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REVIEW

Heart failure/cardiomyopathy

Mineralocorticoid receptor antagonists in patients with heart failure: current experience and future perspectives

Bertram Pitt[1]*, João Pedro Ferreira[2], and Faiez Zannad[2]

[1]University of Michigan School of Medicine, Ann Arbor, MI, USA; and [2]INSERM, Centre d'Investigations Cliniques Plurithématique 1433, INSERM U1116, Université de Lorraine, CHRU de Nancy, F-CRIN INI-CRCT, Nancy 54500, France

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The 2016 European Society of Cardiology Heart Failure society as well as the 2016 American Heart Association/American College of Cardiology/Heart Failure Society of America heart failure (HF) guidelines confirm the class I indication for mineralocorticoid receptor antagonists (MRAs) in patients with chronic HF and a reduced left ventricular ejection fraction (HF-REF). MRAs in addition to an angiotensin converting enzyme inhibitor (ACEi), or an angiotensin receptor antagonist if an ACEi is not tolerated, along with a beta receptor antagonist and a diuretic (if required for congestion relief) make up the baseline therapy for all patients with chronic HF-REF. However, despite the finding that MRAs have been shown to reduce mortality as well as total and repeated hospitalizations in all patients with chronic HF-REF, as well as their class I indication in international guidelines, their use in guideline eligible patients remains suboptimal. Although much has been written about the mechanisms and role of MRAs in HF, this article will review the clinical studies and mechanisms thought responsible for their benefits in an attempt to increase their use in guideline eligible patients with HF as well as to provide the basis for understanding potential new opportunities for their use in patients with HF.

Keywords Heart failure • Mineralocorticoid receptor antagonists • Trials

Introduction

The steroidal mineralocorticoid receptor antagonist (MRA), spironolactone has been used to treat patients with heart failure (HF) for over 50 years. Prior to the late 1990s spironolactone was however considered mainly as a potassium (K^+) sparring diuretic and was used alone and/or in conjunction with a loop or thiazide diuretic to relieve the symptoms and signs of volume overload in patients with HF as well as to reduce blood pressure in patients with hypertension. The mineralocorticoid receptor (MR) was known to be expressed in renal tubular cells and associated with sodium retention and K^+ loss. Increasing evidence since that time has shown that the MR is expressed in vascular smooth muscle cells, endothelial cells, myocardium, brain, kidney, as well as a number of other tissues including the eye.[1] This increasing evidence has led to an intense investigation in the following years.

Current experience with mineralocorticoid receptor antagonists in patients with heart failure: storyline and therapeutic appraisal

In the late 1990s, the RALES investigators began to evaluate whether or not the use of an MRA in patients with severe chronic heart failure with reduced ejection fraction (HF-REF) would be associated with a reduction in cardiovascular mortality and hospitalizations for HF.[2] The focus of therapy in patients with chronic HF-REF at that time was on the use of angiotensin converting enzyme inhibitors (ACEi). It was felt that the use of an ACEi and a beta-blocker (BB) would suppress the adrenal production of aldosterone because the angiotensin

*Corresponding author. Tel: +35 1965246809, Fax: 965246809, Email: bpitt@med.umich.edu

II type 1 (AT1) receptor was known to be a major stimulus for the adrenal production of aldosterone. One of the major reasons for initiating the RALES study was the finding (in patients with essential hypertension by Staessen *et al.*[3]) that although ACEi were effective in reducing plasma aldosterone levels over time, usually around 6 months, plasma aldosterone levels tended to rise back to or exceeded baseline levels ('aldosterone escape' or 'aldosterone breakthrough'). A study by Brilla *et al.*[4] in Weber's group had suggested that spironolactone could suppress myocardial and vascular fibrosis. However, at the time the RALES programme was conceived this finding had not as yet been confirmed and was thought controversial. In addition, textbooks at that time warned against the combination of ACEi and spironolactone, because of perceived risk of hyperkalaemia and worsening renal function (WRF). Although it went hardly unnoticed that in the CONSENSUS trial half of the patients randomized in the trial and given enalapril were receiving spironolactone at high diuretic dose of 75 mg/day on average, without excessive harm.[5]

Before embarking upon a large scale double-blind randomized trial evaluating the effectiveness and safety of spironolactone in patients with chronic HF-REF, the RALES investigators[2] first performed a dose-ranging study with doses of spironolactone of 12.5, 25, 50, and 75 mg/day compared with placebo on top of standard care at that time in patients with chronic HF-REF.[6] Prior to that time some clinicians were using doses of 100–200 mg/day of spironolactone to overcome diuretic resistance in patients with HF and signs of volume overload.[7] In the RALES dose-ranging study, the level of atrial natriuretic factor was used as a surrogate for efficacy and the level of serum K^+ as an index of safety. At a dose of 75 mg/day, spironolactone was found to be more effective than at the lower doses. However, at this dose there was a significant increase in serum $K^+ > 5.5$ mmol/L and it was reasoned that although a dose of 75 mg/day was more effective than the lower doses that a dose of 25 mg/day would be better to test in an 'attempt to treat' analysis, because it was anticipated that a relatively large percentage of patients might discontinue blinded study medication due to the occurrence of hyperkalaemia. A dosing strategy beginning with 25 mg/day of spironolactone was therefore chosen with the option of decreasing the dose to 12.5 mg/day if there was evidence of an increase in serum $K^+ > 5.5$ mmol/L or to increase the dose to 50 mg/day after 1 month if there was evidence of progressive HF and the serum K^+ remained < 5.0 mmol/L. To minimize the potential risks of hyperkalaemia, patients with a serum $K^+ > 5.0$ mmol/L and/or a serum creatinine > 2.5 mg/dL were excluded from randomization into the trial.

Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction and post-myocardial infarction

To enter the RALES trial, patients had to suffer from severe chronic HF-REF, with a history of having been in NYHA HF class IV, within the 6 months prior to randomization or NYHA class III at the time of randomization. All were on standard therapy for HF at that time, including a diuretic, digoxin, and ACEi were entered into the study. At the time the RALES trial was designed BBs had not as yet been shown to be effective or safe in patients with severe chronic HF. After a mean follow-up of 24 months, the trial was stopped prematurely due to the finding of a significant 30% decrease in all-cause mortality (ACM) as well as a reduction in the incidence of hospitalizations for HF in patients randomized to spironolactone: hazard ratio (HR) = 0.70; 95% confidence interval (95% CI): 0.60–0.82; $P < 0.001$. However, despite the significant reduction in ACM many clinicians remained sceptical regarding the application of these results to clinical practice. One concern was that only around 10% of patients had been on a BB at baseline prior to randomization, although, as mentioned, at the time the RALES trial was designed BBs had not yet been shown to be effective or safe in patients with severe chronic HF. It should however be pointed out that that the point estimate for benefit of spironolactone in RALES was greater in those patients on a BB compared with those not on a BB at baseline.

Shortly after publication of the results of RALES in 1999 the next generation steroidal MRA, eplerenone, became available for clinical evaluation. Eplerenone was known to be more selective but less tightly bound to the MR than spironolactone. It was postulated that due to its greater specificity for the MR, eplerenone would have a lower incidence of gynecomastia, and breast pain in men and a lower incidence of menstrual irregularities in premenopausal females than spironolactone. After a small dose finding trial a dosing strategy of eplerenone 25 mg/day, with the option of increasing the dose to 50 mg/day after 1 month if there was evidence of progressive HF and the serum potassium remained < 5.0 mmol/L was chosen for the study.[8] As in RALES spironolactone had been tested in patients with chronic HF-REF, it was decided to test eplerenone in patients with evidence of left ventricular systolic dysfunction/HF and/or diabetes mellitus early post-acute myocardial infarction (post-MI). Approximately 6000 patients with evidence of HF and/or diabetes mellitus were randomized to eplerenone or placebo from Day 3–14 post-MI. Earlier administration of eplerenone post-MI was discussed but due to the lack of experience in the use of an MRA in the early hours post-myocardial infarction it was reasoned that it would be prudent to wait until the patient was stable before attempting randomization. As in RALES patients with a serum $K^+ > 5.0$ mmol/L and/or a serum creatinine > 2.5 mg/dL were excluded. Patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 were also excluded, as it was realized that in the very old eGFR was a better index of renal dysfunction than a serum creatinine alone. After a mean follow-up of 16 months it was found that patients randomized to eplerenone had a significant reduction in total mortality as well as a reduction in the combined endpoint of cardiovascular mortality and hospitalization for HF (HR = 0.87; 95% CI: 0.79–0.95; $P = 0.002$).[8] In contrast to the patients randomized into RALES, approximately 85% of patients randomized into EPHESUS were on a BB. Eplerenone was beneficial on top of all of the existing therapies for HF post-myocardial infarction at that time including aspirin, reperfusion, statin, ACEi, or angiotensin receptor antagonist (ARB), BB, and a diuretic. It was also found that early administration of eplerenone between Days 3 and 7 was more effective in reducing mortality than latter,[9] and that by 30 days post-randomization (37 days post-myocardial infarction, on average) there was already a significant reduction in total

mortality, mainly due to a reduction in sudden cardiac death.[10] In contrast to the findings in RALES with spironolactone, there was no significant increase in the incidence of sexually related side effects, attesting to the greater specificity of eplerenone for the MR than spironolactone.

These were good results for patients with MI and systolic dysfunction/HF or diabetes, but whether these results could be generalizable to all MI patients was not known. A recently reported clinical trial (REMINDER: impact of eplerenone on cardiovascular outcomes in patients post-myocardial infarction, NCT-01176968) has shown that early use of eplerenone, within the first hours from onset of symptoms after an acute ST Segment Elevation Myocardial Infarction (STEMI) without HF, was safe and could improve the primary composite endpoint of cardiovascular mortality, re-hospitalization, or, extended initial hospital stay, due to diagnosis of HF, sustained ventricular tachycardia or fibrillation, ejection fraction $\leq$40%, or elevated BNP/NT-proBNP at 1 month or more after randomization at a mean follow-up of 10.5 months. In the REMINDER trial, eplerenone reduced the primary outcome (HR = 0.58; 95% CI: 0.45–0.76; P = 0.0001). However, the primary endpoint was driven by higher BNP/NT-proBNP level in the placebo group. Therefore, no robust conclusion on morbidity and mortality could be thrived in this study.[11] The ALBATROSS (aldosterone blockade early after acute myocardial infarction; NCT-01059136) was a multicentre, open-labelled, randomized trial and assessed the effects of MR blockade with 200 mg intravenous bolus of potassium canrenoate followed by 25 mg/day spironolactone for 6 months in 1600 patients with STEMI or high-risk non-STEMI. The primary outcome of the study was the composite of death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for implantable defibrillator, or new or worsening HF at 6-month follow-up. In this trial MRA therapy did not reduce the primary outcome (HR = 0.97; 95% CI: 0.73–1.28; P = 0.81). Of notice, in ALBATROSS patients with STEMI had lower death rates (P for interaction = 0.01), but this was a non-prespecified analysis with low event rates.[12] Despite several positive signs in these studies, until larger and adequately powered trials, MRA therapy cannot be routinely advised in MI patients without systolic dysfunction and/or HF.

