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REVIEW

Novel Therapeutic Concepts

Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice

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Mineralocorticoid receptor antagonists (MRAs) improve survival and reduce morbidity in patients with heart failure, reduced ejection fraction (HF–REF), and mild-to-severe symptoms, and in patients with left ventricular systolic dysfunction and heart failure after acute myocardial infarction. These clinical benefits are observed in addition to those of angiotensin converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers. The morbidity and mortality benefits of MRAs may be mediated by several proposed actions, including antifibrotic mechanisms that slow heart failure progression, prevent or reverse cardiac remodelling, or reduce arrhythmogenesis. Both eplerenone and spironolactone have demonstrated survival benefits in individual clinical trials. Pharmacologic differences exist between the drugs, which may be relevant for therapeutic decision making in individual patients. Although serious hyperkalaemia events were reported in the major MRA clinical trials, these risks can be mitigated through appropriate patient selection, dose selection, patient education, monitoring, and follow-up. When used appropriately, MRAs significantly improve outcomes across the spectrum of patients with HF–REF.

Keywords Heart failure • Aldosterone antagonist spironolactone • Mineralocorticoid receptors

Introduction

Mineralocorticoid receptor antagonists (MRAs), often referred to as aldosterone antagonists, are a key component of evidence-based therapy for patients with heart failure and reduced left ventricular ejection fraction (HF–REF or 'systolic heart failure'). These agents have demonstrated morbidity and mortality benefits across the spectrum of HF–REF, including patients with mild[1] to severe[2] heart failure symptoms, as well as in patients with signs and symptoms of heart failure after acute myocardial infarction (AMI).[3]

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This paper provides both state-of-the-art and practical information regarding the optimal use of MRAs in patients with heart failure. This topic was discussed among a panel of heart failure experts, cardiovascular clinical trialists, biostatisticians, National Institutes of Health (NIH) scientists, US and European government regulators, and pharmaceutical industry researchers during the Eighth Global Cardiovascular Clinical Trialists Forum held in Paris, France in December 2011. This review summarizes the current body of knowledge pertaining to MRAs in heart failure, targets for future research, and strategies practicing clinicians can employ to optimize MRA use in appropriate patients, thereby ultimately improving clinically relevant outcomes.

Review of the evidence and current indications

Primary evidence from randomized controlled trials

Severe heart failure

Recognition of aldosterone as an important neurohormonal modulator of heart failure progression dates back more than six decades.[4–6] These early data led to the conceptual framework that combining an angiotensin converting enzyme (ACE) inhibitor and spironolactone may achieve more complete inhibition of the renin–angiotensin–aldosterone system (RAAS) and may produce further clinical benefits. The findings of a pilot study[6,7] led to the design and conduct of the Randomized Aldactone Evaluation Study (RALES), which was the first large, prospective, randomized mortality trial of an MRA in patients with heart failure.[2] The RALES data have been widely discussed in the literature. Briefly, 1663 patients with LVEF ≤35% and NYHA class IV heart failure symptoms within 6 months before enrolment and NYHA class III or IV symptoms at the time of enrolment were randomized to spironolactone 25 mg per day or placebo. After 8 weeks of treatment, the dose could be increased to 50 mg once daily if the patient showed signs or symptoms of heart failure progression without evidence of hyperkalaemia. It is important to note that strict eligibility criteria and laboratory monitoring were used in RALES and all of the subsequent MRA heart failure trials (*Table 1*). The primary endpoint was all-cause mortality. After a mean follow-up of 24 months, the study was stopped after the data monitoring committee advised the Steering Committee that the pre-specified efficacy boundary for mortality had been crossed. Patients randomized to spironolactone had a lower risk of death from any cause when compared with placebo (RR 0.70, 95% CI 0.60–0.82, $P < 0.001$) (*Figure 1*).[2] Spironolactone also significantly reduced cause-specific mortality. Sudden death was reduced by 29% (RR 0.71, 95% CI 0.54–0.95, $P = 0.02$), and death due to progressive heart failure was reduced by 36% (RR 0.64, 95% CI 0.51–0.8, $P < 0.001$). Beta-blocker use was low (11%). As anticipated in a population receiving background ACE-inhibition, patients randomized to spironolactone had an increase in median potassium concentration of 0.3 mmol/L, but the incidence of serious hyperkalaemia (serum potassium ≥ 6 mmol/L) was not significantly different between the spironolactone and placebo groups [14 spironolactone patients (2%) vs. 10 placebo patients (1%), $P = 0.42$]. Treatment discontinuation due to any adverse event occurred in 8% of patients randomly assigned to spironolactone and in 5% of the placebo group.

Left ventricular systolic dysfunction and heart failure after acute myocardial infarction

The recognition of aldosterone as a mediator of ventricular remodelling and fibrosis led to its investigation in patients with LV

Table 1 Key exclusion criteria and monitoring procedures in major mineralocorticoid receptor antagonist heart failure trials

Trial	Major exclusions			Monitoring schedule	Dose adjustment
	Renal exclusions	Potassium exclusions	Other relevant exclusions		
RALES[2]	SCr > 2.5 mg/dL (221 μmol/L)	>5 mmol/L	Potassium-sparing diuretics Oral potassium supplements (unless hypokalaemia, K < 3.5 mmol/L)	At weeks 1 and 5, and every 4 weeks for first 12 weeks, then every 3 months for 1 year, then every 6 months thereafter	Decrease dose to 25 mg every other day for hyperkalaemia, but dose adjustment of other medications encouraged first
EPHESUS[3]	SCr > 2.5 mg/dL (221 μmol/L)	>5 mmol/L	Potassium-sparing diuretics	At 48 h after initiation; at 1, 4, and 5 weeks; then every 3 months thereafter; and within 1 week after any dose change	Dose reduced or temporarily discontinued for serum potassium >5.5 mmol/L, until it fell below this value
EMPHASIS-HF[1]	eGFR < 30 mL/min/1.73 m^2	>5 mmol/L	Potassium-sparing diuretics	At 4 weeks, then every 4 months thereafter Within 72 h of a dose adjustment due to hyperkalaemia	Decrease dose for potassium 5.5–5.9 mmol/L Withhold drug for serum potassium >6 mmol/L, and restart when potassium < 5 mmol/L

