Non-steroidal mineralocorticoid receptor antagonism for the treatment of cardiovascular and renal disease

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Abstract

Pharmaceutical antagonism of the mineralocorticoid receptor (MR) can protect against organ damage caused by elevated aldosterone levels in patients experiencing heart failure (HF), chronic kidney disease (CKD), primary aldosteronism and hypertension. While traditional steroid-based MR antagonists effectively reduce mortality rates and extend patient survival, their broad application has been limited by significant side effects, most notably hyperkalaemia. Recently, finerenone (BAY94-8862) has emerged as a next-generation non-steroidal dihydropyridine-based MR antagonist designed to minimise off-target effects while maintaining potent efficacy. In this review, the authors explore the outcomes of finerenone therapy in several diseases associated with MR activity. The authors compare the (pre-) clinical efficacy of finerenone with traditional steroid-based MR antagonists. Finally, the authors discuss recent and ongoing clinical trials using finerenone to treat chronic HF, CKD, and diabetic nephropathy. Taken together preclinical and clinical evidence suggests that finerenone may achieve equivalent organ-protective effects with reduced levels of electrolyte disturbance compared to traditional steroid-based MR antagonists. This supports further clinical development of finerenone for the treatment of cardiovascular and renal disease.

Keywords: mineralocorticoid; receptor; antagonist; heart; kidney; failure; disease; finerenone; ARTS, BAY94-8862

Introduction

The specific intracellular steroidal mineralocorticoid receptor (MR) has a major role in the renin-angiotensin-aldosterone system (RAAS), which regulates sodium reabsorption and potassium leakage in nephrons, and achieves co-ordinated control of fluid, extracellular volume, and electrolyte balance to regulate blood pressure (BP) [1]. The MR binds several ligands, including aldosterone and cortisol. Under normal conditions, aldosterone acts as a MR agonist, while cortisol acts as an antagonist [2], and both bind the MR with similar affinities [3].

Several disease states are associated with elevated activation of the MR, including heart failure (HF), chronic kidney disease (CKD), primary aldosteronism, and hypertension. Enhanced MR activity can be driven by increased levels of circulating aldosterone, switches in cortisol activity from MR antagonist to MR agonist, or elevated local expression of the MR [4]. Such changes are observed following disruptions in hormonal homeostasis during cardiovascular, renal, or adrenal pathology [5]. Pathophysiological levels of aldosterone or cortisol, especially in combination with inappropriate salt and redox status, can damage multiple tissues that express the MR [2, 6-8]. Blockade of the aldosterone/cortisol signalling pathway through MR antagonism is a clinically effective method of preventing organ pathologies.

MR antagonist therapy for cardiovascular and renal disease

Current clinically-approved steroid-based MR antagonists, including spironolactone, canrenone and the later developed eplerenone, mimic the molecular structure of the natural MR ligands, aldosterone and cortisol (**Figure 1**) [9]. These agents have demonstrated significant clinical efficacy in the treatment of several disease conditions, including chronic HF [10-14], CKD [15, 16], primary aldosteronism, and hypertension [17-21]. Spironolactone and eplerenone are considered highly effective strategies for the management of cardiorenal disease, and current guidelines recommend the addition of MR antagonists during the management of symptomatic systolic HF in patients already receiving angiotensin-converting enzyme (ACE) inhibitors and beta-blockers [22]. Yet, surprisingly, only low numbers (9–30%) of eligible hospitalised HF patients are prescribed MR antagonists [23]. Despite these clear clinical benefits, there remains a bias that prevents the prescription of MR antagonists to patients displaying HF.

Such bias is undoubtedly related to the side effects associated with spironolactone and eplerenone therapy. While the first-generation spironolactone displays significant MR antagonistic potency, it also antagonises the androgen receptor (AR) to drive the development

of gynaecomastia and impotence in men, and acts as an agonist of the progesterone receptor to cause amenorrhoea in pre-menopausal women (**Table 1**) [10, 23]. These side effects typically limit patient adherence to therapy. While the second-generation eplerenone targets the MR with a greater specificity, leading to fewer side effects, it lacks the potency of spironolactone (**Table 1**) [18, 19].

Finally, and perhaps of greatest clinical concern, blockade of MRs in the kidney increases sodium excretion with a subsequent reduction in blood volume, and a corresponding retention of potassium. This effect may be exacerbated by the biodistribution pattern of both spironolactone and eplerenone, which build up to higher concentrations in renal tissue compared to myocardium [24]. Reduced renal elimination of potassium results in hyperkalaemia, where potassium levels in the blood increase to potentially pathological levels [10, 11, 16, 25]. Incidence of hyperkalaemia in the Randomized Aldactone Evaluation Study (RALES) was only slightly greater in the spironolactone arm than in the placebo arm [10]. In a subsequent assessment of the real world situation, however, significant hyperkalaemia-related morbidity and mortality correlated with an increase in the prescription rate of the drug [26]. In a separate study involving a population of unselected heart failure patients treated with spironolactone, 36% reached a serum potassium level of >5 mmol/L [27]. In the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), higher proportions of patients being treated with eplerenone were noted to have potassium levels > 5 mEq/L in comparison to those receiving a placebo (15.6 vs. 11.2%; $p < 0.001$) [28]. A similar trend was found in the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF; 11.8 vs. 7.2% for eplerenone and placebo, respectively; $p < 0.001$) [25]. These high rates of hyperkalaemia appear to be manageable in patients with normal kidney function or mild-to-moderate kidney disease. However, patients with conditions such as CKD or diabetes are at increased risk of developing elevated potassium levels, and display increased rates of hyperkalaemia-related hospitalisation and death following MR antagonist therapy [29-32]. Ultimately, all patients receiving spironolactone or eplerenone therapy require careful serial monitoring of serum potassium levels and renal function [28], which may represent a practical impediment to routine clinical prescription.