The EMPHASIS-HF trial[13] enrolled 2584 patients with chronic stable HF and mild symptoms (NYHA class II) plus history of cardiovascular hospitalization within the past 6 months. Patients were randomized to eplerenone 25–50 mg/day or placebo on top of standard care for patients with HF. After a mean follow-up of 21 months the trial was stopped prematurely due to a significant 37% reduction in total mortality as well as total hospitalizations (HR = 0.63; 95% CI: 0.54–0.74; $P < 0.001$). The largest observed benefit was the reduction of first occurrence and recurrent of HF hospitalization.[13] Of note, a subsequent analysis of the high-risk subgroups including those patients with a history of chronic kidney disease (CKD), diabetes mellitus, the very old ($\geq$75 years of age), and those with a blood pressure less than the mean revealed that eplerenone was equally effective in these high-risk individuals as in those without these characteristics, with predictably more frequent hyperkalaemia and WRF, but keeping a net survival benefit.[14,15] Based on risk stratification according to a validated clinical score, eplerenone was equally effective across all degrees of severity, even in the lowest risk subgroup, as well independently of the intensity of background HF therapy.[16] The benefit could be seen significantly as early as 30 days and was consistent short after the index CV hospitalization as well as at a distance from hospitalization.[17] Eplerenone was also shown to decrease the rate of new onset atrial fibrillation, as pre-specified in the protocol.[18]

Impact in other knowledge areas

Before 1999 (the year of RALES publication[2]) there were 311 articles in *PubMed* searching by 'spironolactone' and 'heart failure'. After 1999 there are 1323 articles with the same search parameters. In fact, RALES actioned an 'inverse translational effect' with a tremendous increase not only in clinical, but also in basic and translational studies allowing a better understanding of the underlying mechanisms and pathways by which MRAs induce their effects. Additionally, the trials with MRAs in humans also led veterinarians to test spironolactone in dogs with HF.[19] In canines, spironolactone also reduced the number of deaths due to cardiac disease, renal disease, or both (30.7% in placebo group vs. 13.7% in spironolactone group; P = 0.0043).

Underlying mechanisms for mineralocorticoid receptor antagonists effect

Although both spironolactone and eplerenone have been shown to be effective in reducing mortality in patients with HF-REF as well as hospitalizations for HF, recent evidence from EMPHASIS-HF suggests that their benefits may in large part be most prominent in patients with an increased waist circumference suggesting an increase in visceral fat and/or the metabolic syndrome. Patients with HF increased abdominal adiposity benefited to a greater extend from eplerenone but had similar safety profile compared with thinner patients. Moreover, after publication of RALES it was noted that almost all of the benefits of spironolactone on mortality were observed in those patients with ongoing collagen formation as evidenced by an increase in procollagen I and III levels.[20] While of interest and mechanistically important, the difficulty in determining the level of procollagen I and III and/or the presence of ongoing myocardial fibrosis in clinical practice kept this observation from influencing the selection of patients with HF for administration of an MRA. Although waist circumference was not collected in the RALES study it can be postulated that those patients in RALES who had evidence of ongoing collagen formation as evidenced by an increase in procollagen I and III also had an increase in visceral fat. Support for this hypotheses comes from the finding that a high-fat diet is associated with an increase in MR expression.[21,22] Adipocytes stimulate the adrenal production of aldosterone as well as to locally produce aldosterone resulting in a paracrine effect with a resultant increase in inflammatory cytokines. An increase in plasma aldosterone levels is associated with brown fat dysfunction and white fat inflammation.[22,23] Patients with the metabolic syndrome have been found to have an increase in plasma aldosterone levels and myocardial fibrosis which can be reduced by administration of an MRA.[24] Additionally, high plasma levels of aldosterone have been shown to be associated with the development of the metabolic

syndrome.[25] Thus, although further prospective studies will be required, it is suggested that even though eplerenone should be prescribed to all HF-REF patients, those presenting with an abdominal obesity may derive a greater benefit.

Mineralocorticoid receptor antagonists for heart failure with preserved ejection fraction

More recently, spironolactone has been evaluated in the National Heart, Lung, and Blood Institute (NHLBI) sponsored TOPCAT trial[26] in which 3445 patients with chronic HF with a preserved left ventricular ejection fraction (HF-PEF) were randomized to spironolactone in a dosing strategy starting with 15 mg/day with possible up titration to 30 mg and eventually 45 mg/day. TOPCAT had a singular spironolactone dosing because it was thought safer to begin with 12.5 mg/day in elderly patients and uptitrate afterwards, but that would mean splitting the 25 mg tablet which was not practical. For this reason, the manufacturer created these 'new' dosages with the hope that by having a new tablet form they would be able to market their pills in the case of a positive trial.

