroidal MRAs, and may point towards a specific MR-target gene regulation programme induced by this antagonist (Arai, Homma, et al., 2015) (Figure 3). In preclinical models, the pharmacokinetic profile of esaxerenone is the basis for a long-lasting action (plasma half-life rats: 6.5–6.9 h), high oral bioavailability and predominant excretion via faeces (Arai, Homma, et al., 2015; Wan et al., 2021). A long plasma half-life has been confirmed in healthy human volunteers (plasma half-life: 30 h) (Yamada et al., 2019) (Figure 3). Esaxerenone induced nephroprotective effects in the deoxycorticosterone acetate (DOCA)/salt and Dahl salt-sensitive hypertensive rat models and reduced the development of cardiac hypertrophy in Dahl salt-sensitive rats (Arai et al., 2016; Arai, Tsuruoka, & Homma, 2015).

The antihypertensive action of esaxerenone was examined in multiple Phase II clinical studies. In 426 Japanese patients with essential hypertension treated for 12 weeks, systolic sitting BP was lowered by −10.7, −14.3 and −20.6 mmHg using 1.25-, 2.5- or 5-mg·day^{-1} esaxerenone, respectively, compared with −7.0-mmHg reduction in the placebo group (Ito et al., 2019) (Figure 3). Efficacy and safety of esaxerenone was also tested in two multicentre, open-label, non-randomized dose-escalation studies in Japanese hypertensive patients with moderate kidney dysfunction (eGFR ≥ 30 and <60 ml·min^{-1} per 1.73 m^2) who did not have type 2 diabetes mellitus (T2D) with albuminuria (Ito et al., 2021). Primary endpoints were changes from baseline in sitting systolic and diastolic BP after 12-week treatment. The use of esaxerenone as monotherapy or as add-on to RAAS inhibitor therapy demonstrated robust antihypertensive effects in both studies. Maximum serum potassium increases from baseline were 0.3 ± 0.3 and 0.4 ± 0.3 mM in the monotherapy and add-on therapy groups, respectively (Ito et al., 2021). A serum K^+ level of ≥5.5 mM was observed in 12.1% of patients receiving add-on therapy (0% receiving monotherapy), but no patient met predefined serum K^+ level criteria for dose reduction or therapy discontinuation (Ito et al., 2021).

Esaxerenone was further tested in two Phase III studies: ESAX-HTN and ESAX-DN. In the ESAX-HTN study, 1001 patients with arterial hypertension were randomized to esaxerenone 2.5 or 5 mg·day^{-1} or eplerenone 50 mg·day^{-1} and treated for 12 weeks (Ito, Itoh, et al., 2020). The low-dose esaxerenone (2.5 mg·day^{-1}) led to similar reductions of sitting BP as eplerenone 50 mg·day^{-1} (sitting systolic

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BP change: esaxerenone 2.5 mg·day^{-1}: −13.1 mmHg vs. eplerenone 50 mg·day^{-1}: −11.9 mmHg), whereas the 5-mg·day^{-1} esaxerenone dose was significantly more effective in BP lowering than the low dose (sitting systolic BP change: esaxerenone 5 mg·day^{-1}: −16.5 mmHg) (Ito, Itoh, et al., 2020) (Figure 3). One proposed mechanism for its improved antihypertensive efficacy was its long duration of action (plasma half-life: 18.6 ± 2.4 h) (Ito, Itoh, et al., 2020). There was a slightly higher incidence of increased serum potassium levels in the esaxerenone groups compared with eplerenone (Ito, Itoh, et al., 2020) (Figure 3).

The second trial, ESAX-DN, was a multicentre Phase III clinical trial evaluating the efficacy and safety of esaxerenone in 455 patients with T2D and microalbuminuria (urinary albumin-to-creatinine ratio [UACR] of 45- to 300-mg·g^{-1} creatinine) (Ito, Kashihara, et al., 2020). Patients already treated with blockers of the RAAS were randomized to placebo or esaxerenone 1.25 mg·day^{-1} and gradually up-titrated to 2.5 mg·day^{-1} depending on serum potassium levels (Ito, Kashihara, et al., 2020). After 52 weeks, esaxerenone treatment resulted in a significantly higher number of patients reaching UACR remission, which was defined as the primary endpoint and included UACR < 30-mg·g^{-1} creatinine and a ≥30% reduction in UACR from baseline at two consecutive time points (Ito, Kashihara, et al., 2020). Consistent with the data from ESAX-HTN, the esaxerenone group exhibited significantly higher rates of hyperkalaemia including serum potassium ≥6.0 or ≥5.5 mEq on two consecutive measurements (placebo: 2% vs. esaxerenone: 9%) and discontinuation due to increased serum potassium (placebo: 0.4% vs. esaxerenone: 4%) (Ito, Kashihara, et al., 2020) (Figure 3).

Taken together, the data indicate that esaxerenone is a novel non-steroidal MRA with high affinity and selectivity for the MR that effectively lowers BP in hypertensive patients and reduces microalbuminuria in T2D patients.