Patients with an S810L gain-of-function mutation within the MR, which contributes to early-onset or gestational hypertension, are also ineligible for MR antagonist therapy, since both eplerenone and spironolactone paradoxically enhance signalling through this mutant receptor to promote hypertension [33, 34]. Further, older patients (≥75 years) appear to be at significantly elevated risk of hyperkalaemia-related hospital admissions and subsequent in-hospital deaths following MR antagonist therapy [35]. Nevertheless, several risk-to-benefit assessments

ultimately support the use of MR antagonists in patients across a spectrum of low-, medium-, and high-risk.

Finerenone, an alternative non-steroidal MR antagonist

The molecular structure of MR antagonists can impact the profile of biodistribution, potency, selectivity, physicochemistry and, ultimately, the balance between clinical efficacy and side effects [24]. Thus, in an effort to maximise cardiac and/or vascular activity and minimise disruptions in renal sodium/potassium homeostasis, the development of next-generation MR antagonists has focussed on non-steroidal compounds. This approach has the potential to extend the cardioprotective benefits of MR antagonists to multiple patient populations that are currently contraindicated for this therapy [36]. In particular, dihydropyridines, traditionally known for their utility as L-type calcium channel antagonists, have been identified as a new class of non-steroidal MR antagonists [37].

Finerenone (BAY94-8862) is a third-generation potent, specific, orally bioavailable, non-steroidal MR antagonist that was generated during high-throughput screening and subsequent remodelling of cyano-1,4-dihydropyridine compounds [38]. Finerenone is accommodated in the MR ligand binding cavity in a distinct manner from steroid-based MR antagonists, and shows good steric binding with a MR IC_{50} of 17.8 nM (**Table 1**) [38, 39]. Importantly, finerenone is over 500-fold more selective for the MR versus steroid receptors within the same superfamily, including the glucocorticoid receptor (GR), androgen receptor (AR), and progesterone receptor (PR) (**Table 1**). Structural studies suggest that this selectivity is predominantly mediated through a hydrogen bond donor interaction with the unique MR-specific residue, Ser810 [38]. Further, finerenone has no observed off-target interactions with over 65 biological receptors and ion channels [38], and lacks the ability to block L-type calcium channels, which is associated with many other dihydropyridine-based MR antagonists [38, 40, 41].

Finerenone displays substantially altered biochemical and biophysical properties compared to spironolactone and eplerenone (**Table 1**). Organ distribution of radioactively-labelled finerenone one hour after oral administration in Wistar rats is predominantly confined to the vascular and interstitial spaces, and can be clearly detected in well-vascularised organs such as the heart, lung, liver, and kidney [42]. While traditional steroid-based MR antagonists typically build up to higher concentrations in the kidney versus the heart [24], a property that may contribute to hyperkalaemic side effects, finerenone achieves an equivalent distribution between cardiac and renal compartments [42]. In healthy subjects, the plasma half life of finerenone is ~2 h, much shorter than spironolactone (~15 h) [24, 43] although roughly equivalent to eplerenone (4–6 h). The relatively long half-life of spironolactone has the pharmacokinetic

consequence of a slow onset of action, and effects that persist for several days following drug discontinuation [44]. However, the kinetics of the downstream effects of finerenone on target organs has not been extensively studied [24]. Finally, the metabolic consequences of finerenone oral application have yet to be explored. Thus it remains to be determined if this drug breaks down to generate multiple active metabolites (similar to spironolactone) or remains essentially intact (similar to eplerenone).

In healthy rats, finerenone has little impact on the total urinary volume (except at very high doses [100 mg/kg]), and no measurable impact on urinary potassium levels [42]. However, rat models are typically resistant to the development of hyperkalaemia following RAAS inhibition [45]. Conversely, natriuretic responses, which can act as a surrogate marker for renal electrolyte homeostasis in rat models, increase in a dose-dependent manner following finerenone therapy [42]. In a direct comparison with the steroid-based MR antagonist, eplerenone, equivalent natriuretic responses were observed at 1 mg/kg finerenone and 10–30 mg/kg eplerenone [42], suggesting that finerenone represents a more potent MR antagonist.

Pre-clinical assessment of finerenone in models of cardiovascular and renal disease

Finerenone has been tested in several pre-clinical rat models of cardiorenal disease in comparison to the traditional steroid-based MR antagonist, eplerenone. These include a model of hyperaldosteronism-induced end-organ damage (induced by a 10-week treatment with deoxycorticosterone-acetate (DOCA)/salt) [42], a model of post-MI HF (induced by coronary artery ligation) [42], and a model of severe arterial hypertension (induced by maintaining spontaneously hypertensive, stroke-prone rats (SHRSP) on a 7-week high-salt diet) [46].