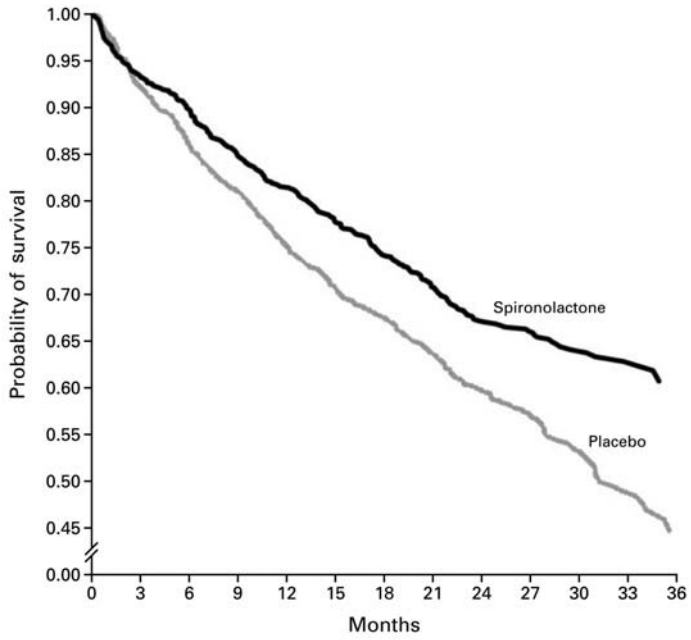

Figure 1 RALES Kaplan–Meier survival analysis. From New England Journal of Medicine, Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure, Volume 341, page 712. Copyright © (1999) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

dysfunction and heart failure after acute MI in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).[3] Patients were randomized to eplerenone 25 mg per day or placebo for 4 weeks, after which the dose of eplerenone was increased to a maximum of 50 mg per day. The major exclusion criteria and monitoring procedures are shown in *Table 1*. Eplerenone reduced time to death from any cause (RR 0.85, 95% CI 0.76–0.96, $P = 0.008$) and the composite of time to cardiovascular death or first cardiovascular hospitalization (defined as admission with heart failure, AMI, stroke, or ventricular arrhythmia) (RR 0.87, 95% CI 0.79–0.95, $P = 0.002$) when compared with placebo (*Figure 2*).[3] The majority of patients (86%) received concomitant background ACE-inhibitor or angiotensin receptor blocker (ARB) therapy. Serious hyperkalaemia (≥6 mmol/L) was reported more often in the eplerenone group (5.5 vs. 3.9%, $P = 0.002$); conversely, patients randomized to eplerenone had a lower incidence of serious hypokalaemia (<3.5 mmol/L) when compared with placebo (8.4 vs. 13.1%, $P < 0.001$).[3] One hundred forty-seven patients (4.4%) in the eplerenone group and 149 (4.5%) in the placebo group withdrew due to adverse events.

Heart failure with reduced ejection fraction and mild symptoms

Most recently, the clinical efficacy of an MRA has been confirmed in patients with HF–REF and mild symptoms in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial (*Figure 3*).[1] Patients >55 years of age were enrolled with NYHA class II symptoms and LVEF ≤ 35% (QRS duration >130 ms was also required if LVEF was >30–35%) within 6 months of a cardiovascular hospitalization. Additional BNP eligibility criteria were required for patients who had not been hospitalized within the previous 6 months [BNP level ≥250 pg/mL, or NT pro-BNP ≥ 500 pg/mL (men) or 750 pg/mL (women)]. Patients with a recent acute MI or those with NYHA class III or IV symptoms were excluded, as were patients with serum potassium >5.0 mmol/L or an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (*Table 1*). Patients were randomized to eplerenone or placebo, and the eplerenone dose was based on renal function. Patients with eGFR ≥ 50 mL/min/1.73 m^2 were started on 25 mg daily, which was increased to 50 mg daily after 4 weeks if serum potassium remained <5 mmol/L. Patients with eGFR 30–49 mL/min/1.73 m^2 were started on 25 mg every other day, and the dose was increased to 25 mg once daily after 4 weeks if serum potassium remained <5 mmol/L. The primary endpoint of cardiovascular death or heart failure hospitalization was significantly lower in the eplerenone group (HR 0.63, 95% CI 0.54–0.74, $P < 0.001$). Importantly, eplerenone also significantly reduced the secondary endpoint of all-cause mortality (HR 0.76, 95% CI 0.62–0.93, $P = 0.008$).[1] Serum potassium >5.5 mmol/L was observed in 11.8% of patients randomized to eplerenone and 7.2% of placebo patients ($P < 0.001$). The incidence of serum potassium >6 mmol/L was not different among eplerenone- and placebo-treated patients (2.5 vs. 1.9%, $P = 0.29$). Hypokalaemia (<3.5 mmol/L) was reported less often among eplerenone-treated