4.2 | AZD9977

AZD9977 (AstraZeneca) is a novel non-steroidal MRA with an MR affinity and MR selectivity comparable with eplerenone (Bamberg et al., 2018) (Figure 3). AZD9977 induces a partial MR antagonism and shows partial agonistic activity in the absence of aldosterone (Bamberg et al., 2018) (Figure 3). Cocrystalization studies revealed an MR-binding mode of AZ9977 different from eplerenone accompanied by a distinct MR-cofactor recruitment pattern (Bamberg et al., 2018). However, the interpretation of these data is limited because the cofactor-binding studies are lacking concentration response studies for both antagonistic ligands (Bamberg et al., 2018). AZD9977 reduced UACR in a dose-dependent manner and protected against renal injury in preclinical rodent models (Bamberg et al., 2018).

In clinical Phase I studies, AZD9977 was safe and well tolerated with a plasma half-life after single dosing of 2–3 h and after 8-day administration between 4 and 9 h (Erlandsson et al., 2018; Whittaker et al., 2020) (Figure 3); 24–37% of AZD9977 was excreted in the urine (Whittaker et al., 2020) (Figure 3). After a **fludrocortisone** challenge, a single dose of AZD9977 (200 mg) resulted in a significant increase of the urine Na^+/K^+ ratio similarly to eplerenone (100 mg) (Erlandsson et al., 2018). Currently, one Phase II study is ongoing, which investigates the efficacy, safety and tolerability of AZD9977 in combination with the **sodium–glucose cotransporter 2 (SGLT2)** inhibitor, **dapagliflozin** in patients with heart failure (LVEF < 55%) and CKD (NCT04595370).

It is unclear whether this low-affinity non-steroidal MRA that exerts renoprotective actions in preclinical models is effective clinically.

4.3 | Apararenone

Apararenone (Mitsubishi Tanabe) is a very long-acting, non-steroidal MRA. Unfortunately, no preclinical data on this compound are available. Recently, the results of two Phase I studies and a Phase II study have been published (Nakamura et al., 2020; Nakamura & Kawaguchi, 2021; Wada et al., 2021). In the introduction of these studies, some pharmacodynamic characteristics were described. An IC_{50} of 280 nM makes it less potent than spironolactone and more comparable with eplerenone (Nakamura & Kawaguchi, 2021) (Figure 3). Apararenone exerts a high selectivity for the MR, with IC_{50} values for the androgen, progesterone and glucocorticoid receptors above 100 μM (Nakamura & Kawaguchi, 2021). The molecular binding mode to the MR has not been reported. No published efficacy or safety data in preclinical rodent models are available.

In a Phase I study, administration of single and multiple doses of apararenone was safe and well tolerated in 223 healthy adults (Nakamura & Kawaguchi, 2021). Noteworthy is the extremely long plasma half-life of the drug (275–285 h) and its active metabolite 1118174 (1126–1250 h) that is observed after single and multiple dosing (Nakamura & Kawaguchi, 2021) (Figure 3). The drug is metabolized in the liver, likely undergoes enterohepatic circulation and regulates cytochrome P450 enzyme and P-glycoprotein activity; however, only a minimal risk for potential drug–drug interactions has been described (Nakamura et al., 2020). Additionally, 14% of apararenone is excreted in urine (Nakamura & Kawaguchi, 2021) (Figure 3). Urinary Na^+/K^+ ratios after a fludocortisone challenge were increased with a delayed time course compared with eplerenone (Nakamura & Kawaguchi, 2021).

A Phase II study in 293 patients with early stage diabetic kidney disease (UACR of ≥50- to 300-mg·g^{-1} creatinine) showed that apararenone significantly lowers UACR after 24 weeks in a dose-dependent manner when compared with placebo (Wada et al., 2021). Apararenone administration resulted in a mild eGFR decrease (−6.6% to 8.8% median change from baseline) as well as a maximal increase of serum potassium of 0.3 mM at the highest dose (10 mg·day^{-1}).

4.4 | KBP-5074

KBP-5074 (KBP BioSciences) is a novel, high-affinity and selective non-steroidal MRA. Its binding affinity to the MR is higher than for both steroidal MRAs (KBP-5074: IC_{50}: 2.7 nM), and it selectively binds to the MR when compared with other steroid hormone receptors (Chow et al., 2017) (Figure 3). The efficacy and safety were tested in preclinical

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rodent models. In the Dahl salt-sensitive hypertensive rat model, KBP-5074 dose-dependently lowered BP, significantly reduced 24-h urinary albumin excretion and resulted in a reduced kidney-to-body weight and heart-to-body weight ratio (Chow et al., 2017). These beneficial actions were confirmed in stroke-prone spontaneously hypertensive rats, in which KBP-5074 also inhibited the increase in BP, reduced urinary albumin excretion and decreased kidney-to-body and heart-to-body weight ratios (Chow et al., 2017). Recently, a comparative study with eplerenone in high-salt diet-fed rats with aldosterone infusion showed an improved efficacy and therapeutic index, calculated as the ratio of the EC_{50} for increasing K^+ to the EC_{50} of decreasing UACR, with KBP-5074 (Jaisser et al., 2021). Preclinical analyses were completed by toxicity and safety studies in rats and dogs, in which no toxicity and good tolerability were demonstrated (Chow et al., 2018).