In TOPCAT, patients could be enrolled (and were stratified) with either a history of hospitalization within the past year, the major reason for which was HF, or elevated natriuretic peptides (BNP or NT-pro BNP). The mean follow-up was 40 months. Overall, spironolactone did not reduce the primary outcome consisting of time to cardiac death, resuscitated cardiac arrest, or hospitalization for HF as compared with placebo (HR = 0.89; 95% CI: 0.77–1.04; $P = 0.14$). However, HF hospitalization had a significantly lower incidence in the spironolactone group as compared with the placebo group (HR = 0.83; 95% CI: 0.69–0.99, $P = 0.04$). The TOPCAT trial showed marked geographical differences regarding treatment effect. Patients from 'the Americas' (Canada, USA Argentina, and Brazil) showed a marked response to treatment whereas patients from Eastern Europe (Russia and Georgia) did not (HR for cardiovascular mortality = 0.74; 95% CI: 0.57–0.97 in 'the Americas' vs. 1.31; 95% CI: 0.91–1.90 in Eastern Europe; P for interaction = 0.012). Subsequent analysis revealed that the patients randomized from Eastern Europe, who comprised about one-half of the patients randomized into the study, had a placebo event rate that was approximately one-fifth of that in 'the Americas' and was not compatible with data from prior epidemiological or randomized studies of patients with HF-PEF. In fact, death rates in Russia and Georgia were similar to those of the general population in those countries.[27–29] Of note, patients from Russia and the Republic of Georgia who were randomized to receive spironolactone had also a lesser increase in serum K^+ and a lesser decrease in systemic blood pressure than those in 'the Americas'. This difference in the response to serum K^+ to spironolactone persisted when matched for baseline renal function, suggesting that many of the patients from Russia and the Republic of Georgia may not have taken their study medication. Thus, it would appear that in appropriately selected patients with chronic HF-PEF that spironolactone is likely effective in reducing cardiovascular mortality and hospitalizations for HF.[27] These findings have led Pfeffer and Braunwald[30] to state that 'based on the findings in TOPCAT in North and South America and in the absence of other more definitive data, it now appears reasonable to treat patients with HF-PEF resembling those enrolled in North and South America with spironolactone to improve outcomes'. Furthermore, several *post hoc* analyses have identified subgroup where spironolactone is also likely to be benefitial.[31–33] Unfortunately, these *post hoc* analyses are not randomized evidence. However, TOPCAT had a stratification by the entry criteria and stratification is a randomization gatekeeper.[34] In TOPCAT, patients were either randomized according to BNP strata or HF hospitalization strata (TOPCAT online supplemental material[26]). Those in the BNP strata had a positive response to spironolactone treatment with a major (≈35%) primary outcome event rate reduction (HR = 0.65; 95% CI: 0.49–0.87 in BNP stratum vs. 1.01; 95% CI: 0.84–1.21 in hospitalization stratum; P for interaction = 0.01). Despite strata analysis has power and precision limitations, using this strategy TOPCAT is a positive trial in patients with HF-PEF and elevated BNP. It should however be emphasized that the overall result of the trial was not significant and that further prospective adequately powered randomized clinical trials will be required to confirm the hypotheses that spironolactone is effective in reducing cardiovascular outcomes in patients with HF-PEF. However, given the aforementioned, is our opinion that, unless contraindicated, spironolactone should be provided to HF-PEF patients with the characteristics of those enrolled in 'the Americas' and to those with elevated natriuretic peptides.

Mechanisms associated with the beneficial effects of mineralocorticoid receptor antagonists in heart failure

The mechanisms whereby MRAs decrease the risk of death and hospitalizations for HF in patients with chronic HF-REF, and likely appropriately selected patients with HF-PEF, remain speculative but likely include the fact that MR receptors are present, not only in the epithelial cells of the renal tubule but also in the myocardium, vascular wall, endothelium, macrophages, intestines, and the eye. Mineralocorticoid receptors are unregulated in patients with HF as well as in patients on a high-sodium or high-fat diet.[25] The MR receptor can be activated by aldosterone as well as cortisol.[35] Under normal circumstances, the MRs in the heart are occupied but not activated by cortisol. Cortisol has a greater affinity for the MR than aldosterone. In tissues where aldosterone is co-expressed with the enzyme 11-beta hydroxysteroid dehydrogenase 2 (11βHSD2), such as the epithelial cells of the renal tubule, cortisol is converted to cortisone which cannot activate the MR. However in patients with HF, hypertension, and/or CKD, 11βHSD2 may be down-regulated and therefore cortisol may be available to activate the MR. In tissues such as the myocardium where 11βHSD2is not expressed, the MR may be occupied by cortisol.[36] The mechanism by which the MRs in the myocardium are activated is thought to be related to the presence of an increase in sodium and various cofactors. Although the presence of sodium was thought to be essential for activation of the MR by aldosterone, evidence has emerged suggesting that the MR may be activated by an increase in reactive oxygen species (ROS) independent of an increase in sodium[37] (*Figure 1*). Once activated, the MRs are