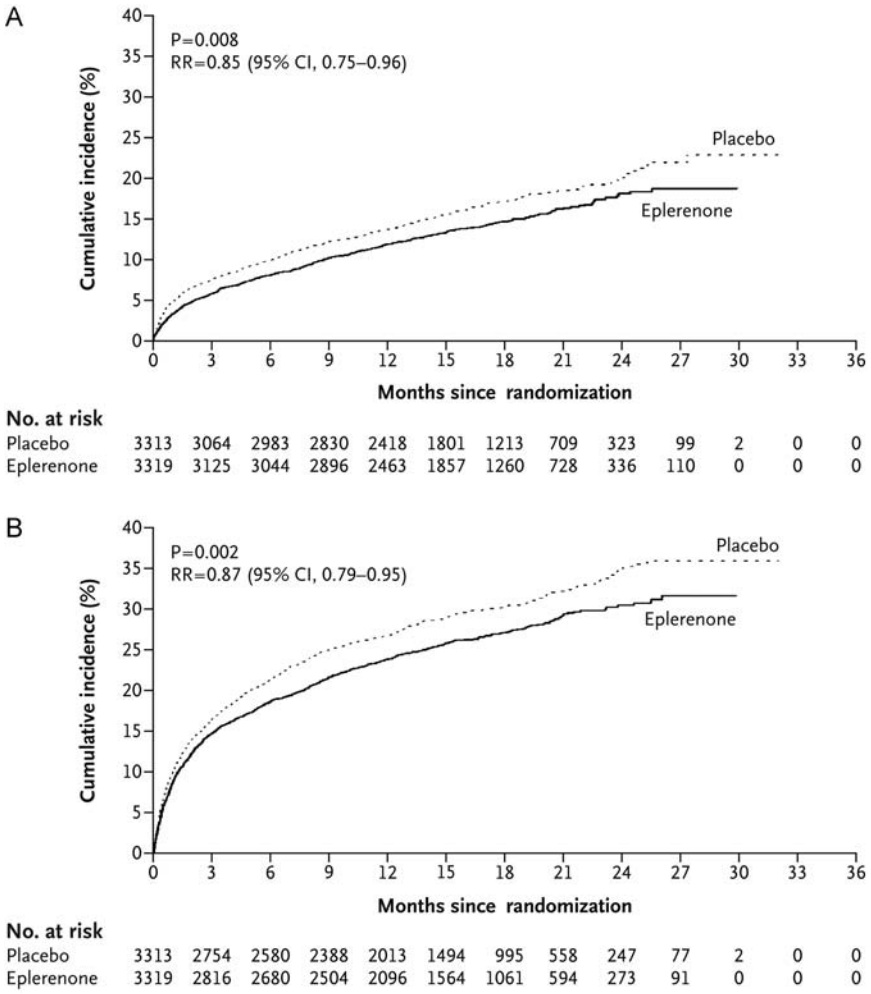

Figure 2 Kaplan–Meier estimates of all-cause death (*A*) and cardiovascular death or cardiovascular hospitalization (*B*) in EPHESUS. From New England Journal of Medicine, Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M, Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction, volume 348, page 1314, copyright (c) 2003 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

patients (7.5 vs. 11%, $P = 0.002$).[1] Study drug was discontinued due to an adverse event in 13.8% of eplerenone patients and 16.2% of placebo patients ($P = 0.09$). EMPHASIS-HF reflected contemporary use of evidence-based therapies, with 94% of patients receiving an ACE-inhibitor, ARB, or both, and 87% of patients receiving a beta-blocker (*Table 2*).

Current indications

The evidence supports the conclusion that an MRA improves survival in patients with HF–REF and mild-to-severe symptoms, and in patients with left ventricular systolic dysfunction and heart failure after AMI. The consistent findings in all three landmark trials of a significant benefit on all-cause mortality and on cardiovascular hospitalization in the overall study populations and across a variety of subgroups provide a robust level of evidence similar to that supporting ACE-inhibitor and beta-blocker use in HF–REF. An MRA is recommended by major professional society guidelines for patients with chronic heart failure and left ventricular systolic dysfunction and heart failure after AMI (*Table 3*).[8–12] Although adverse renal and potassium effects occur with these agents, they can be managed with appropriate patient selection, close monitoring, and regular follow-up as addressed later in this manuscript.

Potential mechanisms of benefit for mineralocorticoid receptor antagonists

Fibrosis and remodelling

Aldosterone has long been recognized as an important contributor to heart failure pathophysiology (*Figure 4*).[13–16] It stimulates the reabsorption of sodium and the excretion of potassium in the

renal distal tubule. Aldosterone stimulates cardiac fibrosis, and this mechanism is one of the particular interest with regard to heart failure progression, although it is unlikely to be the only important mechanism.[17–21] Several studies in animal models have shown increases in myocardial collagen and fibrosis in the presence of aldosterone.[17,18,22–24] Treatment with spironolactone blocked the aldosterone-mediated increase in collagen synthesis[17,22] and other measures of remodelling[25] in the rat. Dogs with systolic dysfunction produced by serial coronary microembolization randomized to receive eplerenone had a significantly higher LVEF and significantly lower LV volumes and end-diastolic pressure after 3 months when compared with controls.[26] These experimental observations may provide insight into the underlying mechanism of benefit for MRAs in humans, and they provide the basis for testing the hypothesis that MRAs may reduce remodelling. Remodelling is a known predictor of poor outcome, and it is a major determinant of heart failure progression.[27]

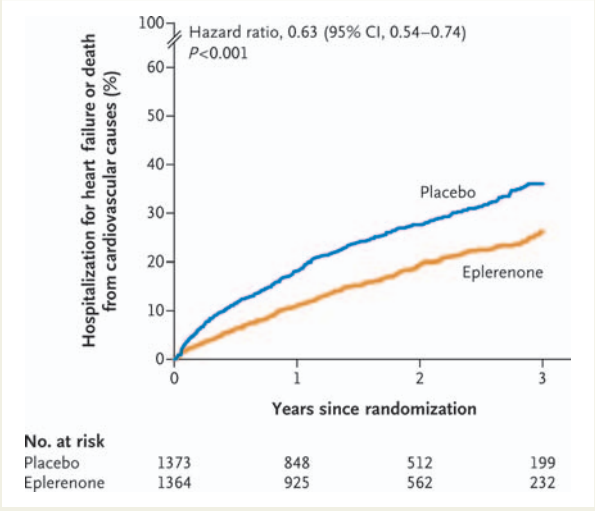

Figure 3 Kaplan–Meier estimates of cardiovascular death or heart failure hospitalization in EMPHASIS-HF. From New England Journal of Medicine, Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms, Volume 364, page 16. Copyright © (2011) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

In a substudy of the RALES trial, blood samples at baseline and 6 months were collected in 151 patients for analysis of markers of extracellular matrix (ECM) turnover [procollagen type III amino-terminal peptide (PIIINP), procollagen type I carboxy-terminal peptide (PICP), procollagen type I amino-terminal peptide (PINP), matrix metalloproteinase 1 (MMP1), tissue inhibitor of metalloproteinase 1 (TIMP1), and the MMP1/TIMP1 ratio].[28] Compared with baseline, PINP and PIIINP levels were significantly lower at 6 months in patients randomized to spironolactone but not placebo. A hypothesis-generating subgroup analysis based on a small number of patients and events suggested that the effect of spironolactone on all-cause mortality was most apparent among patients with ECM turnover markers above the median value.[28] Further research is needed to determine the clinical relevance of these preliminary findings.