Phase I and II clinical trials were conducted in different adult populations including healthy volunteers, mild/moderate CKD (Stages 2 and 3), severe CKD (Stage 4) or haemodialysis (Bakris et al., 2021; Bakris, Yang, & Pitt, 2020). Safety and tolerability were confirmed in these studies. In healthy volunteers, KBP-5074 (2.5–5.0 mg) was administered once daily for 14 days resulting in time to peak plasma concentration of 6 h and a plasma half-life of 60 h (Bakris, Yang, & Pitt, 2020) (Figure 3). Similar results were documented for patients with mild/moderate CKD. Based on the favourable Phase I results, data from the first Phase II study with KBP-5074 were recently published. The multicentre, randomized, double-blind, placebo-controlled BLOCK-CKD study investigated the safety and efficacy of KBP-5074 (0.25 or 0.5 mg·day^{-1}) in 162 patients with resistant or poorly controlled hypertension and advanced CKD (Stage 3b/4, eGFR ≥ 15 and ≤44 ml·min^{-1} per 1.73 m^2) (Bakris et al., 2021). Patients had a mean baseline BP of 155.3 mmHg systolic and 87.7 mmHg diastolic; 64 (39.5%) had Stage 4 CKD; 125 (77.25%) had proteinuria (UACR ≥ 30 mg·g^{-1}); mean estimated GFR at baseline was 31.9 ml·min^{-1} per 1.73 m^2; and 144 (88.9%) were taking at least three antihypertensive drugs (Bakris et al., 2021). The primary endpoint was systolic BP change from baseline at Day 84. KBP-5074 was well tolerated. Both doses of KBP-5074 resulted in a significantly lower systolic BP at the end of the study. After 84 days, the placebo-subtracted treatment difference was −7.0 mmHg with KBP-5074 0.25 mg and −10.2 mmHg with 0.5 mg (Bakris et al., 2021) (Figure 3). Treatment differences for diastolic BP were not significant (Bakris et al., 2021). Changes in UACR after 84 days between the groups showed a trend towards lower values in the KBP-5074 groups, which did not reach statistical significance (Bakris et al., 2021). Hyperkalaemia incidence (≥5.6 < 6.0 mM) was increased in all three groups (placebo: 5 [8.8%]; KBP-5074 0.25 mg: 6 [11.8%]; and KBP-5074 0.5 mg: 9 [16.7%]) with the highest rate in the 0.5-mg dose group; hyperkalaemia ≥6.0 mM was not observed (Bakris et al., 2021) (Figure 3). Based on these data, a Phase III outcome study is planned and will start very soon.

4.5 | Finerenone

Finerenone (Bayer) is a novel non-steroidal MRA with the most advanced global clinical development programme. Finerenone is a dihydronaphthyridine-based compound with high selectivity for the MR over all other steroid hormone receptors and high binding affinity (IC_{50}: 18 nM) (Barfacker et al., 2012; Pitt et al., 2012) (Figures 2 and 3). Molecular modelling studies revealed that finerenone has a specific binding mode to the MR-LBD (Amazit et al., 2015; Barfacker et al., 2012). By binding as a 'bulky' antagonist, finerenone changes the positioning of helix 12 in a specific manner, which results in distinct MR cofactor-binding profiles compared with other MRAs (Amazit et al., 2015; Fagart et al., 2010; Grune et al., 2018) (Figures 2 and 4). This molecular binding pattern induces an antagonistic ligand-specific target gene programme, which may explain, at least in part, the differential clinical responses observed with finerenone (Agarwal et al., 2021; Grune et al., 2018).

The non-steroidal chemical structure of finerenone determines not only specific interactions with amino acids in the MR-LBD but also the physicochemical properties of the compound, which has a direct impact on plasma protein binding, as well as tissue penetration and distribution (Kolkhof & Barfacker, 2017). Finerenone is 6- to 10-fold less lipophilic than steroidal MRAs and does not cross the blood–brain barrier (Agarwal et al., 2021). By using quantitative whole-body autoradiography with [^{14}C]-labelled finerenone, a balanced distribution of finerenone between the heart and kidneys in rats could be demonstrated, which is in contrast to a predominant renal accumulation of eplerenone and spironolactone (Kolkhof et al., 2014). This distribution may explain some of the observed clinical actions of finerenone including robust cardioprotection.