associated with a number of effects including: increase in ROS, decrease in nitric oxide availability, increase in inflammatory cytokines, activation and infiltration of macrophages. In the kidney activation of the MR is associated with sodium retention and potassium loss, as well as an increase in mesangial fibrosis and podocyte loss resulting in progressive renal dysfunction. In the myocardium MR activation is associated with myocardial hypertrophy, fibrosis, and cell death, whereas in the vascular wall MR activation is associated with endothelial dysfunction, perivascular fibrosis, and vascular stiffening.[38] Mineralocorticoid receptor activation has also been shown to be important in the development of atrial fibrillation, ventricular fibrillation and sudden cardiac death, in part related to an effect on myocardial cell calcium flux as well as an increase in fibrosis and electrical inhomogeneity.[39] Moreover, MR activation is also associated with an increase in insulin resistance which has important implications for the therapy of not only HF but also diabetes mellitus.[25] Interestingly, MR activation is also associated with an increase in salt taste due to an increase in central 11-βHSD2 levels.[40] Although MRAs are thought to block the effects of aldosterone and/or cortisol, they also have been shown to have an important role in blocking the effects of norepinephrine from sympathetic nerve terminals and increasing myocardial norepinephrine uptake.[41]

Although stimulation of the angiotensin type 1 receptor (AT1R) is associated with an increase in aldosterone release from the adrenal gland, it should also be pointed out that aldosterone can increase the expression of the AT1R and angiotensin converting enzyme levels resulting in a viscous cycle (*Figure 2*). Both preclinical and clinical data suggest that the best way to block this cycle is to block both angiotensin and activation of the MR.[42,43] Although both angiotensin and aldosterone share some common signalling pathways, they have in dependent signalling such that blocking both angiotensin and aldosterone is important to achieve optimal results as evidenced by the results of EPHESUS and EMPHASIS HF trials. The pathophysiologic effects of aldosterone beyond Na^+ and K^+ are summarized in *Figure 3*. Although it can be anticipated that our understanding of MR activation and MRAs will continue to evolve, it is understandable why blockade of the MR in addition to blockade of angiotensin and norepinephrine forms the basis for therapy of patients with HF in the current HF guidelines.[44,45]

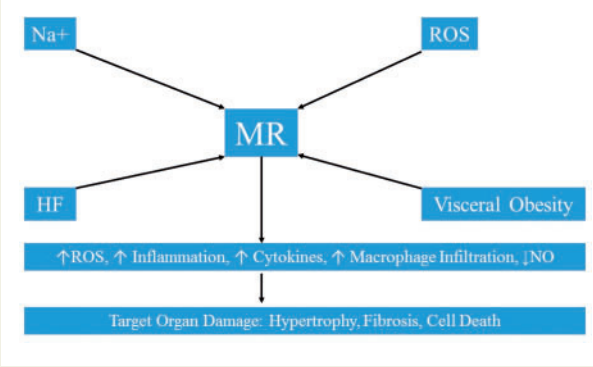

Figure 1 Mineralocorticoid Receptor Activation. ROS, reactive oxygen species; MR, mineralocorticoid receptor; HF, heart failure; NO, nitric oxide.

Mineralocorticoid receptor antagonists' choice and therapeutic guidance

Most guidelines while recommending an MRA for patients with chronic HF-REF do not make a clear recommendation as to whether spironolactone or eplerenone should be the MRA of choice. It would be prudent to use the MRA and dosing strategy used in the respective pivotal HF-REF trials, for example spironolactone 12.5–50 mg/day in patients with severe chronic HF-REF based upon the results of RALES[2] and eplerenone 25–50 mg day in patients with chronic HF-REF and mild symptoms, based upon the results of EMPHASIS-HF.[13] In clinical practice, most likely because of low cost, and also lack of education about and promotion of eplerenone in most of Europe and the USA, spironolactone is the most widely used MRA regardless of whether or not the

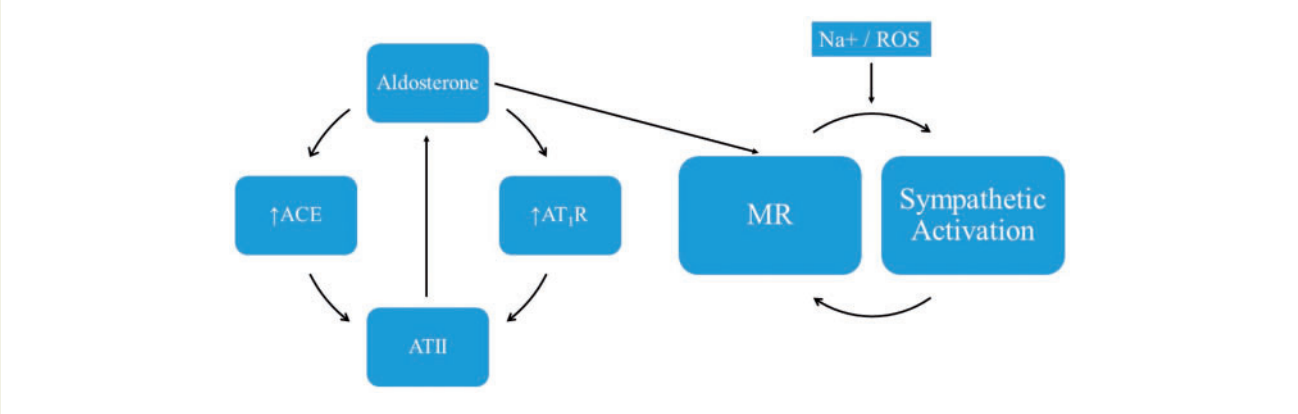

Figure 2 The vicious cycle of mineralocorticoid receptor activation. AT1R, angiotensin type 1 receptor; ATII, angiotensin II; ACE, angiotensin converting enzyme; ROS, reactive oxygen species; MR, mineralocorticoid receptor.