In a model of hyperaldosteronism-induced end-organ damage, low doses of finerenone outperformed eplerenone in protecting both the heart and kidney against structural and functional damage [42]. Direct comparisons were drawn between outcomes with equivalent natriuretic doses of finerenone (1–10 mg/kg) and eplerenone (30–100 mg/kg). In the heart, finerenone treatment decreased systolic BP (SBP) and minimised cardiac hypertrophy at the ultrastructural level [42]. Eplerenone had no significant impact on cardiac hypertrophy. Similarly, finerenone significantly reduced plasma levels of prohormone of brain natriuretic peptide (pro-BNP), a pathological marker of ventricular remodelling and myocardial ischaemia, beyond the level observed with eplerenone, suggesting lower levels of heart stress [42]. At the kidney level, histological analysis demonstrated less glomerular and tubulointerstitial damage, and less kidney hypertrophy following finerenone treatment [42]. Finerenone also reduced levels of genotoxic damage, characterised by double-strand DNA breaks, in renal cells [47]. Conversely, eplerenone and placebo groups displayed more evidence

of glomerular sclerosis, tubular degeneration, tubular dilation, and proteinuria casts [42]. Proteinuria was also ameliorated to a greater degree following finerenone treatment compared to eplerenone. Finally, the expression levels of genes involved in pro-inflammatory and pro-fibrotic processes in the kidney, including *PAI-1*, *MCP-1*, *osteopontin*, and *MMP-2*, were reduced to the greatest degree following finerenone treatment [42].

In a model of post-MI HF, lower doses of finerenone (0.1, 0.3, or 1 mg/kg/day) were directly compared with eplerenone (100 mg/kg/day). Finerenone treatment achieved clinical efficacy at a dose of 1 mg/kg/day; lower doses had no impact, equivalent to eplerenone [42]. Both systolic and diastolic left ventricular function was improved following finerenone administration, with significant enhancements in cardiac contractility and relaxation. Similarly, finerenone reduced plasma levels of pro-BNP without impacting BP [42]. Plasma levels of aldosterone were also analysed as an indirect measure of finerenone occupancy at the MR, since antagonism of the MR typically increases circulating levels of unbound aldosterone [48], and the magnitude of this increase can reflect the efficiency and extent of MR blockade. Finerenone significantly increased circulating levels of aldosterone compared to placebo controls [42]. Eplerenone achieved a similar increase in plasma aldosterone concentrations, suggesting that while eplerenone was capable of effectively blocking the MR, this was ultimately not translated into a downstream impact on cardioprotective parameters.

Finally, doses of finerenone at 10 mg/kg/day were reported to significantly improve the survival of severely hypertensive rats compared to either eplerenone (30 mg/kg/day) or spironolactone (30 mg/kg/day) [46]. Both steroid-based MR antagonists had no significant impact on mortality rates. Simultaneous reductions in urinary protein/creatinine ratios and osteopontin expression levels following finerenone treatment indicated a beneficial impact on kidney health [46]. This was supported by histopathological analysis demonstrating that finerenone treatment reduced vascular, glomerular, and tubulointerstitial damage. In contrast, no such effects were found on analysis of animals treated with either spironolactone or eplerenone.

Progress of finerenone to clinical trials

ARTS

Finerenone has been tested through phase I safety and tolerability studies to phase IIb safety and efficacy trials (**Table 2**). The phase II Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) represents the most extensive published trial of finerenone in patients with HF with a reduced ejection fraction (HFREF) and mild-to-moderate CKD [49]. ARTS was designed as a 4-week randomised, double-blind, placebo-controlled, parallel-group, safety and

tolerability study that was divided into two parts. The first part compared finerenone (2.5, 5, or 10 mg per day) vs. placebo in 65 patients with HF and mild CKD. The second part compared finerenone (2.5, 5, or 10 mg or (2 × 5 mg) per day) vs. spironolactone (25 or 50 mg per day) vs. placebo in 392 patients with HF and moderate CKD [50]. Primary outcome measurements centred on renal parameters, including serum potassium levels and markers of kidney health and function, such as urinary albumin to creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). Secondary outcomes included changes in markers of cardiac health, pharmacokinetic profiles, and safety and tolerability [49]. Outcome measurements were made at visit 4 (d15 ± 1; approximately half way through the trial) and visit 7 (d29 ± 2; at the conclusion of the trial).

Mean increases in serum potassium concentrations were significantly lower in all finerenone groups compared to spironolactone (**Figure 2**) [50]. Indeed, at 2.5 mg and 5 mg daily doses of finerenone, there was no significant change in serum potassium levels compared to placebo controls. Minimal finerenone disruptions in serum potassium levels were also evident in sub-analyses of either older (>75 years) patients, individuals with HFREF of greater severity (NYHA class III), or patients who had previous experience with MR antagonist therapy. The lack of observed hyperkalaemia in aged individuals receiving finerenone therapy was particularly important, since spironolactone has previously been associated with increased hyperkalaemia-associated mortality in this population [26].

Although not statistically significant, there was a trend towards a reduction in the UACR across all treatment groups (finerenone and spironolactone) compared to placebo [50]. Spironolactone (25 or 50 mg per day) significantly reduced eGFR compared to placebo controls, indicating a negative impact on kidney function at this clinically relevant dose [10]. On the other hand, for finerenone, eGFR only deteriorated significantly at the highest dose prescribed (10 mg/day) (**Figure 2**) [50]. All other finerenone doses (2.5 mg, 5 mg, (2 × 5mg) per day) demonstrated no significant deviation in eGFR from placebo control. Ultimately, tracking degeneration of renal function either through changes in serum creatinine levels or eGFR following finerenone treatment demonstrated similar changes to placebo controls. Worsening renal function was observed in <11% of patients across both the placebo and all finerenone groups, but in 38% of patients receiving spironolactone.