In preclinical studies, finerenone demonstrated a convincing and consistent protection against cardiorenal damage (Figure 4). In DOCA salt-challenged rats, finerenone markedly reduced cardiac hypertrophy and pro-B-type natriuretic peptide (BNP) levels (Kolkhof et al., 2014). In addition, the UACR was dose-dependently reduced by finerenone, and rats were protected against glomerular, tubular and vascular damage in the kidney (Kolkhof et al., 2014). Importantly, these beneficial effects were achieved by dosages not reducing BP, and protection by finerenone was more efficient than by eplerenone comparing equinatriuretic doses (Kolkhof et al., 2014). Potent anti-hypertrophic, antiproliferative, anti-inflammatory and antifibrotic actions by finerenone were corroborated in different rodent models, which often showed a stronger protection by finerenone compared with non-steroidal MRAs (Dutzmann et al., 2017; Grune et al., 2016; Grune et al., 2018; Lavall et al., 2019). An explanation for finerenone's improved antifibrotic actions has been suggested in its specific MR-LBD binding behaviour, which leads to selective MR-cofactor recruitment and distinct target gene regulation (Grune et al., 2018). Thus, finerenone has been shown to suppress specific profibrotic cardiac genes that are less efficaciously regulated by eplerenone and spironolactone resulting in a markedly stronger antifibrotic action in the left ventricle (Grune et al., 2018).

The safety, tolerability and clinical pharmacokinetic profile of finerenone has been studied in a comprehensive Phase I programme. Finerenone is safe and well tolerated, excreted to a minor degree (<1%) by the kidney, has a short plasma half-life (2–3 h), also in patients with renal failure, and no active metabolites have been identified (Agarwal et al., 2021) (Figure 3). The Phase II

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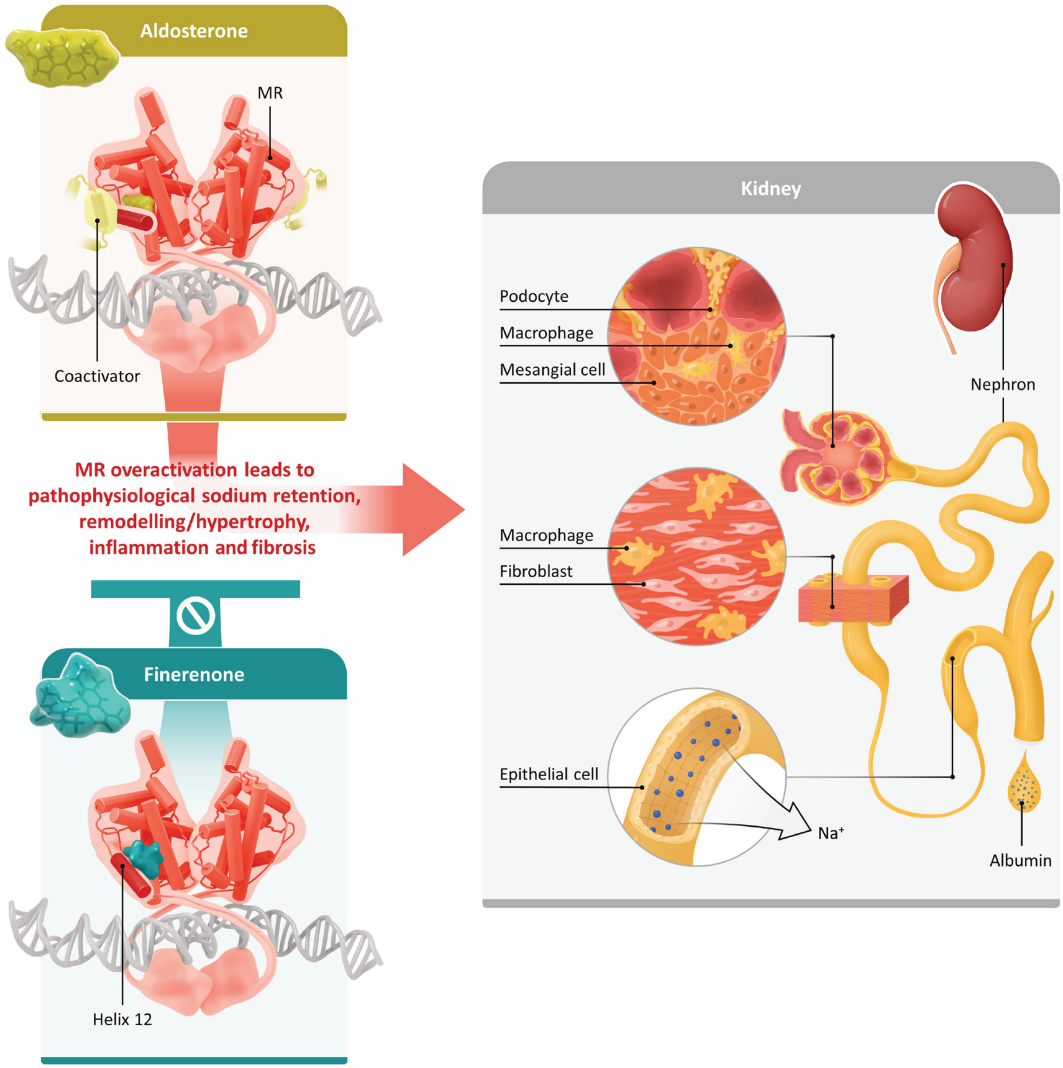