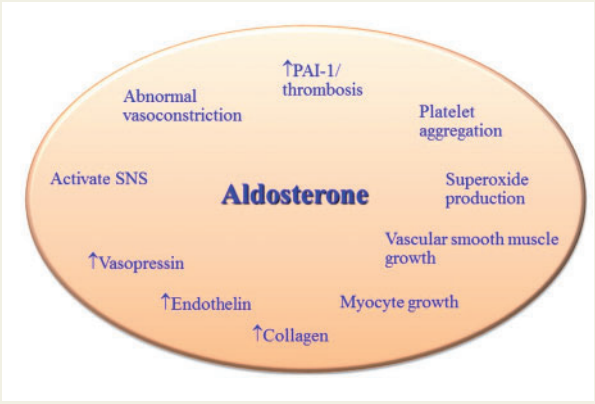

Figure 3 Aldosterone effects beyond sodium and potassium.

Table 1 Mineralocorticoid receptor antagonists' doses and main cardiovascular indications

Condition and dosage	Spironolactone (mg/day)	Eplerenone (mg/day)
HF-REF/Post-MI	25–50	Up to 50
HF-PEF	25–50[a]	Up to 50
Acute heart failure[b]	100 (first 3 days)	?
Dialysis/ESRD[c]	12.5–25	?

HF-REF, heart failure with reduced ejection fraction; Post-MI, post-myocardial infarction; HF-PEF, heart failure with preserved ejection fraction; ESRD, end-stage renal disease.
[a]For the TOPCAT trial, 'special' spironolactone doses (of 15, 30, and 45 mg) were created but they are not currently available for clinical use.
[b]Single-centre non-randomized open-label study.
[c]Small randomized trials.

patient has evidence of severe chronic HF-REF. There are however a number of important differences between these agents that could favour the use of eplerenone over spironolactone in patients with HF, especially those with concomitant diabetes mellitus and/or CKD.[46] As mentioned above, eplerenone is more specific, although less tightly bound to the MR. Thus, in younger males, eplerenone has the advantage of being relatively devoid of the sexually related side effects associate with the use of spironolactone. Moreover, eplerenone is now generic in the USA (and in some other parts of the world) and although its cost will remain considerably higher than that of spironolactone due to the greater costs associated with its production, in the long run it may be cheaper if the patient can be maintained on an MRA such as eplerenone than having spironolactone discontinued. Alternatively one might recommend the use of spironolactone in those patients in whom cost is an important factor and to switch to eplerenone only in those patients who cannot tolerate spironolactone. Despite the cost differential, eplerenone might still be the MRA of choice in certain circumstances such as in those patients with diabetes mellitus and/or CKD. Although there have not been any large scale comparative randomized trials of spironolactone and eplerenone, there is at least one small study in patients with HF and diabetes mellitus.[46,47] In that study, spironolactone increased the level of glycated haemoglobin (HbA1c) and cortisol whereas eplerenone did not. There are also studies showing that although spironolactone improves endothelial function in patients with HF, it fails to do so in those with diabetes mellitus whereas eplerenone does.[46,48] This has been attributed to the relative non-specificity of spironolactone for the MR. Thus, in patients with HF and diabetes mellitus one might consider the use of eplerenone over spironolactone. Similarly, in patients with CKD and/or diabetes mellitus who are at increased risk for developing hyperkalaemia one might suggest eplerenone because it has a shorter plasma half-life than spironolactone and it could be postulated that should hyperkalaemia develop it would resolve faster after discontinuation of eplerenone than that of spironolactone. The shorter plasma half-life of eplerenone might also allow the kidney time to excrete K^+ more effectively than with spironolactone and therefore avoid the risks of hyperkalaemia. It should however be emphasized that adequately powered prospective comparative randomized studies will be required to determine whether or not there are any significant differences in safety and clinical outcomes between the use of spironolactone and eplerenone in guideline appropriate patients with chronic HF-REF.

Although MRAs have been shown to be effective in reducing total mortality in patients with chronic HF-REF and have been accorded a class I indication in international guidelines their use remains suboptimal in comparison to the use of an ACEi or ARB, and a BB, largely due to the fear of inducing hyperkalaemia and WRF.[48] This is in part the result of the paper by Juurlink *et al.*[49] who reported an increase in hospitalizations for hyperkalaemia shortly after publication of the RALES trial. A careful review of this report suggests that many of the patients included in the study received higher doses of spironolactone than in RALES and, most importantly, had contra-indications for MRA therapy or did not undergo serial monitoring of serum K^+ and renal function. Although hyperkalaemia is clearly a risk in patients using an MRA, especially those with concomitant CKD and/or diabetes mellitus, careful patient selection and serial monitoring of serum K^+ and renal function should minimize this risk. In the large-scale randomized trials of MRAs in patients with HF-REF including RALES, EPHESUS, EMPHASIS-HF, and TOPCAT, the incidence of hyperkalaemia (serum $K^+ > 5.5$ mmol/L) was relatively low (up to a maximum of ≈12%), and there has not been, to our knowledge, a single death attributable to hyperkalaemia in a patient randomized to an MRA in the major pivotal trials. Similarly, although there has been an increase in serum creatinine after initiation of an MRA, there have not been any significant increases in the incidence of end-stage renal disease (ESRD) or need for dialysis. Unfortunately, the lack of serial monitoring for serum K^+ and renal function has persisted over the years and a recent study has suggested that a serum K^+ may not be obtained immediately prior to initiating an MRA or in the month after initiation in the vast majority of patients.[50] The gap between the number of guideline eligible patients with HF-REF and the actual number receiving them provides a major opportunity to further reduce cardiovascular mortality and health care costs. A practical guidance for MRA dosing is presented in *Table 1*.

