Mineralocorticoid receptor antagonism: therapeutic potential in acute heart failure syndromes

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Acute heart failure syndromes (AHFS) are a heterogeneous group of commonly encountered and difficult to manage clinical syndromes associated with high morbidity and mortality. Dyspnoea, pulmonary, and systemic congestion often characterize AHFS due to acutely elevated intracardiac filling pressures and fluid overload. Diuresis, respiratory support, vasodilator therapy, and gradual attenuation of the activation of renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) are the keystones of AHFS management. Despite available therapies, post-discharge mortality and re-hospitalization rates remain unacceptably high in AHFS. Neurohumoral-mediated cardiorenal dysfunction and congestion may contribute to these high event rates. Mineralocorticoid receptor antagonists (MRAs) serve a dual therapeutic role by enhancing diuresis and attenuating the pathological effects of RAAS and SNS activation. Although these agents are indicated in patients with chronic, severe heart failure with reduced ejection fraction (HF/REF) and in patients with HF/REF post-myocardial infarction (MI), they have not been systematically studied in patients with AHFS. The purpose of this review is to explore the potential efficacy and safety of MRAs in AHFS.

Keywords Mineralocorticoid receptor antagonists (MRAs) • Acute heart failure syndromes (AHFS) • Aldosterone • Renin–angiotensin–aldosterone system (RAAS) • Neurohumoral

Introduction

Acute heart failure syndromes (AHFS) have been defined as new onset or worsening heart failure (HF) signs and symptoms necessitating urgent therapy and hospitalization.1 Over 1 million patients are admitted with AHFS each year accounting for 60–74% of the total cost of caring for HF patients.2–5 Hospital readmission rates and post-discharge mortality rates in AHFS range from 24 to 30% and ~10% at 60–90 days, respectively.6

Neurohumoral compensatory mechanisms in HF, including activation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS), act to preserve cardiac output by increasing water and salt retention, cardiac contractility, arterial vasoconstriction, and by activation of inflammatory cascades that contribute to cardiovascular repair and remodelling.6–8 Unregulated and prolonged neurohumoral activation in HF may, however, mediate a multitude of harmful effects.9,10

Aldosterone and cortisol levels are elevated in patients with AHFS, and may contribute to cardiorenal dysfunction through a variety of mechanisms.11–19 The deleterious neurohumoral profile of aldosterone and cortisol (Figure 1) and the observation that mineralocorticoid receptor antagonists (MRAs) significantly reduce morbidity and mortality in chronic HF with reduced ejection fraction (HF/REF) and HF/REF post-myocardial infarction (MI) has prompted interest in studying the utility of mineralocorticoid receptor (MR) antagonism in AHFS (Table 1).1,20,21

This review article will discuss the neurohumoral mechanisms that underlie progressive and decompensated HF in the context of the therapeutic properties of MRAs and the profile of AHFS patients.

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Acute heart failure syndrome pathophysiology

Excess RAAS and the resultant end-organ injury in HF may predispose the chronically failing heart to decompensation from a variety of precipitating factors and to further progression of cardiovascular and renal dysfunction (Figure 2). Neurohumoral activation, autonomic dysregulation, and molecular/cellular changes in patients with acutely decompensated chronic HF may, therefore, serve as potential pathophysiological targets for MRAs.

Neurohumoral excess

Compensatory RAAS activation in chronic HF has been well documented; however, the role of the RAAS has yet to be fully defined in AHFS. Excess RAAS may have many of the same deleterious effects observed in chronic HF. Neurohumoral-mediated vasoconstriction, fluid retention, and cardiorenal dysfunction may represent common pathophysiological mechanisms in the development of AHFS and progression of HF/REF and heart failure with preserved ejection fraction (HFrEF).

Aldosterone and cortisol levels are inappropriately elevated in patients hospitalized with worsening HF despite the use of angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and beta-blockers. While little contemporary data exist demonstrating elevations in aldosterone and cortisol above baseline in patients with AHFS, several studies have documented reductions in circulating neurohumoral factors, including aldosterone, following improvement in the clinical and haemodynamic abnormalities that characterize AHFS. Furthermore, myocardial MR expression is up-regulated in chronic HF and may be associated with elevated aldosterone and cortisol levels. Since most AHFS patients present with acutely decompensated chronic HF, up-regulated MRs theoretically provide a therapeutic target for MRAs in the acute setting.