FIGURE 4 Mechanism of action of the non-steroidal mineralocorticoid receptor (MR) antagonist finerenone. Upper left panel: binding mode of aldosterone (yellow) to the MR; magnification (red): 3D structure of the MR-LBD dimer with bound aldosterone (yellow); dark red: positioning of helix 12. Lower left panel: binding mode of finerenone (green) to the MR; magnification (red): 3D structure of the MR-LBD dimer with bound finerenone (green); dark red: unique positioning of helix 12. Right panel: cellular targets of MR in the kidney

mineralocorticoid receptor antagonist tolerability study (ARTS) programme investigated finerenone in over 2000 patients (Bakris et al., 2015; Filippatos et al., 2016; Pitt et al., 2013). In ARTS, patients with HFrEF plus mild/moderate CKD were included, and safety/tolerability of finerenone was assessed (Pitt et al., 2013). The primary outcome was a change in serum potassium in direct comparison with spironolactone (Pitt et al., 2013). Finerenone was associated with significantly smaller mean increases in serum potassium and lower incidences of hyperkalaemia than the steroidal MRA spironolactone (Pitt et al., 2013). In addition, finerenone decreased the levels of BNP, NT-proBNP and albuminuria at least as much as spironolactone (Pitt et al., 2013). In ARTS-HF, patients with HFrEF and T2D and/or CKD were randomized to different doses of finerenone or eplerenone (Filippatos et al., 2016). All finerenone dose groups exhibited a similar proportion of patients with >30% decline in NT-proBNP compared with the eplerenone group, but more importantly, the prespecified exploratory composite CV clinical endpoint including all-cause death, CV hospitalizations or emergency presentation for worsening heart failure occurred numerically less frequently with finerenone compared with eplerenone (Filippatos et al., 2016).

Finally, ARTS-DN conducted in patients with CKD and T2D demonstrated a dose-dependent reduction of UACR with finerenone in the presence of low discontinuation rates due to hyperkalaemia (Bakris et al., 2015). Interestingly, a post hoc analysis revealed that the decline in UACR was independent of changes in BP or eGFR supporting the preclinical data of BP-independent actions by finerenone (Agarwal et al., 2021; Bakris et al., 2015). Based on these promising Phase II results, with convincing cardiorenal protection by finerenone accompanied by minimal effects on potassium and BP, an event-driven Phase III clinical programme was initiated in more than 18,000 patients with CKD and T2D (FIDELIO-DKD and

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FIGARO-DKD) or patients with symptomatic heart failure and LVEF ≥ 40% (FINEARTS-HF) (Agarwal et al., 2021).

In FIDELIO-DKD, 5734 patients with CKD (UACR 30 to <300 mg·g^{-1} and eGFR ≥ 25 to <60 ml·min^{-1} per 1.73 m^2 or UACR ≥ 300 mg·g^{-1} and eGFR ≥ 25 to <75 ml·min^{-1} per 1.73 m^2) and T2D were randomized to placebo or finerenone (10 or 20 mg·day^{-1}) (Bakris, Agarwal, et al., 2020; Bakris et al., 2019). All patients were treated with RAAS blockade (ACE inhibitors or ARBs) at the maximum tolerable dose (Bakris, Agarwal, et al., 2020). After a median follow-up of 2.6 years, finerenone significantly lowered the primary composite outcome (time to onset of kidney failure, sustained decrease of eGFR ≥ 40% from baseline or renal death) compared with placebo (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; $P = 0.001$) (Bakris, Agarwal, et al., 2020). Additionally, the secondary outcome event (time to cardiovascular death, nonfatal MI or stroke, or hospitalization for heart failure) occurred significantly less in the finerenone group (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; $P = 0.03$) (Bakris, Agarwal, et al., 2020). The incidence of hyperkalaemia-related discontinuation of the trial regimen was higher with finerenone (2.3%) compared with placebo (0.9%), but lower than in other trials with dual RAAS blockade (Bakris, Agarwal, et al., 2020; Parving et al., 2012).

FIGARO-DKD is conducted in a similar patient population as FIDELIO-DKD and focusses with its primary cardiovascular composite endpoint (time to death, nonfatal MI or stroke, or hospitalization for heart failure) on CV morbidity and mortality (Ruilope et al., 2019); 7437 randomized patients have earlier stage CKD compared with FIDELIO-DKD, defined by UACR 30 to <300 mg·g^{-1} and eGFR 25 to ≤90 ml·min^{-1} per 1.73 m^2 or UACR ≥ 300 mg·g^{-1} and eGFR ≥ 60 ml·min^{-1} per 1.73 m^2 and T2D (Ruilope et al., 2019). The renal key secondary endpoint replicates the primary composite of FIDELIO-DKD (Ruilope et al., 2019). All patients are treated with optimal RAAS blockade (Ruilope et al., 2019). Patients are randomized to placebo or finerenone (10–20 mg·day^{-1}) (Ruilope et al., 2019). As recently published, after a median follow-up of 3.4 years, finerenone significantly reduced the primary cardiovascular composite endpoint compared with placebo (hazard ratio, 0.87; 95% CI, 0.76 to 0.98; $P = 0.03$) (Pitt et al., 2021).