No significant changes in biomarkers of heart health were observed following finerenone or spironolactone therapy [50]. In patients receiving >2.5mg finerenone or spironolactone (25 or 50 mg), there was a trend towards decreased median concentrations of both N-terminal pro-BNP (NT-pro-BNP) and BNP itself compared to placebo controls. NT-pro-BNP levels are strongly predictive of long-term mortality in patients with heart disease [51]. SBP remained a highly

variable measurement within each patient group. Only patients receiving spironolactone demonstrated a significant reduction in SBP compared to placebo controls; no anti-hypertensive effects were observed across finerenone treatment groups [50].

Indirect effects of finerenone were also analysed by measuring aldosterone levels in plasma. All finerenone doses above 2.5 mg were associated with significant increases in serum aldosterone levels [50]. Yet the most substantial increase was observed following spironolactone therapy, almost certainly as a consequence of the higher dosage reflecting a greater occupancy of MR sites. Since finerenone achieved more substantial benefits on biomarkers of cardiac health than spironolactone, despite having less impact on plasma aldosterone levels, this suggests an uncoupling of the relationship between circulating aldosterone levels and cardioprotective/nephroprotective effects.

Finally, and of crucial clinical importance, the majority of finerenone treatment-associated adverse events were mild. Serious adverse events across all treatment groups (including spironolactone) were observed in 25/457 patients (5.5%). In *post-hoc* analyses across all finerenone groups, rates of hyperkalaemia, renal impairment, or renal failure were not significantly different from placebo controls [50]. Unexpectedly, this difference was even smaller when comparing only the highest finerenone dose groups (5 mg or 10 mg per day). Conversely, rates of hyperkalaemia-related renal dysfunction were significantly elevated in patients receiving spironolactone. Due to limitations of the ARTS clinical study design (including the number of recruited patients and the relatively short clinical schedule for therapy), the ability of finerenone to protect against major cardiovascular events and improve survival rates could not be investigated. This limitation also prevented the analysis of rates of gynaecomastia, impotence, and amenorrhoea, which represent common side effects for spironolactone therapy.

ARTS-DN

Following on from the ARTS trial, a similar study was carried out to compare the effects of finerenone with placebo in patients with type 2 diabetes and diabetic nephropathy [52]. Patients were randomised to receive once daily doses of finerenone (7.5, 10, 15, or 20 mg) or placebo. The primary endpoint was the ratio of UACR from baseline to the end of the 90-day follow-up period, with other endpoints including serum potassium levels, eGFR, and adverse events. For the patients receiving finerenone, the ratio of UACR from 90 days to baseline decreased in a dose-dependent manner, a trend which was maintained when the values were adjusted by those of the placebo group (**Figure 3**) [53]. By the end of the study, a reduction in UACR of ≥50% from baseline was achieved for 17.2%, 17.2%, 33.6%, and 40.2% of the patients in the

finerenone 7.5, 10, 15, and 20 mg groups, respectively, compared to only 13.6% of patients receiving the placebo. No significant correlation was found between changes in UACR and changes in SBP, indicating that the reduction in albumin excretion was not mediated by a reduction in BP. Intraglomerular pressure also appeared to be independent of changes in UACR, remaining relatively stable during the 90 days of the study in all treatment groups.

In terms of serum potassium levels, hyperkalaemia (potassium ≥ 5.6 mmol/L) occurred in 10 (2.3%) of the patients receiving finerenone (7.5–20 mg; N = 439), with 8 of these cases resulting in discontinuation of the study treatment. There were no cases of hyperkalaemia in the placebo group (N = 94). Absolute levels of serum potassium increased by between 0.11 and 0.37 mmol/L in the patients treated with finerenone, with no correlation with dosage evident. No significant differences were found in incidence of adverse events or serious adverse events between the placebo and finerenone groups.

A dosage of 20 mg was investigated in the ARTS-DN trial, while 10 mg was the highest dose used in the preceding ARTS trial [50]. This dosage was added as a result of recommendations by an independent data monitoring committee after evaluation of safety data. The higher finerenone dosage resulted in a greater decrease in UACR in conjunction with no difference in terms of eGFR, SBP, and serum potassium levels, in comparison with the lower doses.

ARTS-HF

The ARTS-HF trial was designed to investigate finerenone for the treatment of patients with HFREF in addition to type 2 diabetes or CKD. Patients were randomised to either finerenone (2.5–20 mg once daily) or eplerenone (25 mg every second day to 50 mg once daily) within 7 days of emergency presentation at hospital for worsening HF [54]. The primary objective was to compare the efficacy of the two drugs by evaluating changes in NT-pro-BNP levels from baseline to the end of a 90 day follow-up period.

It was found that the proportions of patients that achieved a reduction in NT-pro-BNP levels of greater than 30% by the end of the 90 days were similar for all doses of finerenone, as well as for eplerenone (**Figure 4**)[55]. The combined endpoint of all-cause death, cardiovascular hospitalisation, or emergency presentation for worsening HF was reached by fewer patients receiving finerenone in comparison to eplerenone; this was with the exception of those on the lowest dose of finerenone (2.5–5 mg). Individually all-cause death and cardiovascular hospitalisation were more common in the eplerenone group than in the finerenone (all dosages pooled), with analysis of the highest finerenone dose (10–20 mg) showing a much lower probability of each event.