The underuse of MRAs in HF due to the fear of inducing serious hyperkalaemia has been a stimulus for the development of new non-

steroidal MRAs, new targeted delivery systems for MRAs, the development of new K+ lowering drugs, and new potassium home monitoring tools.

New non-steroidal mineralocorticoid receptor antagonists

Several new non-steroidal MRAs have been developed. The one that has undergone the most extensive clinical evaluation is finerenone.[51] Finerenone is tightly bound to and highly specific for the MRA. Therefore, its use would not be expected to be associated with the sexually related side effects associated with spironolactone. Similarly, due to its greater specificity than spironolactone for the MR it would not be expected to raise HbA1c or cortisol levels in patients with diabetes mellitus. Finerenone also has a different bio distribution than the steroidal MRAs, spironolactone and eplerenone.[52] Both spironolactone and eplerenone accumulate to a greater extent in the kidney than in the heart whereas finerenone is equally distributed providing relatively greater cardiac/renal mineralocorticoid receptor antagonism. More importantly, finerenone has a different mode of binding to the MR than does the steroidal MRAs resulting in activation of different gene pathways. In the ARTS trial,[53] finerenone was compared with spironolactone in patients with chronic HF-REF and CKD. Finerenone was found to reduce BNP and NT-pro BNP, as well as urinary albuminuria, significantly more than placebo but similar to that of spironolactone 25–50 mg/day. The incidence of hyperkalaemia was less with finerenone than with spironolactone. Spironolactone was however more effective in reducing systemic blood pressure than finerenone. The explanation for the lesser effect of finerenone on blood pressure remains unclear. However, as cerebral MR antagonism has been shown to be important in reducing sympathetic activation and blood pressure, the finding that spironolactone has greater access across the blood–brain barrier than finerenone could in part explain this finding. If confirmed in future studies, the relative lack of effect of finerenone on blood pressure has potential advantages and disadvantages. In patients with HF-REF and concomitant cerebral, coronary, and/or renal vascular disease, a decrease in systemic blood pressure could precipitate cerebral, coronary, and/or renal ischaemia and therefore the lesser effect of Finerenone on blood pressure could be an advantage. In patients with HF and manifest hypertension, such as those patients with HF-PEF, the lesser effect of finerenone on blood pressure might however be a disadvantage.

In the ARTS-HF study,[54] finerenone (at doses of 2.5, 5, 7.5, 10, or 15 mg, uptitrated to 5, 10, 15, 20, or 20 mg/day) was compared with eplerenone 12.5–50 mg/day in patients with chronic HF-REF complicated by CKD and/or diabetes mellitus. In this study, finerenone 10–20 mg/day was found to reduce BNP or NT-proBNP (primary endpoint) as well as the incidence of albuminuria and hyperkalaemia to a similar degree as eplerenone. However, finerenone had a more favourable effect on cardiovascular mortality and hospitalizations for HF (exploratory endpoint). The explanation for the possible greater reduction in cardiovascular outcomes with finerenone remains uncertain but could be attributed to the findings in preclinical studies in which finerenone has a more specific binding to the MR and activation of gene pathways.[55] It should however be cautioned that the number of clinical events in ARTS-HF was very small and thus the relative effectiveness of finerenone in comparison to eplerenone remains to be determined. Finerenone is currently under evaluation in patients with diabetic nephropathy (FIDELIO trial: NCT02540993) and in patients with renal disease at increased risk for cardiovascular events (FIGARO trial: NCT02545049).

Future uses of mineralocorticoid receptor antagonists and potassium binders for heart failure, cardiovascular prevention, and end-stage renal disease patients