Prospective, randomized trials in humans evaluating the effect of MRA therapy on remodelling markers have shown inconsistent results. In a randomized study of canrenoate, an intravenous MRA, followed by spironolactone for 1 month in 134 patients with acute MI, patients treated with the MRA had significantly less absolute change in LVEF and LV volumes when compared with non-MRA-treated patients.[29] The absolute change in ECM turnover (e.g. PIIINP values) was also significantly less in the MRA group when compared with the non-MRA group, which correlated with the absolute change in LV volumes.[29]

However, a randomized, double-blind, placebo controlled study in 226 patients with LVEF $\leq$ 35% and NYHA class II-III heart failure found no difference in LVEDI or LVESI after 36 weeks of treatment with eplerenone 50 mg/day or placebo. The population was well treated at baseline with >95% on an ACE-inhibitor or ARB and 97% on a beta-blocker.[30] The authors speculated that the lack of observed effect on remodelling may have been due to the short observation period in the setting of excellent background therapy. They also acknowledged that additional effects on remodelling may not be possible on top of optimal neurohormonal blockade. The authors reported an exploratory, hypothesis-generating finding of greater reductions in EDVI and ESVI in patients treated with eplerenone whose baseline PINP levels were greater than the median.[30] This finding warrants further study.

Table 2 Comparison of study populations

Trial/drug	*N*	NYHA class II/III/IV (%)	Mean LVEF	Ischaemic Aetiology (%)	Background therapy (%)				Placebo Mortality (1-year) (%)	NNT (to save 1 life in 1 year)
					ACEI or ARB	Beta-blocker	CRT	ICD		
RALES[2] and spironolactone	1663	0.5/72/27	25.6 ± 6.7	55	95	11	n/a	n/a	27.3	9
EPHESUS[3] and eplerenone	6642	90% with HF symptoms	33 ± 6	100	86	75	n/a	n/a	13.6	50
EMPHASIS-HF[1] and eplerenone	2737	100/0/0	26.2 ± 4.6	69.7	94	86.6	2.8	13	7.1	51

Table 3 Guideline recommendations for mineralocorticoid receptor antagonist

	ESC[11]	HFSA[9,12]	ACC/AHA[8]	Canadian[10]
Chronic HF	An MRA is recommended for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤35%, despite treatment with an ACE-inhibitor (or an ARB if an ACE-inhibitor is not tolerated) and a beta-blocker, to reduce the risk of HF hospitalization and the risk of premature death Class I, level of evidence A	Is recommended for patients with NYHA class II*-IV HF from reduced LVEF (<35%) while receiving standard therapy, including ACE-inhibitor (or ARB if ACE-inhibitor is not tolerated) and beta-blocker. Strength of evidence A *For NYHA class II, high-risk modifiers should also be present: LVEF ≤30% (if LVEF 30–35, then QRS > 130 ms should also be present), age >55 years, HF hospitalization within 6 months [if no hospitalization within 6 months then BNP > 250 pg/mL or NT-proBNP > 500 pg/mL (men) or 750 pg/mL (women) should be present].	Is recommended in selected patients with moderately severe-to-severe symptoms of heart failure and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Class I recommendation, level of evidence B	An aldosterone receptor blocking agent such as eplerenone should be considered for patients with mild-to-moderate (NYHA II) HF, aged >55 years with LV systolic dysfunction (LVEF ≤30%, or if LVEF > 30% and ≤35% with QRS duration >130 ms), and recent hospitalization for CVD or elevated BNP/NT-pro-BNP levels who are on standard HF therapy. Strong recommendation, high-quality evidence
Post-MI LVD	No separate recommendation, included in chronic HF recommendation	Should be considered in patients following an acute MI with clinical HF signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE-inhibitor (or ARB) and a beta-blocker. Strength of evidence A	Is recommended in carefully selected patients with LV dysfunction early after MI	

In a substudy of EPHESUS involving 476 patients, the procollagen peptide PINP increased in all patients from baseline to month 1. By 6 months and persisting at 9 months, PINP and PIIINP levels were significantly lower among patients randomized to eplerenone with values approaching those at baseline. No between-group differences in TIMP-1 or type I collagen telopeptide (ICTP) were observed.[31]

A *post hoc* analysis of the EPHESUS data suggests that eplerenone produced a mild short-term diuretic effect associated with a potassium-sparing effect, which were both independently associated with better outcomes.[32] However, eplerenone's beneficial effects on long-term survival and cardiovascular outcomes were independent from the early potassium-sparing or diuretic effects, suggesting that MRAs provide cardiovascular protection beyond the diuretic and potassium-sparing properties.[32]

The clinical relevance of the potential effect of MRAs on remodelling in humans has not been conclusively demonstrated. More research is needed to determine the clinical application of these findings. Several hypotheses have been developed around the concept of MRAs and remodelling. It is possible that in the future, fibrosis markers can be used to identify high-risk patients that would particularly benefit from MRA therapy. It is also plausible that early MRA treatment may limit the development of cardiac fibrosis, which could have a major impact on heart failure development and disease progression. These and other hypotheses, such as the role of MRAs in the treatment of heart failure with preserved ejection fraction, are currently being studied.[33]

Most important is the fact that both spironolactone and eplerenone have improved survival and reduced morbidity in large, prospective, randomized trials. Seeking to understand the potential mechanisms underlying observed clinical benefits can be useful to develop hypotheses for further study.