Elevations in neurohumoral factors increase the risk of death and ventricular arrhythmias in AHFS. Acute heart failure
Acute heart failure syndrome therapy

Limitations and promise

The management of AHFS initially focuses on life-threatening reversible precipitants, and therapeutic fluid removal to relieve symptomatic congestion, optimize cardiac function, and minimize end-organ damage. Agents aimed at relief of symptoms through diuresis and lowering of intracardiac filling pressures predominate initial therapy in most patients, while inotropes and inodilators predominate in patients with advanced HF. Achieving haemodynamic goals and volume reduction with inotropes and diuretics alone has not, however, been demonstrated to improve outcomes in AHFS.140

Antagonism of the SNS and RAAS with ACE-Is, ARBs, beta-blockers, and MRAs has significantly reduced morbidity and mortality in patients with chronic HF/REF and HF/REF post-MI.20,41–44 However, similar reductions in mortality have not been realized in patients with HFpEF with ACE-Is, ARBs, or beta-blockers.35–48 Angiotensin-converting enzyme inhibitors/ARBs directly attenuate the powerful angiotensin II (ANGII) stimulus for aldosterone production; however, after a period of initial suppression aldosterone concentrations ‘breakthrough’ to normal or above normal levels.10,49,50 Importantly, aldosterone levels are elevated in AHFS despite therapy with ACE-Is/ARBs and beta-blockers, and MR activation may contribute to both the acute decompensation (i.e. fluid retention and vasoconstriction) and progressive cardiorenal dysfunction (i.e. fibrosis, inflammation, oxidative stress, and hypertrophy) in patients with HF.51,52

The use of MRAs in AHFS may be a key therapeutic intervention in patients with worsening HF by virtue of their ability to augment diuresis and attenuate the pathologic effects of MR activation.53–54 The use of MRAs may be, however, limited by the risk of hyperkalaemia and worsening renal function in many AHFS patients with comorbid chronic kidney disease (CKD).20,21,55

Is there a role for mineralocorticoid receptor antagonism in acute heart failure syndrome?

The benefit of MRAs in chronic HF/REF was unequivocal in chronic, severe HF/REF, and HF/REF post-MI in the RALES (Randomized Aldactone Evaluation Study) and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trials, respectively (Table 1).20,21 The improved morbidity and mortality observed in RALES and EPHESUS, is thought to be in part due to suppression of neurohumoral activation by MRAs, thereby prompting interest in early initiation of MRAs in AHFS since these neurohumoral mechanisms are also implicated in the pathogenesis of AHFS.28,53

Novel therapeutic agents that have shown promise in preclinical studies have failed to show a mortality benefit in AHFS trials.38,56 The lack of therapeutic benefit observed in these trials may have resulted from inappropriate patient and biochemical target selection as well as timing of intervention. In addition, agents that have a demonstrated benefit in chronic HF have not been specifically tested in AHFS.37,58 Thus, the potential for MRAs as a viable therapy in AHFS depends upon not only the pathophysiological targets available in the acutely decompensated state, but also the clinical profile of AHFS patients, and the safety and efficacy of the chosen drug.

Acute heart failure syndrome clinical profiles

Cardiac dysfunction and fluid overload

Given the anti-hypertensive and diuretic effects of MRAs, ideal candidates for MRAs would manifest elevated blood pressure
and fluid overload (Figure 3). Acute heart failure syndrome are characterized by acutely elevated intracardiac filling pressures leading to symptomatic cardiogenic pulmonary oedema and frequently systemic oedema. The majority of patients with AHFS present with acute on chronic HF. Nearly half of these patients have HFP EF and often present with elevated systolic BP, associated with rapid clinical deterioration and predominantly pulmonary rather than systemic congestion. Another group of patients that accounts for 40–50% of AHFS admissions are often younger and may present with a normal systolic BP. These patients experience a more gradual development of primarily systemic congestion in the setting of a depressed ejection fraction (HF/REF).

Few AHFS patients (~5–10%) present with low-output, hypotensive decompensated HF, often in the setting of refractory signs and symptoms of advanced HF. Thus, the clinical profile of many AHFS patients (hyper- and normotensive, fluid overloaded without evidence of cardiogenic shock) is theoretically highly amenable to MRA therapy.

**Myocardial injury and remodelling**

Troponin release reflecting myocardial injury is common in AHFS, particularly in patients with coronary artery disease who may present with or without acute coronary syndromes. In addition to MRAs anti-hypertensive and diuretic effects, the anti-fibrotic influence of MRAs in patients with ischaemic myocardial necrosis provides an additional therapeutic benefit as demonstrated in post-MI patients with LV dysfunction in the EPHESUS trial.