Current doses of spironolactone 12.5–50 mg/day and eplerenone 25–50 mg/day while effective in reducing cardiovascular events in patients with HF have only a minimally effective diuretic effect.[56] Prior to initiation of the RALES study, doses of 100–200 mg/day of spironolactone were used to overcome diuretic resistance and doses of up to 400 mg/day are commonly used in patients with liver cirrhosis to reduce ascites.[56] The clinical benefit and safety of high-dose MRA use in AHF was recently supported by a single-centre, single-blind trial of 100 patients treated with standard therapy alone or with addition of spironolactone initiated within 24 h.[57–59] However, this was a single-centre non-randomized study and the intervention was not blinded to the investigators, which raises concerns for potential bias. The HF network of the NHLBI is currently evaluating the effectiveness and safety of spironolactone 100 mg/day in patients with acute decompensated HF (ATHENA trial: NCT02235077). The study will however likely be limited by the selection of patients with relatively well-preserved renal function due to the risk of inducing hyperkalaemia and further renal dysfunction. One possible way to overcome diuretic resistance and to reduce volume overload in those patients with CKD and/or diabetes mellitus who are at increased risk for developing hyperkalaemia would be to use high-dose spironolactone in conjunction with one of the new potassium lowering drugs such as patiromer or sodium zirconium cyclosilicate (ZS9).[60–63] Both of these agents have been shown to be effective in lowering serum potassium to normokalaemic levels in patients with hyperkalaemia.[60,63] One could therefore contemplate reducing serum potassium in patients with hyperkalaemia to <5.0 mmol/L and then to add a high-dose MRA while continuing the potassium binder. In those patients who have CKD but are normokalaemic but at increased risk of developing hyperkalaemia, one could consider simultaneous administration of one of the new potassium lowering drugs with a high-dose MRA. In view of the fact that current therapies have not as yet been shown to be effective in reducing the relatively high rate of death and hospitalizations for HF in patients with acute decompensated HF, the use of high-dose MRAs in conjunction with a one of the new potassium lowering agents holds great promise. Another potential use of the new potassium lowering agents would be to allow the use of MRAs in patients with an eGFR ≤ 30 mL/min/1.73 m^2 in whom they

are currently contraindicated due to the fear of inducing hyperkalaemia and further renal dysfunction. One could envision the simultaneous administration of an MRA and a potassium lowering agent in patients with stable stage 5 CKD in whom the serum potassium is <5.0 mmol/L or in those with a serum potassium >5.0 mmol/L first administering one of the potassium lowering agents to achieve normokalaemia and then adding an MRA such as eplerenone at a dose of 12.5 mg/day with subsequent up titration to 25 mg/day at 1 month if the serum potassium remains <5.0 mmol/L. Another potential use of the new potassium lowering agents in association with an MRA could be in patients with ESRD on renal dialysis who are at a high risk for HF and sudden cardiac death. However, these latest putative uses of MRAs, potentially with or without potassium binders, must be tested in appropriate randomized clinical trials.

The use of these new potassium lowering agents might also increase the use of MRAs in guideline eligible patients with HF-REF, which as mentioned above remains suboptimal. The use of one of the new potassium lowering drugs might therefore allow more patients to be maintained on an MRA and thus benefit from their proven effects on mortality and hospitalizations for HF. Further prospective randomized trials will however be required to prove this hypothesis as it has been suggested that at least part of the benefit of MRAs in reducing mortality in patients with HFREF can be attributed to their increasing serum potassium levels.[64]

Regarding HF prevention, the HOMAGE (Heart OMics in AGEing) project aims to identify and validate specific biomarkers of HF in order to prevent the development of HF affecting elderly population. The project will use an innovative 'omic-based' approach which investigating simultaneously a huge amount of genes, proteins and metabolites in order to investigate new ways of preventing HF. Furthermore, a substudy of HOMAGE will randomize patients at risk for HF development to spironolactone or 'usual care' to identify patients who are likely to respond based on cardiac collagen markers[50] (NCT02556450).

In HF patients undergoing haemodialysis, the ALCHEMIST trial is designed to establish the effects of spironolactone vs. placebo on major cardiovascular events on chronic haemodialysis patients (NCT01848639).

The role of MRAs in the 'cardiovascular continuum' is summarized in *Figure 4*.

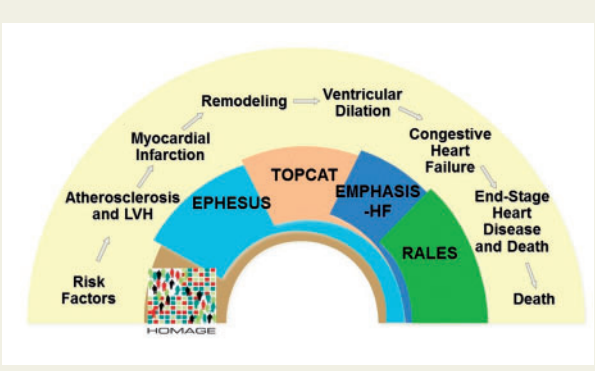

Figure 4 The role of mineralocorticoid receptor antagonists in the 'cardiovascular continuum'. LVH, left ventricular hypertrophy.

Conclusion

In conclusion, the steroidal MRAs, spironolactone and eplerenone, have been shown to be effective in reducing mortality and hospitalizations for HF in patients with chronic HF-REF and are likely effective in appropriately selected patients with chronic HF-PEF. Although the use of MRAs has been suboptimal largely due to the fear of inducing hyperkalaemia it can be anticipated over the next several years that the use of new non-steroidal MRAs (such as finerenone) and/or the use of the new potassium lowering agents (such as patiromer and ZS9) will enable the increased use of MRAs in patients with HF, especially those complicated by advanced CKD and/or diabetes mellitus, potentially leading to a further decrease in cardiovascular mortality, hospitalizations for HF, health care costs, and patient wellbeing.

Conflict of interest: B.P. is consultant for Bayer, Merck, Astra Zeneca, Takeda, Relypsa*, SCPharmaceuticals*, PharMain*, Kbp pharmaceuticals*, Tricida*, Stealth Peptides, DaVinci Thereputics*, Sarfez Pharmaceuticals, and Aurasense* (* =stock options).

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