There were no significant differences found in terms of treatment-emergent adverse events between the groups. Hyperkalaemia (potassium ≥ 5.6 mmol/L) was more common in the patients receiving eplerenone (4.7%) than those receiving any dose of finerenone (3.6–3.8%) apart from the highest (6.3%). The mean increase in potassium level from baseline to the end of the 90-day follow-up period was significantly lower for doses of finerenone of 2.5–15 mg, and numerically lower for the higher doses, in comparison to that for eplerenone. In terms of eGFR, similar proportions of patients in each treatment group experienced a reduction of more than 40% at any point after baseline.

Critical Appraisal

It has proven difficult to identify a single steroid-based MR antagonist that combines the potency of spironolactone with the improved MR specificity and minimal renal impact of eplerenone for the treatment of cardiovascular disease (CVD) and CKD [24, 56]. The development of finerenone, a non-steroidal dihydropyridine-based third-generation compound, represents a key step in the evolution of MR antagonists from potassium-sparing diuretics to cardiovascular drugs.

In a phase II clinical trial, 5 mg daily doses of finerenone improved biomarkers associated with heart health to an equivalent degree as did 25–50 mg per day of spironolactone, suggesting an enhanced ability to minimise ventricular remodelling [50]. Simultaneously, finerenone was associated with a significantly lower impact on kidney function. When compared with eplerenone, heart damage was found to be equivalent between the two drugs [55]. Of particular clinical relevance was the association of finerenone with lower serum potassium levels than those found with both spironolactone and eplerenone treatment [50, 55]. Indeed, rates of both hyperkalaemia-related and total adverse events across all finerenone doses were less than those observed with spironolactone, and similar to those found for eplerenone.

The more even distribution of finerenone throughout renal and cardiac tissue in comparison the predominantly renal localisation of spironolactone and eplerenone may confer a strong benefit in minimising hyperkalaemic side effects. However, the development of new MR antagonists designed to further skew this biodistribution in favour of the heart over the kidney may be of limited clinical utility. Certainly, for the treatment of patients with primary aldosteronism, maintaining a degree of MR antagonist activity within the kidney is important, since these individuals would otherwise be at significant risk of hypokalaemia, an inherently more dangerous state than hyperkalaemia [2]. Moreover, biodistribution alone is certainly not the only factor responsible for differing activity of structurally unique drugs within different

organs. Tissue-specific transporter proteins may control the level of cellular uptake, while various co-regulatory species could affect gene activation [24, 57, 58]. The development of a drug that works in combination with specific transporters and/or co-regulators could provide targeted MR antagonistic activity in a certain tissue, potentially reducing unwanted side-effects generated by activity in other organs. In the development of novel fourth generation MR antagonists, it will be essential to closely monitor the effects of new agents on different diseases. Hypertensive patients, for example, are more likely to benefit from agents with tubule-sparing effects, while those with HF will benefit more from higher cardioprotective activity.

It is intriguing to note that in both pre-clinical models and in clinical trials, finerenone often exerted beneficial cardioprotective effects without significantly impacting SBP [42, 50, 53]. This is in sharp contrast to spironolactone and eplerenone, which have both demonstrated overt SBP reductions. This again demonstrates the impact of biodistribution and tissue-specific factors in regulating the activity of these dugs. Indeed, finerenone may not only accumulate in lower concentrations in the kidneys, in comparison to steroid-based MR antagonists, but may also exhibit lower activity in such tissue.

Interestingly, in one study, hypertensive patients treated with eplerenone showed similar serum potassium levels whether they were responders or non-responders in terms of SBP reduction [59]. Thus, MR antagonists may provide anti-hypertensive effects independent of mechanisms involving kidney epithelial electrolyte and fluid transport.

From a clinical perspective, finerenone may therefore have tremendous value in the treatment of patients with low, stable, or artificially-controlled BP. Indeed, under current European and North American guidelines, the majority of HF patients would theoretically receive finerenone alongside standard interventions that are already controlling BP [60]. Conversely, in patients who require more aggressive BP control, finerenone may not represent the MR antagonist of choice. Indeed, spironolactone may retain value in these patient populations, such as those with resistant hypertension. Yet regular monitoring of serum potassium levels would remain critical for safety during spironolactone therapy. Such serial monitoring may ultimately prove unnecessary for patients receiving finerenone therapy, with low rates of hyperkalaemia being reported in recent trials [53-55].

While finerenone currently represents the most clinically advanced non-steroidal MR antagonist in development, several other candidate compounds are also being explored. Two of these, BR-4628 and SM-368229, originate from the same dihydropyridine class as finerenone. BR-4628 is a bulky MR antagonist that shows potent MR selectivity over other steroid receptors and L-type calcium channels [39]. Interestingly, BR-4628 predominantly

antagonises the MR through passive mechanisms, interfering with the recruitment of transcriptional co-regulators [39]. In rat models of DOCA/salt-induced hypertension and nephropathy, BR-4628 ameliorated symptoms of inflammation and kidney pathology to an equivalent degree as spironolactone-treated animals, and achieved this independently of changes in BP [61]. SM-368229 is a MR antagonist that paradoxically retains partial MR agonist activity [62]. Of note, SM-368229 achieved anti-hypertrophic and cardioprotective effects in aldosterone/salt-treated hypertensive rat models while simultaneously demonstrating greater reductions in SBP compared to spironolactone therapy [63]. While it is clear that individual dihydropyridine-based MR antagonists differ in their anti-hypertensive capabilities, these compounds nevertheless exhibit equivalent or improved cardiorenal protection over eplerenone and/or spironolactone. This may suggest that different MR antagonists have distinct activities in pathways involved in cardioprotection versus those involved in BP regulation.