Mineralocorticoid receptor antagonists decrease myocardial fibrosis, inflammation, oxidative stress, apoptosis, and remodelling in animal models and patients with chronic HF. Mineralocorticoid receptor antagonist therapy reduces biochemical markers of ventricular remodelling and improves LV function and structure. Acute heart failure syndrome patients experience a short-term improvement following each hospitalization, however, the cardiovascular injury resulting from each decompensation leads to further decreases in cardiac function and progression of HF. Mineralocorticoid receptor antagonists may attenuate the
Renal dysfunction and mineralocorticoid receptor antagonists

Safe and effective institution of MRAs in AHFS also depends upon appropriate patient selection with respect to renal function. Renal impairment is present in the majority of patients admitted with AHFS, and worsening renal function occurs in ~30% of patients during hospitalization and in 20% of patients shortly after discharge (Figure 3). Reduced cardiac output, increased central venous congestion, vasodilatation, and administration of high-dose loop diuretics in AHFS may lead to rapid worsening or new onset renal dysfunction, in part, through neurohumoral mechanisms (Figure 2). The RAAS and SNS have a multitude of effects in the kidney, including arteriolar vasoconstriction and increased tubular reabsorption of sodium and blood urea nitrogen (BUN). Elevated serum BUN levels may provide an early marker of the ‘vasomotor nephropathy’ observed in AHFS patients, reflecting the afferent/efferent arteriolar perfusion mismatch provoked by neurohumoral, haemodynamic (e.g. loop diuretics and inodilators), and inflammatory factors.

Mineralocorticoid receptor antagonists have not been specifically studied in the context of worsening renal function in AHFS. However, MRAs have been shown to attenuate ventricular and vascular hypertrophy in patients with CKD, potassium and magnesium loss, glomerulosclerosis, renal interstitial fibrosis, proteinuria, and sympathetic activation. Furthermore, MRAs were well tolerated in large clinical trials when patients with a serum creatinine > 2.5 mg/dL and serum potassium > 5 mmol/L were excluded (Table 1).

Thus, MRAs may reduce the harmful acute and chronic effects of MR activation on the kidney, effectively augment diuresis in diuretic-resistant patients, and attenuate the development of the vasomotor nephropathy related to neurohumoral activation in AHFS. Repeated renal injury in AHFS mediated, in part, by MR activation may contribute to the development of CKD and lead to worsening cardiovascular function through cardiorenal interactions, and establish the pathophysiological substrate for AHFS and increased risk of future cardiovascular events. In addition, compensatory RAAS activation by the kidney and structural changes in the nephron in response to chronic loop diuretics predisposes patients with worsening chronic HF to diuretic resistance (see Discussion below) and, thereby, provides an additional therapeutic target for MRAs in AHFS.

Autonomic dysregulation and sudden cardiac death

Malignant ventricular arrhythmias are common causes of sudden cardiac death (SCD) in patients with decompensated chronic HF. Impaired autonomic reflex control in patients with HF/REF may permit unregulated surges in RAAS activity that not only contribute to worsened fluid overload and cardio renal failure, but also lead to electrical instability during AHFS episodes. In the EuroHeart Failure Survey II, arrhythmias were a common cause of decompensation in patients with both de novo and acute on chronic AHFS.

Clinical trials have documented the risk of SCD during the early post-MI period in HF/REF patients; however, an overall mortality benefit from placement of implantable cardioverter defibrillators (ICDs) 6–40 days post-MI was not observed. In EPHEBUS, eplerenone was given an average of 7 days post-MI in patients with LV dysfunction and HF, and was observed to reduce SCD by 37% at 30-days following randomization and by 21% at 16 months of follow-up (Tables 1 and 2). Mineralocorticoid receptor antagonists were not, however, instituted in the acute 48-h interval that is generally considered to be the most critical phase of acute decompensation in AHFS. Nonetheless, the MRA eplerenone reduced the risk of SCD in those patients not eligible for ICD placement during the critical 30-day period post-MI.