Arrhythmia

Myocardial fibrosis has been linked to arrhythmogenesis.[34–36] Sudden cardiac death is a common mode of death among patients with heart failure, and it accounts for the greatest proportion of deaths in patients with mild symptoms. Atrial fibrillation is also common in the heart failure population.[37,38]

Animal studies have shown reductions in interstitial fibrosis, atrial fibrosis, and inducible arrhythmias for both spironolactone and eplerenone.[39,40] In a transgenic mouse model with conditional cardiac-specific overexpression of the human mineralocorticoid receptor (MR), mice exhibited a high rate of death that was prevented by spironolactone. Cardiac MR overexpression led to ion channel remodelling, resulting in prolonged ventricular repolarization at both the cellular and integrated levels and in severe ventricular arrhythmias.[41]

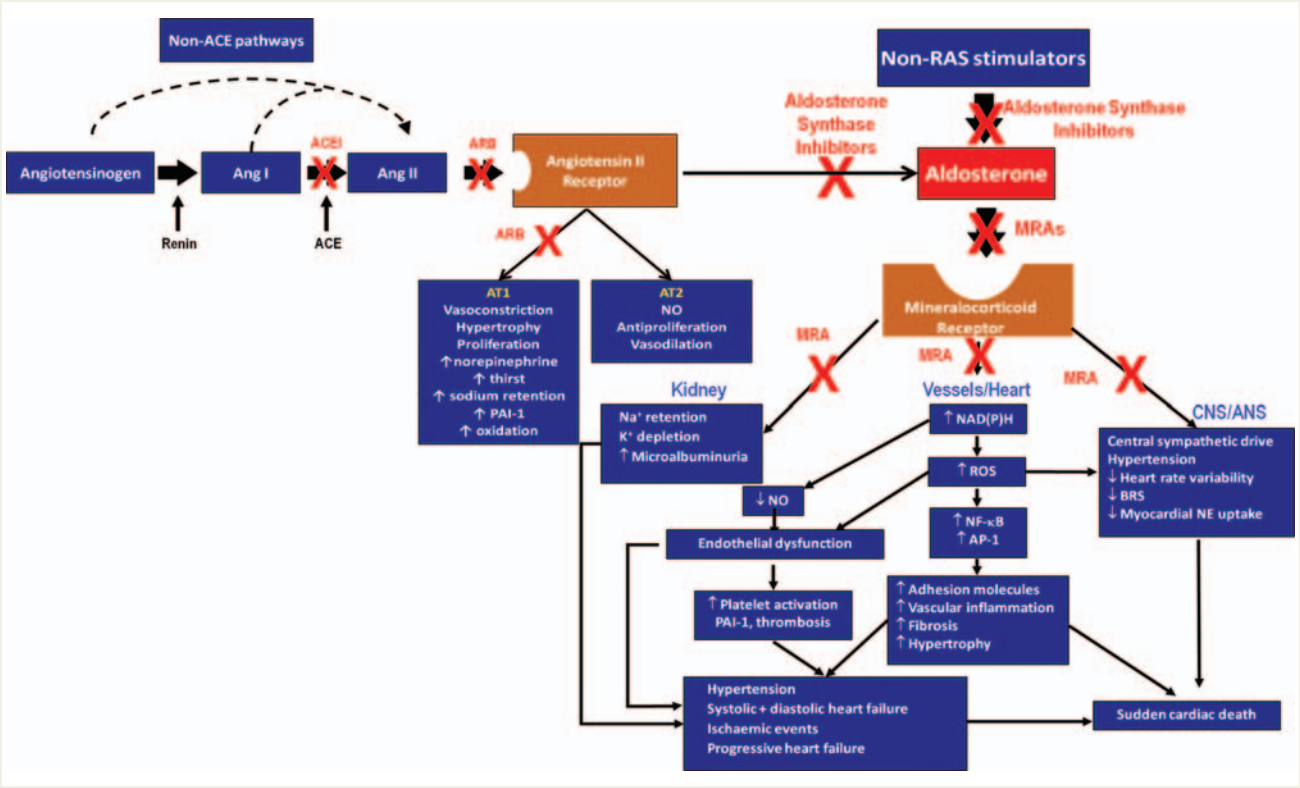

Figure 4 The renin–angiotensin–aldosterone system and mineralocorticoid receptor antagonist mechanism of action.

In the RALES trial, spironolactone reduced sudden death [10 vs. 13.1%, RR 0.71 (95% CI 0.54–0.95), $P = 0.02$] as well as heart failure death [15.5 vs. 22.5%, RR 0.64 (95% CI 0.51–0.80), $P < 0.001$].[2] In EPHESUS, eplerenone significantly reduced sudden death [4.9 vs. 6.1%, RR 0.79 (95% CI 0.64–0.97), $P = 0.03$].[3] Deaths due to acute MI and heart failure were numerically lower in the eplerenone group and the point estimate for risk reduction favoured eplerenone, but the difference did not reach statistical significance.[3] Eplerenone was also associated with significant reductions in sudden death and total mortality in the early post-MI period (first 30 days), when patients are at the greatest risk of sudden death.[42]

In EMPHASIS-HF, the incidence of new onset atrial fibrillation or flutter was a pre-specified secondary endpoint. A subanalysis was performed that included 911 patients in the eplerenone group and 883 patients in the placebo group without a history of atrial fibrillation or flutter at baseline.[43] The incidence of new onset atrial fibrillation was 2.7% in the eplerenone group and 4.5% in the placebo group (HR 0.58, 95% CI 0.35–0.96, $P = 0.034$). The reduction in new onset atrial fibrillation or flutter observed with eplerenone occurred in patients already treated with a RAAS inhibitor (94% on ACE-inhibitor or ARB in the overall EMPHASIS-HF population). Previous retrospective studies and meta-analyses have shown reductions in new onset atrial fibrillation with other RAAS inhibitors,[44–47] although treatment with valsartan did not reduce recurrent atrial fibrillation in a prospective study in patients without heart failure.[48] Although MRAs may reduce arrhythmogenic potential by a number of different possible mechanisms, the exact mechanism is unknown.[49] It should be acknowledged that any therapy that reduces left atrial size or stretch has the potential to influence the occurrence of atrial fibrillation. Thus, this observation may not be specific to MRAs.