Pyrazoline-based compounds have also been developed as novel MR antagonists. PF-03882845 is a potent, selectively orally bioavailable pyrazoline-based MR antagonist that retains a degree of PR inhibition. In rat models of hypertension, PF-03882845 outperformed eplerenone in decreasing SBP while maintaining renal function [64, 65]. However, multi-dose phase I safety studies testing PF-03882845 in healthy volunteers were terminated due to safety concerns (NCT00856258), while a single dose phase I study in healthy individuals has been successfully completed but results remain unpublished (NCT01314898). Subsequently, extension of this drug into phase Ib trials in patients with type 2 diabetic nephropathy was not completed due to poor recruitment and economic issues (NCT01488877).

Conclusion

Novel MR antagonists that maximise cardiovascular protection while minimising disturbances in renal homeostasis would offer a substantial clinical advantage in the treatment of multiple diseases characterised by aberrant MR activity. Pre-clinical assessment of the dihydropyridine-based MR antagonist, finerenone, suggests that alterations in biodistribution allow positive effects in the heart to predominate over negative effects in the kidney, leading to improved outcomes. Finerenone represents the most recent advancement in the use of MR antagonists in the treatment of cardiac and renal disease. Evaluation of its efficacy in real-world settings will provide a clearer picture of its potential.

Conflicts of Interest

Roland Schmieder is on the advisory board of the ARTS-DN study. The other authors have no specific conflict of interest related to the work to disclose.

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Figures

Figure 1. Molecular structures of natural MR ligands and synthetic MR antagonists.

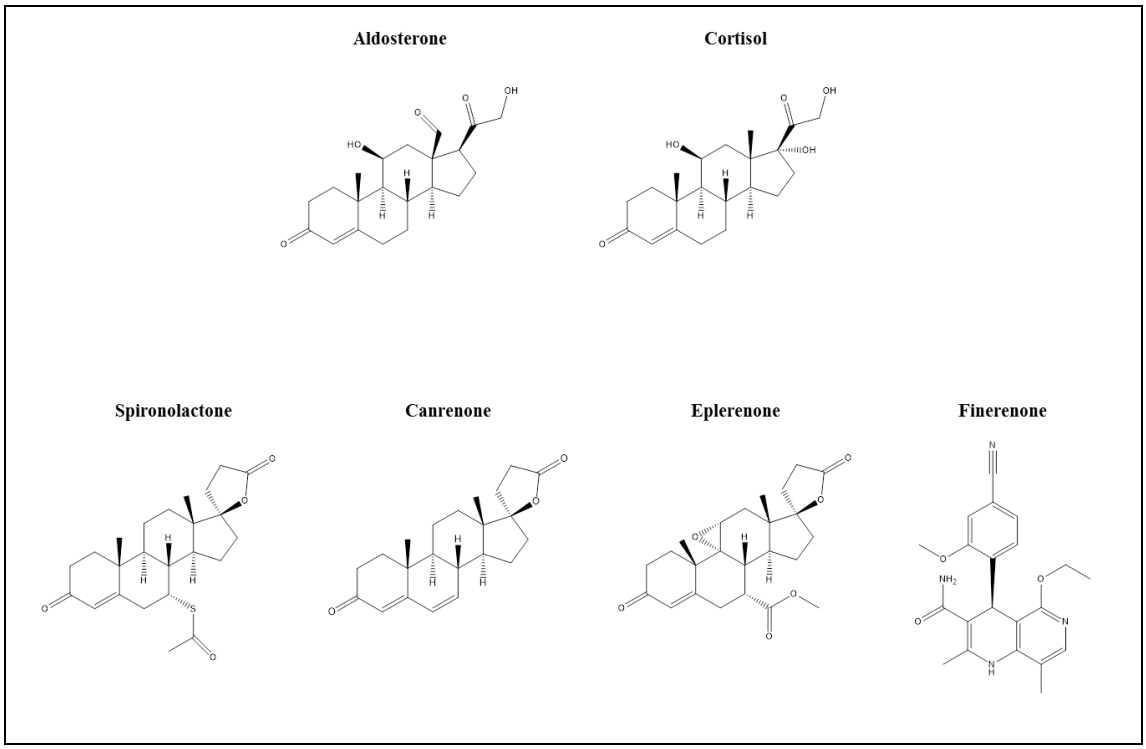
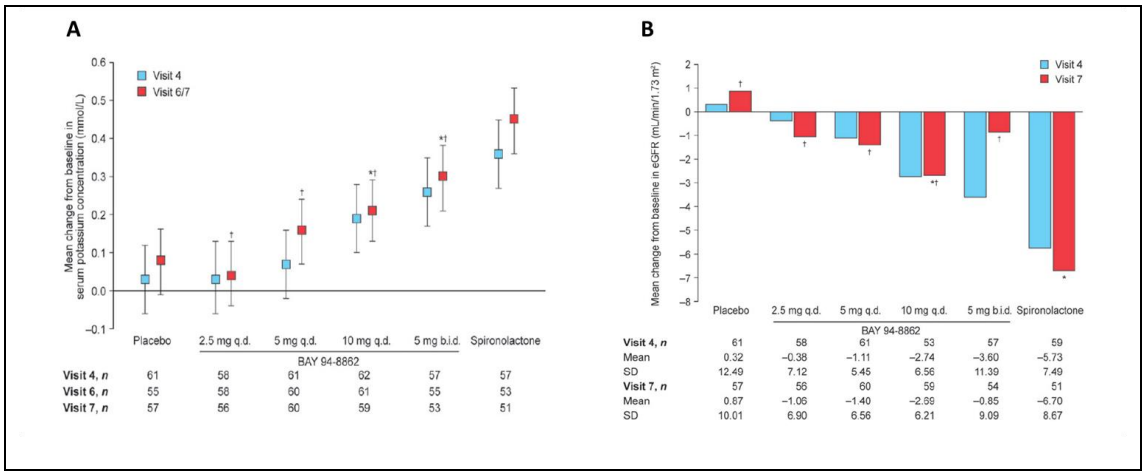
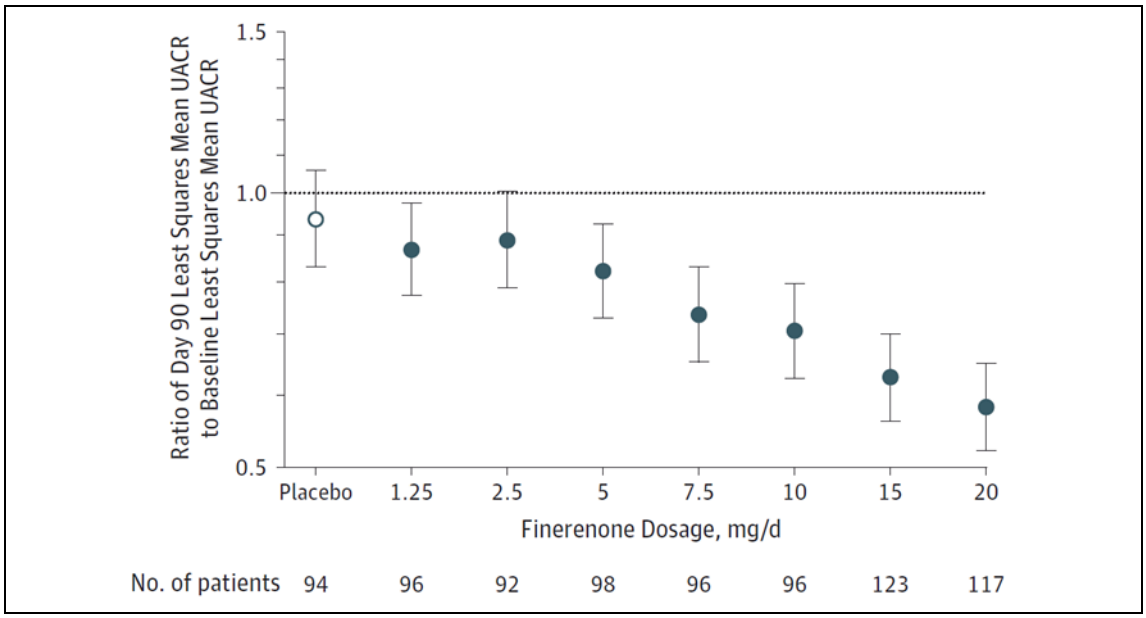