Mineralocorticoid receptor antagonists attenuate the potassium and magnesium depletion caused by loop diuretics that may contribute to myocardial electrical instability and increase the risk of ventricular arrhythmias and SCD. Elevated circulating levels of aldosterone in AHFS may up-regulate calcium channels in the myocardium and contribute to the development of malignant cardiac arrhythmias and SCD in HF, which can be ameliorated with MR blockade. Mineralocorticoid receptor antagonists...
Mineralocorticoid receptor antagonists: types and molecular mechanisms

The right drug

The MRA spironolactone undergoes extensive hepatic metabolism into the active metabolites canrenone and alpha-spirolactone with prolonged half-lives ranging from 13.8 to 16.5 h. Furthermore, these active metabolites may be more potent than the parent drug. Following a single dose of oral spironolactone, peak serum concentrations of the drug and its metabolites occur at 1–2 and 2–4 h, respectively. The peak onset of diuretic action of spironolactone ranges from 48 to 72 h in humans; however, the initial onset of action may be sooner if first-pass metabolism can be bypassed. It has been suggested that the delay in onset of action may result from the time required for active metabolites to reach steady-state. A few studies have demonstrated the fairly rapid effect of administering MRA metabolites in order to avoid first-pass metabolism and hasten the onset of steady-state.

The MRA eplerenone also undergoes extensive metabolism; however, the metabolites are inactive and its elimination half-life is only 4–6 h. Eplerenone has a 20-fold lower affinity for the MR; however, approximately half the dose of eplerenone is required to inhibit aldosterone binding by 50% compared with spironolactone. In addition, eplerenone is much more specific for the MR with significantly less affinity for androgen, glucocorticoid, and progesterin receptors.

Table 2  EPHESUS: 30 days

<table>
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<tr>
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<th>Eplerenone (%)</th>
<th>Placebo (%)</th>
<th>Risk reduction (%)</th>
<th>P-value</th>
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<tr>
<td>All-cause mortality</td>
<td>3.2</td>
<td>4.6</td>
<td>31</td>
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<tr>
<td>CV mortality/CV</td>
<td>8.6</td>
<td>9.9</td>
<td>13</td>
<td>0.074</td>
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<tr>
<td>hospitalization</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV mortality</td>
<td>3.0</td>
<td>4.4</td>
<td>32</td>
<td>0.003</td>
</tr>
<tr>
<td>Sudden cardiac</td>
<td>0.9</td>
<td>1.4</td>
<td>37</td>
<td>0.051</td>
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<tr>
<td>death</td>
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<tr>
<td>Fatal/non-fatal HF</td>
<td>3.4</td>
<td>4.2</td>
<td>18</td>
<td>0.106</td>
</tr>
<tr>
<td>hospitalization</td>
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Data from EPHESUS at 30 days following institution of MRA therapy in patients 3–14 days (mean 7 days) post-MI with LV dysfunction and/or diabetes demonstrate significant reductions in all-cause and cardiovascular (CV) mortality as well as sudden cardiac death.

Aldosterone: genomic vs. non-genomic effects

Aldosterone is known to exert its deleterious effects on fluid and electrolyte balance via genomic mechanisms that require binding of aldosterone to the cytosolic MR and translocation of the MR–steroid complex to the nucleus with subsequent transcriptional regulation. These genomic mechanisms are thought to take hours to days to occur. In addition to the classical actions of aldosterone on gene expression via MR activation, non-genomic effects that do not require gene transcription and occur within minutes in the kidney, heart, and vasculature may predominate in AHFS. Non-genomic effects of aldosterone include coronary vasoconstriction leading to worsening metabolic and contractile function in the ischaemic heart, a negative inotropic effect in human heart trabeculae, potentiation of the vasoconstrictor effect of ANGII on human coronary arteries, and increased systemic vascular resistance. Aldosterone also non-genomically increases renal vascular resistance in human subjects in the setting of endothelial dysfunction, and acutely impairs baroreflex sensitivity when infused in healthy humans.

Mineralocorticoid receptor antagonism with eplerenone appears to be more effective in antagonizing the non-genomic effects of aldosterone than spironolactone. Importantly, MRAs appear to block both genomic and non-genomic actions of aldosterone, and antagonize MR activation by cortisol.
tubules and collecting ducts. An additional consequence of chronic diuretic therapy is hypertrophy and hyperplasia of distal tubular cells in response to persistently elevated distal tubular sodium delivery. Under physiologic conditions, the distal convoluted tubule and collecting tubules reabsorb 7–11% of filtered sodium, however enhanced distal tubular sodium resorption occurring in the setting of chronic loop diuretic therapy may be successfully antagonized with distally-acting diuretics. Mineralocorticoid receptor antagonists have been observed to stimulate a substantial natriuresis and improve diuretic responsiveness in patients with HF. A small open-label, non-randomized trial conducted by Hensen et al. examined the effect of 200 mg spironolactone given twice daily to patients with worsening HF/REF. There was no reported incidence of hyperkalaemia, creatinine clearance remained stable, and mean body weight decreased by 2 kg after treatment.