Taken together, finerenone is a novel non-steroidal MRA with a high MR selectivity, high binding affinity and a specific MR-LBD binding mode. In two Phase III clinical trials, finerenone showed substantial cardiorenal protection in patients with CKD and T2D. On 9 July 2021, the FDA has approved finerenone to reduce the risk of kidney function decline, kidney failure, CV death, nonfatal heart attacks and hospitalization for heart failure in adults with CKD associated with T2D.

5 | COMPARATIVE VIEW OF THE NOVEL NON-STEROIDAL MRAs

5.1 | Molecular and clinical pharmacology

The respective binding mode to the MR-LBD is crucial for the pharmacological effects of MRAs and determines, among other pharmacodynamic and pharmacokinetic factors, the clinical differences observed with various MRAs. MR-LBD binding characteristics have been investigated for esaxerenone, AZD9977 and finerenone (Amazit et al., 2015; Bamberg et al., 2018; Barfacker et al., 2012; Takahashi et al., 2020). These non-steroidal MRAs differ in their binding behaviour from the steroidal MRAs, spironolactone and eplerenone. Ligand-specific binding to the MR-LBD induces a conformational change in the LBD resulting in ligand-specific MR-cofactor recruitment and MR-target gene expression. The most comprehensive data set to assess this molecular pharmacological sequence from MRA-binding to MR-target gene regulation is available for finerenone.

Finerenone has been shown to bind to the MR-LBD as a 'bulky' antagonist, thereby positioning helix 12 of the MR-LBD in a specific manner, which clearly differs from steroidal MRAs (Amazit et al., 2015; Barfacker et al., 2012; Fagart et al., 2010; Kolkhof et al., 2017). This protrusion of helix 12 by finerenone leads to an unstable receptor–ligand complex and prevents recruitment of transcriptional coregulators (Kolkhof et al., 2017). This has been proven for finerenone in direct comparison with spironolactone and eplerenone (Amazit et al., 2015; Grune et al., 2018). More importantly, this specific binding mode leads to a distinct cardiac MR-target gene expression profile induced by finerenone when compared with eplerenone (Grune et al., 2016) and may explain, at least in part, the distinct clinical actions of finerenone.

All novel non-steroidal MRAs exhibit high selectivity for the MR over other steroid hormone receptors, which prevents antiandrogenic and progestational side effects. Remarkable differences occur in MR-binding affinity of the novel MRAs, so that a group of high-affinity non-steroidal MRAs with KBP-5074, esaxerenone and finerenone can be distinguished from a lower-affinity group with AZD9977 and apararenone. This translates into variances of clinical potencies and the need to define equipotent dosages for clinical efficacy assessment comparing non-steroidal MRAs with each other and with steroidal MRAs. A classical and accurate way to determine at least natriuretic potency of MRAs is the acute clinical experiment of a fludrocortisone challenge with subsequent MRA application followed by analysis of the urinary Na^+/K^+ ratio in healthy volunteers.

A summary of different studies with various novel non-steroidal MRAs compared with spironolactone or eplerenone is provided in Figure 5. de Gasparo et al. (1989) originally described equipotency of 50-mg spironolactone and 50-mg eplerenone (Figure 5a). AZD9977 200 mg was found to be equipotent to 100-mg eplerenone (Erlandsson et al., 2018) (Figure 5b), and a 10-mg solution of finerenone was found to be equipotent to 50-mg eplerenone (Lentini et al., 2012) (Figure 5c). Thus, the following natriuretic potency can be deduced from these three fludrocortisone challenge studies in healthy volunteers: 10-mg finerenone ≈ 50-mg eplerenone (≈50-mg spironolactone) ≈ 100-mg AZD9977 (de Gasparo et al., 1989; Erlandsson et al., 2018; Lentini et al., 2012) (Figure 5). Data like this should definitively be taken into account when assessing current and future comparative clinical studies with these drugs.