Figure 2. Effect of finerenone on kidney function in the ARTS trial.



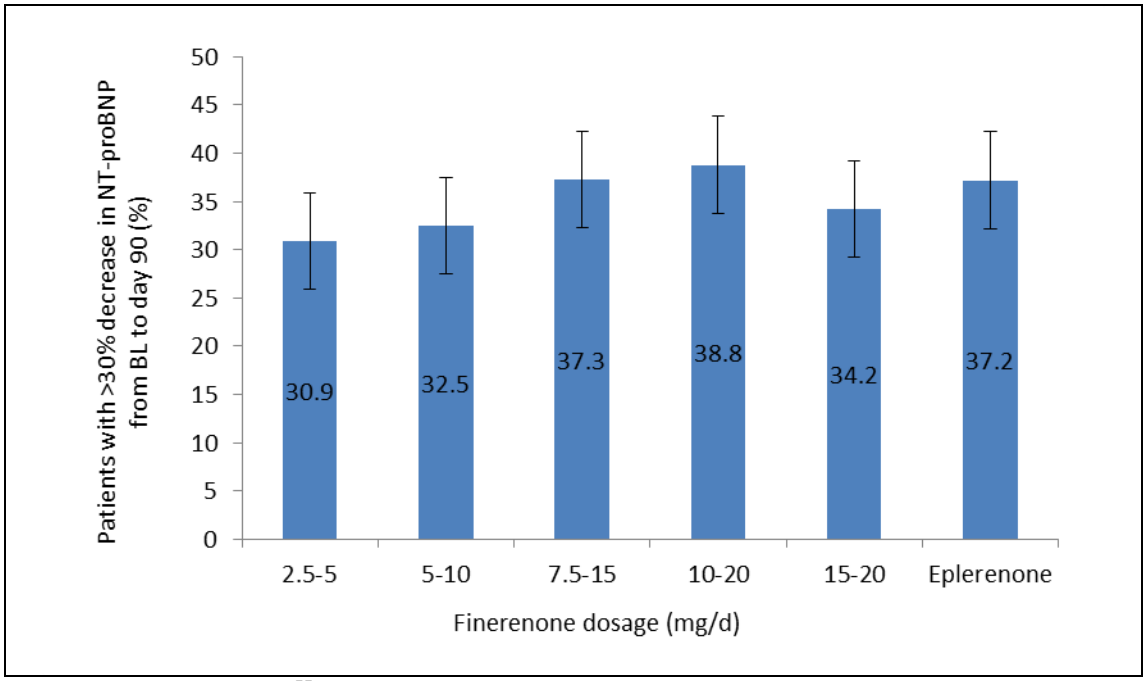
Legend: Selected results from the ARTS trial. A) Change in serum potassium levels from baseline to visit 4 and 6/7, B) Change in eGFR from baseline to visit 4 and 6/7. Reproduced from [50].