In another small study of decompensated HF/REF patients, van Vliet et al. examined the effect of spironolactone on diuretic resistance and volume overload. After 5 days of high-dose bumetanide, patients exhibiting further evidence of diuretic resistance were given 100 mg of spironolactone for 7 days resulting in marked increases in natriuresis, a 64% decrease in body weight, and rapid clinical improvement. Only 1 of 13 patients responding to spironolactone experienced worsening renal function and hyperkalaemia (K⁺ 6.6 mmol/L); renal function and serum potassium normalized 1 day after medication discontinuation. The study by van Vliet et al. suggests that MRAs may be safe and effective in augmenting diuresis in patients with decompensated HF and diuretic resistance concurrently treated with ACE-Is and loop diuretics.

Similarly, Ceremuzynski et al. administered a single 200 mg dose of intravenous canrenone to hospitalized chronic HF patients with worsening fluid overload and diuretic resistance. Patients with a good diuretic response (defined as over 500 mL within 6 h) had significantly higher levels of plasma aldosterone at baseline. Thus, the clinical and neurohumoral profile of patients with worsening chronic HF, and the pharmacokinetics of MRAs appear key to the potential therapeutic benefits of MR blockade in AHFS.

**Conclusion**

Activation of the SNS and RAAS in HF, and the eventual aldosterone breakthrough that results with ACE-I/ARB therapy and high-dose loop diuretics, advances a series of acute decompensations characterized by MR activation, and worsening cardiovascular and renal function. In spite of optimal treatment with ACE-Is/ARBs and beta-blockers, early post-discharge re-hospitalization and mortality rates remain unacceptably high in AHFS patients. Mineralocorticoid receptor antagonists may augment diuresis, reduce dyspnoea, and minimize neurohumoral-mediated renal dysfunction, an important predictor of post-discharge events. Current limitations in AHFS therapy may be due to incomplete suppression of the neurohumoral axis and/or delayed implementation of neurohumoral antagonists. Mineralocorticoid receptor antagonists may provide an additional means of neurohumoral

![Figure 4](https://example.com/figure4.jpg)
inhibition in AHFS, and therefore reduce the risk of progressive HF, worsening renal function, SCD, and death due to progressive HF.

Future directions

Given the positive results with MRAs in outpatients with varying degrees of chronic HF and post-MI patients, and the negative results in AHFS trials with different agents, there is an unmet need to reduce the enormous post-discharge event rate in AHFS patients.20,21,56,129,130 Acute heart failure syndrome patients differ from chronic HF patients in several ways, including mechanism of death (progressive rather than SCD) and exceedingly high event rate. Importantly, AHFS patients differ from their ambulatory counterparts in that they manifest worsening neurohumoral, electrolyte, renal, and haemodynamic profile that serve as a therapeutic target for an effective and safe diuretic that may reduce HF progression and improve outcomes. This, the authors contend, sets the stage for the use of MRAs in the setting of AHFS.

In the early phases of AHFS presentation, fluid overloaded patients may require doses of MRAs far higher than those used in RALES and EPHEBUS in order to overcome the effects of inappropriate levels of aldosterone, cortisol, and diuretic resistance. Dosing regimens of MRAs need to be carefully evaluated in patients with AHFS and titrated to prevent intravascular volume depletion, renal dysfunction, and hyperkalaemia yet still preserve the favourable neurohumoral and diuretic effects of MRAs. The presence of CKD in a relatively high percentage of patients with AHFS and the need to reduce the enormous post-discharge event rate in AHFS patients may require doses of a MRA to overcome diuretic resistance, at least transiently, poses a challenge for the safe use of currently available MRAs. The recent introduction of highly specific and potent non-steroidal MRAs, which in preclinical studies appear to have a more favourable effect on Na+/K+ than the currently available steroidal MRAs, and/or the use of a new K+ binding polymer in conjunction with a high-dose steroidal MRA hold the promise of overcoming diuretic resistance in these high-risk patients with greater safety.131,132 Thus, while MRAs show great promise in patients with AHFS, further studies to evaluate the efficacy and safety of doses of MRAs associated with overcoming diuretic resistance will be necessary before undertaking the large-scale randomized, prospective trials necessary to elucidate their effect on clinical outcomes in patients with AHFS.

Conflict of interest: none declared.

References

Decompensated Heart Failure: Analysis from the EVEREST trial (late breaking clinical trial). Paper presented at: European Society of Cardiology. September 2; Munich, Germany. 2008.


54. Francis GS, Siegel RM, Goldsmith SR, Oliviare M, Levine TB, Cohn JN. Acute vasconstrictor response to intravenous furosemide in patients with chronic