Finally, differences in plasma half-life are significant. Finerenone exhibits the shortest (2–3 h), followed by AZD9977 (4–9 h), by

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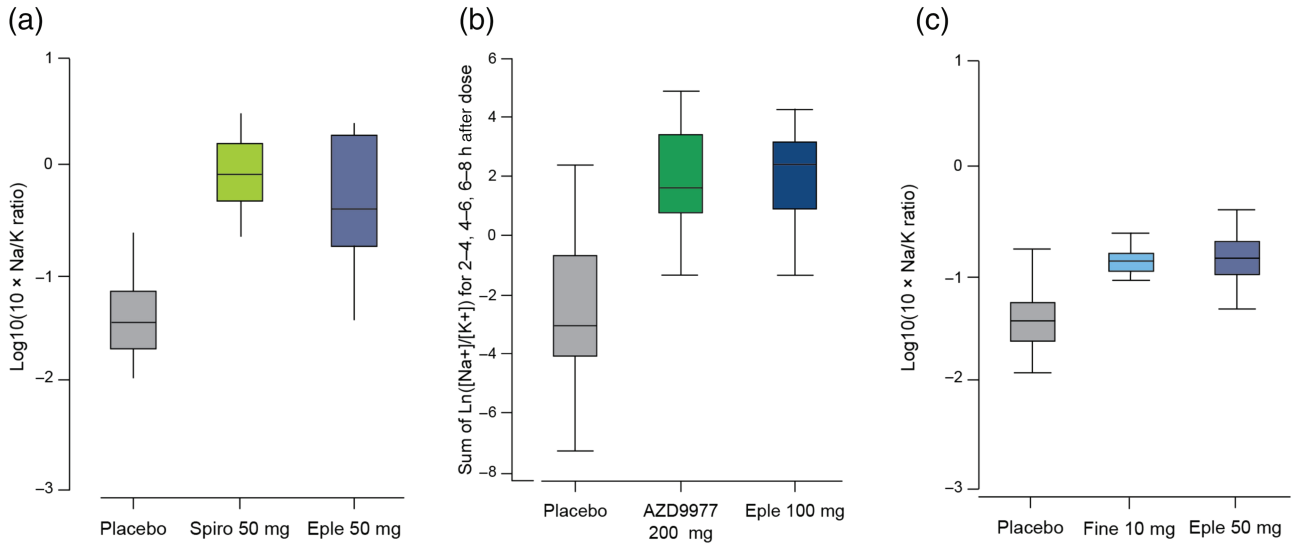

FIGURE 5 Comparison of the natriuretic potency of the steroidal mineralocorticoid receptor (MR) antagonists (MRAs) and non-steroidal MRAs in the acute clinical experiment of a fludrocortisone challenge with subsequent MRA application followed by analysis of the urinary Na^+/K^+ ratio (Y axis) in healthy volunteers. (a) Comparison of spironolactone (Spiro) and eplerenone (Eple) (de Gasparo et al., 1989). (b) Comparison of AZD9977 and Eple (Erlandsson et al., 2018). (c) Comparison of finerenone (Fine) and Eple (Lentini et al., 2012). All comparisons of placebo versus both MRAs were statistically significant; all comparisons between MRAs were statistically non-significant

esaxerenone (18 h) and by KBP-5074 (60 h). An exceptional position in this context is shown by apararenone with an extremely long plasma half-life of the drug (275–285 h) and its active metabolite 1118174 (1126–1250 h).

5.2 | Clinical efficacy

Regarding comparisons of clinical efficacy of novel non-steroidal MRAs, we focus on the drugs with most advanced clinical development, namely, esaxerenone, KBP-5074 and finerenone.

Two trials, ESAX-HTN and BLOCK-CKD, investigated the antihypertensive actions of the non-steroidal MRAs, esaxerenone and KBP-5074 (Bakris et al., 2021; Ito, Itoh, et al., 2020). Both studies demonstrated a clear antihypertensive action of two long-acting non-steroidal MRAs in patients at lower and higher risk for CV or renal events.

Renoprotective actions of non-steroidal MRAs have been demonstrated in the Phase III clinical ESAX-DN trial, with esaxerenone conducted in patients with T2D and microalbuminuria (Ito, Kashihara, et al., 2020). Finerenone significantly reduced UACR and significantly slowed the progression of CKD in FIDELIO-DKD (Bakris, Agarwal, et al., 2020). In addition, finerenone significantly reduced cardiovascular morbidity and mortality in this high-risk patient population (Bakris, Agarwal, et al., 2020). These results were recently confirmed in the FIGARO-DKD trial (Pitt et al., 2021). Together, these studies demonstrate a convincing renoprotective action of novel non-steroidal MRAs in diabetic kidney disease, whereby esaxerenone revealed antiproteinuric effects and only finerenone has demonstrated clear evidence of reducing renal and CV morbidity and mortality in these patients.