Class or drug-specific effect?

The MRA drug class is comprised of three agents: spironolactone, eplerenone, and canrenoate. Spironolactone and eplerenone are oral agents and have been widely studied in large randomized controlled trials.[1–3] Potassium canrenoate is available in both intravenous and oral formulations in some countries. It has been evaluated for its anti-remodelling effects both in mild heart failure[50] and after AMI.[51,52] It has not been studied in a prospective, randomized, adequately powered clinical outcome trial, and therefore is used to a lesser extent than spironolactone or eplerenone. Thus, the remainder of this discussion will focus on spironolactone and eplerenone.

Comparative studies

Both spironolactone and eplerenone improve survival and reduce morbidity, but they have been studied in different populations (*Table 2*). Hypertension studies have evaluated spironolactone and eplerenone, but direct comparisons of the agents were not

Table 4 Mineralocorticoid receptor antagonist pharmacology[65–68]

	Spironolactone	Eplerenone
Mineralocorticoid receptor selectivity	Non-selective	Selective
Absorption	~100% bioavailable (with food)	69%
Distribution	90% protein bound	50% protein bound
Metabolism	Hepatic, active metabolites (canrenone)	Hepatic cytochrome P450 3A4 (inactive metabolites)
Excretion	Primarily renal Half-life (parent): 1–2 h Half-life (metabolites): 10–35 h	Primarily renal Half-life: 4–6 h
Drug interactions	Pharmacodynamic interactions with other drugs that also raise potassium: potassium-sparing diuretics, potassium salts or supplements, NSAIDs, pentamidine, drospirenone, trimethoprim, heparin, IV penicillin G potassium, potassium iodide, tolvaptan, cyclosporine, tacrolimus	CYP 3A4 substrate Eplerenone plasma levels will increase in the setting of strong CYP 3A4 inhibitors (i.e. ketoconazole, erythromycin, clarithromycin, see Table 5) Pharmacodynamic interactions with drugs that raise serum potassium, as listed for spironolactone

performed.[53,54] Head to head comparison trials of these agents in heart failure patients are also lacking.

In vitro competition binding assays in the rat model have shown that eplerenone binds to the MR with an approximately 20-fold lower affinity than spironolactone.[55,56] However, the eplerenone dose required to inhibit aldosterone binding *in vivo* was half of that required for spironolactone, suggesting that eplerenone is more potent, even though it binds to the MR with a lower affinity. In the context of its binding properties and its potency, an approximate two-fold higher dose of eplerenone is needed to exert the same pharmacologic effects as spironolactone. This factor should be considered when evaluating any comparative data between eplerenone and spironolactone.

HbA_{1c} and serum cortisol

Eplerenone and spironolactone may have differential effects on biomarkers, but the observed differences are not definitive and the clinical relevance of these effects is unknown. In a study of 107 stable outpatients with mild heart failure, patients randomized to spironolactone 25 mg daily experienced increases in HbA_{1c} and serum cortisol levels. In contrast, patients randomized to eplerenone 50 mg daily demonstrated no change in these markers.[57] Cortisol is an independent risk factor for mortality in patients with HF–REF.[58] Cortisol also binds to and activates the MR, and there is some evidence that eplerenone blocks cortisol-induced MR activation.[59] These results are consistent with previous studies demonstrating that spironolactone was associated with increases in cortisol and HbA_1c.[60,61] Although spironolactone has been shown to improve endothelial function in patients with heart failure,[62,63] it may worsen endothelial function and heart rate variability, and increase HbA_1c and angiotensin II levels in patients with type II diabetes (heart failure patients were excluded in this study).[61] However, these effects may not influence clinically relevant outcomes. Data from randomized trials suggest that patients with diabetes benefit from either eplerenone or spironolactone to a similar degree as patients without diabetes. In a substudy of EPHESUS, the benefit of eplerenone on the primary endpoint of cardiovascular mortality or cardiovascular hospitalization was preserved in patients with diabetes [35.8% eplerenone vs. 40.9% placebo, RR 0.83 (0.71–0.98), $P = 0.031$] and no changes in glycaemic control were reported.[64] Similar findings were reported in RALES, where the mortality benefit of spironolactone compared with placebo was similar in patients with diabetes (HR 0.70, 95% CI 0.52–0.94, $P = 0.019$) and in those without (HR 0.70, 95% CI 0.60–0.82, $P = 0.001$).

Pharmacologic differences

Pharmacologic differences exist between eplerenone and spironolactone (*Table 4*).[65–68] Both drugs improve clinical outcomes; thus, these pharmacologic differences are not related to outcomes, but they may be relevant to individual patients for tolerability or practical reasons. Spironolactone is a non-selective MRA. It also binds to progesterone and androgen receptors, leading to adverse effects such as gynecomastia and impotence in men and menstrual irregularities and breast tenderness in women. In the RALES trial, the incidence of gynecomastia or breast tenderness in men among patients randomized to spironolactone was 10%.[2] Eplerenone is a selective inhibitor of the MR and is generally devoid of antiandrogenic side effects.[67,68] The incidence of gynecomastia in men randomized to eplerenone was 0.5 and 0.7% in the EPHESUS and EMPHASIS-HF trials, respectively.[1,3] Thus, eplerenone should be prescribed to patients who experience gynecomastia or breast tenderness on spironolactone. Rates of renal or potassium related adverse effects are generally similar between the drugs at equipotent doses. Spironolactone as the parent compound has a short half-life (1–2 h), but its active metabolite canrenone has a half-life of up to 35 h. The half-life of eplerenone is much shorter (4–6 h), and it does not have active metabolites. The prolonged half-life of spironolactone may contribute to a slow reversal of hyperkalaemia after spironolactone is down-titrated or discontinued. This hypothesis is based on the known pharmacokinetics of the drug, yet clinical data are lacking.[69]