Figure 3. Change in urinary albumin to creatinine ratio in the ARTS-DN trial



Legend: Reproduced from [53]

Figure 4. Proportion of patients achieving a >30% decrease in NT-proBNP levels during the 90-day ARTS-HF trial



Legend: Adapted from [55].

Tables

Table 1. Characteristics of first-, second-, and third-generation MR antagonists

	Spironolactone	Eplerenone	Finerenone
Trade name(s)	Aldactone	Inspra	
Class	Steroidal	Steroidal	Dihydropyridine
MR IC_{50} (nM)	24	990	17.8
AR IC_{50} (nM)	77	≥21,240	≥10,000
GR IC_{50} (nM)	2,410	≥21,980	≥10,000
PR EC_{50} (nM)	740	≥31,210	≥10,000
Half-life (h)	1.4 (active metabolites 12–35)	4–6 h	1.7–2.8

Legend: MR, mineralocorticoid receptor; AR, androgen receptor; GR, glucocorticoid receptor; PR, progesterone receptor; IC_{50}, concentration of antagonist required to inhibit 50% activation of receptor; EC_{50}, concentration of ligand required to achieve 50% activation of the receptor. (Adapted from [38, 39, 43])

Table 2. Finerenone in clinical trials

Clinical Trial Identifier	Phase	Study	Patient Population	Estimated Patient Group Size	Daily Finerenone Dose (mg)	Time Frame	Comparator Arm(s)	Primary (1°) and Seconday (2°) Outcome Measures	Trial Start Date	Publications
NCT01473108	I	Safety, Tolerability, Pharmacokinetics & Pharmacodynamics after Administration with 0.5mg Fludrocortisone	Healthy male subjects	n = 67	2.5, 5, 10, 15 or 20	Single dose, monitored up to 28 days	Placebo Eplerenone 50mg/day	**1°** Pharmacodynamics (natriuresis) **2°** Pharmacokinetics (maximum concentration [Cmax] & area-under-curve [AUC]) & adverse events	March 2010	[43]
NCT01687920	I	Dose Proportion	Healthy male subjects	n = 25	1.25, 2.5, 5, 7.5 or 10	Single dose, monitored up to 48h	N/A	**1°** Pharmacokinetic dose proportionality **2°** Adverse events	September 2012	
NCT01345656	II	Safety and Tolerability (ARTS)	**Part A**: Subjects with stable chronic HF with left ventricular systolic dysfunction and mild CKD **Part B**: Subjects with stable chronic HF with left ventricular systolic dysfunction and moderate CKD	n = 457	2.5, 5, 10 or (5 x 2)	Daily dose for 4 weeks, monitored up to 4 weeks	Placebo Spironolactone 25-50mg/day	**1°** Change in serum potassium **2°** Change in serum magnesium, BP & heart rate	May 2011	[49, 50]
NCT01874431	II	Safety and Efficacy (ARTS-DN)	Subjects with Type 2 diabetes mellitus and diabetic nephropathy	n = 821	1.25, 2.5, 5, 7.5, 10, 15 or 20	Daily dose for 90 days, monitored up to 120 days	Placebo	**1°** Change in UACR **2°** Change in serum potassium, renal function, quality-of-life & adverse events	June 2013	[52, 53]
NCT01968668	II	Safety and Efficacy (ARTS-DN Japan)	Japanese subjects with Type 2 diabetes mellitus & diabetic nephropathy	n = 96	1.25, 2.5, 5, 7.5, 10, 15 or 20	Daily dose for 90 days, monitored up to 90 days	Placebo	**1°** Change in UACR **2°** Change in serum potassium	October 2013	

NCT01807221	IIb	Safety and Efficacy (ARTS-HF)	Subjects with worsening chronic HF and left ventricular systolic dysfunction and either Type 2 Diabetes Mellitus with or without CKD or CKD alone	n=1058	2.5, 5, 7.5, 10 or 15	Daily dose for 90 days, monitored up to 120 days	Placebo Eplerenone 25-50mg/day	**1°** Relative decrease in NT-pro-BNP **2°** Change in serum potassium, BP, heart rate & adverse events	June 2013	[54, 55]
NCT01955694	IIb	Safety and Efficacy (ARTS-HF Japan)	Japanese subjects with worsening chronic HF and left ventricular systolic dysfunction & either Type 2 Diabetes Mellitus with or without CKD or moderate CKD alone	n=96	2.5, 5, 7.5, 10 or 15	Daily dose for 90 days, monitored up to 90 days	Placebo Eplerenone 25-50mg/day	**1°** % patients with a relative decrease in NT-pro-BNP of >30% **2°** Change in serum potassium	November 2013	

Data compiled from clinicaltrials.gov (May 01st 2015)