5.3 | Safety

Hyperkalaemia is one of the most pressing safety issues in MRA therapy. Both steroidal MRAs have been shown to induce considerable hyperkalaemia, especially in patients with concomitant RAAS blockade or impaired renal function (Alexandrou et al., 2019; Juurlink et al., 2004; Navaneethan et al., 2009). It was therefore the intention of drug discovery programmes to identify novel non-steroidal MRAs with a reduced risk of hyperkalaemia while maintaining clinical efficacy. Direct comparisons with steroidal MRAs are available for esaxerenone and finerenone. In ESAX-HTN, esaxerenone was reported to induce a marginally higher rate of hyperkalaemia compared with eplerenone in patients with an almost normal kidney function (eGFR $\approx$ 78 ml·min^{-1} per 1.73 m^2) (Ito, Itoh, et al., 2020) (Figure 3). In ARTS, finerenone was associated with significant smaller mean increase of serum potassium and a reduced risk for hyperkalaemia than spironolactone, despite a patient population with more advanced CKD than in ESAX-HTN (Pitt et al., 2013) (Figure 3). Comparisons between placebo and non-steroidal MRAs revealed that esaxerenone, apararenone, finerenone and KBP-5074 are associated with higher serum potassium levels than placebo-treated patients; however, the extent is less than with steroidal MRAs (Bakris et al., 2021; Ito, Itoh, et al., 2020; Pitt et al., 2013; Wada et al., 2021). Comparative analysis among the non-steroidal MRAs about drug-mediated hyperkalaemia is missing, and comparisons based on the placebo-controlled trials are limited due to differences in baseline kidney function and concomitant medications in the respective patient cohorts. However, the low discontinuation rates due to hyperkalaemia vs. placebo for KBP-5074 (3.7% vs. 3.5%) (Figure 3) and

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finerenone (2.3% vs. 0.9% in FIDELIO-DKD and 1.2% vs. 0.4% in FIGARO-DKD) (Figure 3) reveal an improved benefit–risk profile for at least two novel non-steroidal MRAs.

6 | CONCLUSIONS AND PERSPECTIVE

The new non-steroidal MRAs exhibit robust anti-inflammatory and antifibrotic actions beyond classical actions of MR inhibition on fluid and electrolyte homeostasis. These effects translate into proven clinical benefit in patients with cardiorenal disease. Comparing these novel compounds with steroidal MRAs as well as with each other reveals significant molecular pharmacological differences that explain variations in clinical efficacy and safety. Along this line, finerenone, for example, shows a specific binding mode to the MR that parallels a clear protective cardiorenal clinical effect.

The clinical development of these drugs is at different stages and varies in the targeted indications. Esaxerenone is already approved for the treatment of arterial hypertension, and KBP-5074 has shown robust antihypertensive effects in a Phase II study in resistant and poorly controlled hypertension in people with advanced CKD Stages 3b and 4. In contrast, finerenone significantly reduced renal and CV endpoints in patients with T2D and CKD in Phase III studies, thereby opening a new avenue for effective cardiorenal protection. In terms of safety, at least the new non-steroidal MRAs KBP-5074 and finerenone appear to impart less hyperkalaemia than conventional steroidal MRAs in patients with CKD on top of RAS blockade (Figure 3). This represents a major advance for their future use especially in patients with concomitant RAAS blockade and/or advanced CKD and possibly heart failure (Kolkhof et al., 2021).

Further development of non-steroidal MRAs and their routine clinical usage requires a broad knowledge of their pharmacological mode of action. In this context, anti-inflammatory effects are highly relevant and a novel mode of action. MR activation in cells of the innate and adaptive immune system has been shown to drive systemic and local inflammation, organ fibrosis and finally vascular, cardiac and renal damage (Ferreira et al., 2021). Novel non-steroidal MRAs demonstrated potent anti-inflammatory actions in preclinical studies (Arai et al., 2016; Kolkhof et al., 2014). A deeper knowledge of the exact immune cell target of non-steroidal MRAs in preclinical and clinical settings, and the relevance for cardiorenal protection, will be tasks of future studies.

Non-steroidal MRAs will be very likely included in the recommendation for the treatment of patients with CKD and T2D (Cosentino et al., 2020). In addition to the currently recommended drug therapy with ACE inhibitors or ARBs, and SGLT2 inhibitors (Cosentino et al., 2020), finerenone, specifically, will represent another important therapeutic pillar for these patients (Kolkhof et al., 2021). Finally, it will be very interesting to see in which other cardiorenal indications or co-morbidities the benefit of non-steroidal MRAs will be proven in future studies. In a prespecified exploratory analysis of the FIDELIO-DKD trial, finerenone has just been shown to significantly lower the incidence of atrial fibrillation or flutter in patients with T2D and CKD (Filippatos et al., 2021). Furthermore, the FINEARTS-HF trial (NCT04435626) will determine whether or not finerenone lowers morbidity and mortality in patients with symptomatic heart failure (NYHA Class II–IV and LVEF > 40%), and if non-steroidal MRAs will have benefit in patients with HFmrEF/HFpEF (Agarwal et al., 2021).

In summary, novel non-steroidal MRAs have various advantages over steroidal MRAs with proven benefit in patients with T2D and CKD and an improved safety profile, so that they can be expected to become an important part of the guideline-compliant therapy for these patients.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander et al., 2021).

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AUTHOR CONTRIBUTIONS

All the authors substantially contributed to the conception and design of the manuscript. U.K. and P.K. drafted the article. All the authors revised the article critically for important intellectual content and finally approved the version to be published.

CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data are generated.

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