Table 5 Select inhibitors and inducers of the cytochrome *P*-450 3A4 isoenzyme[66,103,104]

Concomitant drug	Estimated effect on eplerenone AUC[66]
Inhibitor	
Ketoconazole	5.4-fold increase
Erythromycin Verapamil Saquinavir Fluconazole	2–2.9-fold increase
Grapefruit juice	25% increase
Cisapride Cyclosporine Digoxin Glyburide Midazolam Norethindrone/ethinyl estradiol Simvastatin Warfarin	No clinically significant effect
Indinavir Nelfinavir Ritonavir Clarithromycin Itraconazole Nefazodone Telithromycin Diltiazem Cimetidine Amiodarone Chloramphenicol Ciprofloxacin Delavirdine Fluvoxamine Imatinib Fluoxetine/norfluoxetine Voriconazole Conivaptan Zafirlukast Efavirenz Ranolazine Nilotinib	No data documenting influence of interaction on eplerenone AUC. The potential exists for eplerenone AUC to be increased with concomitant use of these drugs, but the extent and clinical significance of the interaction has not been quantified. Additional monitoring and/or decreased eplerenone dose may be warranted
Inducers	
St John's Wort	30% decrease
Nevirapine Barbiturates Carbamazepine Oxcarbazepine Glucocorticoids Modafinil Phenytoin Pioglitazone Rifampin	No data documenting influence of interaction on eplerenone AUC. The potential exists for eplerenone AUC to be reduced with concomitant administration of these drugs, but the extent and clinical significance of the interaction has not been quantified. Additional monitoring may be warranted

The drug interaction profile also differs between the two agents. Eplerenone is metabolized by the cytochrome *P*-450 3A4 isoenzyme, and eplerenone serum concentrations may increase in the presence of other drugs that inhibit CYP 3A4. This interaction is of particular clinical relevance because it may increase the risk of hyperkalaemia, which is a dose-dependent side effect. Select drugs that inhibit CYP 3A4 are shown in *Table 5*. Co-administration of these drugs with eplerenone should be avoided when possible. If concomitant administration is required, the eplerenone dose may need to be reduced or therapy temporarily interrupted to reduce the risk for hyperkalaemia. Additional monitoring of serum potassium should be implemented. If long-term therapy with an interacting drug is clinically necessary, then prescribing spironolactone may be preferred, since it is not a CYP 3A4 substrate. It should be noted that many compounds inhibit CYP 3A4 but have not been investigated for their effects on eplerenone serum concentrations. A prudent clinical course of action is to monitor serum potassium more closely any time a CYP 3A4 inhibitor is used in conjunction with eplerenone, regardless of whether or not an increase in eplerenone AUC has been reported. The onset of the interaction will depend on the pharmokinetic properties of the CYP 3A4 inhibitor.

Other considerations for drug selection

Robust scientific evidence demonstrating improved survival and reduced morbidity exists for both spironolactone and eplerenone. For spironolactone, the evidence is limited to patients with severe heart failure. For eplerenone, the evidence spans patients with mild heart failure symptoms to patients with left ventricular systolic dysfunction and symptomatic heart failure after AMI, but it does not currently include patients as severe as those enrolled in RALES (*Table 2*). Tangible differences between spironolactone and eplerenone exist: steroid hormone related adverse effects, half-life, drug interactions, and cost. Recognition of these differences may be helpful in guiding drug selection for individual patients. In general, the practice of evidence-based medicine requires that the drugs be used according to how they were studied in clinical trials; e.g. eplerenone in patients with mild heart failure symptoms or acute MI patients and spironolactone in patients with severe symptoms. However, intolerable side effects are appropriate reasons to use eplerenone instead of spironolactone in a patient with severe heart failure. Similarly, an inability to afford the medication or the presence of clinically significant drug interactions is an appropriate reason to use spironolactone in a patient with mild heart failure symptoms. Clinicians must use their knowledge of the evidence and the drug-specific differences to appropriately select the optimal regimen for their patients with heart failure.

Promoting patient safety

Dose response and the balance between efficacy and safety

The dosing strategies used in the major MRA clinical trials are shown in *Table 6*. Dose-related increases in serum potassium and upstream activation of the RAAS (as measured by increases in serum aldosterone and plasma renin) have been observed with MRAs in both hypertensive and heart failure patient populations.[7,54,70,71]

Hyperkalaemia

The rate of hyperkalaemia in the major MRA clinical trials ranges from 2 to 11.8%, depending on the definition. It is important to note that no deaths attributable to hyperkalaemia were reported in RALES, EPHESUS, or EMPHASIS-HF. Several studies have suggested that the rate of hyperkalaemia is higher in general practice where rigorous monitoring protocols required by clinical trials are not consistently in place. In an analysis from Ontario, an increase in hospitalization for hyperkalaemia and hyperkalaemia-related mortality was observed after publication of the RALES data.[72] This finding was not replicated in a longitudinal analysis of the UK National Health Service in Scotland.[73] In this study, an increase in mild hyperkalaemia was reported after the publication of RALES, but it did not translate into increased hospitalizations or death due to hyperkalaemia.[73] The authors attributed the finding to more rigorous monitoring practices. Other studies have also reported higher rates of hyperkalaemia and increases in serum creatinine in clinical practice than observed in randomized controlled trials.[74] However, studies performed in heart failure clinics appear to have rates of hyperkalaemia (4–6%) that are within the range of those observed in clinical trials.[75] In the EPHESUS study, changes in serum potassium did not influence the effect of eplerenone on all-cause mortality. The benefit of eplerenone on total mortality was present regardless of potassium change.[76]

Although hyperkalaemia is generally the aspect of potassium homeostasis that is discussed in the context of MRAs, hypokalaemia is also clinically important. Some data suggest that hypokalaemia in patients with heart failure may be associated with increased mortality, even among patients with chronic kidney disease.[77–79] In the AMI population, a U-shaped curve was identified with respect to post-admission serum potassium and in-hospital mortality. In this analysis, serum potassium levels <3.5 as well as >4.5 mEq/L were associated with higher mortality.[80] In EPHESUS, the rate of serious hypokalaemia (serum potassium <3.5 mmol/L) was 8.4% in the eplerenone group and 13.1% in the placebo group ($P < 0.001$). In EMPHASIS-HF, serum potassium <3.5 mmol/L was reported in 7.5% of the eplerenone group and 11% in the placebo group ($P = 0.002$). Prospective studies are needed to evaluate whether prevention of hypokalaemia by an MRA or other agents alters clinical outcomes.

Renal impairment

The change in serum creatinine observed with a MRA in the highly selected patients enrolled in clinical trials is relatively small (*Table 6*). In a systematic review, worsening renal function was reported in 8.9% of patients randomized to an MRA compared with 1.6% of control patients.[81] However, definitions of worsening renal function differed across trials (e.g. 25% increase in eGFR or serum creatinine increases of >0.3 mg/dL), making these data difficult to interpret. In an analysis of EPHESUS, eplerenone was associated with a lower eGFR within the first month of treatment (adjusted difference, -1.3 ± 0.4 mL/min/1.73 m^2) relative to placebo.[82] In multivariate analyses, in addition to eplerenone treatment, other factors that independently predicted early worsening

Table 6 Dosing strategies used in the mineralocorticoid receptor antagonist randomized controlled clinical trials

Trial	Initial dose (per day)	Titration schedule	Mean dose achieved (per day)	Change in serum potassium	Change in serum creatinine	Incidence of hyperkalaemia
RALES[2] and spironolactone	25 mg	Increased to 50 mg/day after 8 weeks Dose could be reduced to 25 mg every other day for hyperkalaemia	26 mg	0.3 mmol/L (median) during first year of follow-up	0.05 to 0.1 mg/dL (median) during first year of follow-up	Serum potassium ≥6 mmol/L: 2%
EPHESUS[3] and eplerenone	25 mg	Increased to 50 mg/day after 4 weeks Dose reduced or temporarily discontinued for serum potassium >5.5 mmol/L	42.6 mg	0.3 mmol/L at 1 year	0.06 mg/dL at 1 year	Serum potassium ≥6 mmol/L 5.5%
EMPHASIS-HF[1] and eplerenone	25 mg (eGFR ≥50 mL/min/1.73 m^2) or 25 mg every other day (eGFR 30–49 mL/min/1.73 m^2)	Increased to 50 mg/day after 4 weeks For eGFR 30–49 mL/min/1.73 m^2: increased to 25 mg/day Decrease dose for serum potassium 5.5–5.9 mmol/L Withhold drug for serum potassium ≥6 mmol/L	39.1 ± 13.8 mg 60.2% of patients were receiving 50 mg/day at completion of the 5-month dose adjustment phase)	0.16 ± 0.56 mmol/L at trial cut-off date	0.09 ± 0.37 mg/dL at the trial cut-off date	Serum potassium >5.5 mmol/L: 11.8% >6 mmol/L: 2.5%

Table 7 Suggested dosing and monitoring strategies for mineralocorticoid receptor antagonist in heart failure

Recommended dose	Renal and potassium contraindications	Monitoring time points[a]	Dose adjustment
Spironolactone 25 mg once daily, titrated to 50 mg once daily Eplerenone 25 mg once daily (or 25 mg every other day for eGFR 30–49 mL/min/1.73 m^2), titrated to 50 mg once daily (or 25 mg once daily for eGFR 30–49 mL/min/1.73 m^2)	Serum potassium >5 mmol/L or eGFR < 30 mL/min/1.73 m^2	Within 72 h after initiation At 4 weeks Every 3–4 months routinely Within 72 h after any dose adjustment or other change in clinical or drug status that might influence the risk of hyperkalaemia or renal impairment	Decrease dose for serum potassium >5.5 mmol/L Hold dose for serum potassium >6.0 mmol/L Restart therapy or increase back to previous dose when serum potassium <5.0 mmol/L

[a]Slight variations of monitoring time points were used across clinical trials. These suggested monitoring time points are based on those most commonly used in the clinical trials. More frequent monitoring may be clinically indicated in some patients. Clinical judgment is recommended.

renal function (defined as a decrease in eGFR >20% at 1 month) included female sex, age ≥65 years, LVEF <35%, smoking, and baseline use of loop diuretics or antiarrhythmics. Baseline potassium (per 0.5 mmol/L increment), baseline eGFR <60 mL/min/1.73 m^2, baseline use of statins, and mean blood pressure change at 1 month (per 10 mmHg increment) were associated with a lower risk of early worsening renal function. The benefit of eplerenone on clinical outcomes persisted despite the early worsening of renal function in some patients.[82]

Data from non-heart failure patients may lessen concerns related to MRA renal adverse events. Aldosterone has been implicated in the development and progression of renal disease in hypertension and in patients with diabetes.[83,84] Both eplerenone and spironolactone reduce albuminuria in patients with type 2 diabetes mellitus and chronic kidney disease.[85] It should be acknowledged that albuminuria is a surrogate marker, and whether this finding translates into improved outcomes in this population remains to be determined. One could speculate that the combination of an increase in serum creatinine and a reduction in microalbuminuria suggests that MRAs reduce intraglomerular pressure, thereby protecting the kidney in the long term. A meta-analysis of 11 randomized, controlled trials of an MRA in patients with chronic kidney disease, albuminuria, or proteinuria due to both diabetic and non-diabetic nephropathy demonstrated that the MRA

was associated with significant reductions in proteinuria without changes in renal function.[86] Thus, it is possible that, as with ACE-inhibitors, MRAs are associated with short-term harm to the kidneys but provide benefits over the medium to long term.[82] Moreover, studies in diabetic nephropathy demonstrate that the greater the initial decrease of kidney function with RAAS blockade, the greater the long-term preservation of kidney function.[87] This hypothesis requires further study using robust clinical endpoints. It is also important to emphasize that hyperkalaemia and worsening renal function are among the main adverse events of other RAAS inhibitors, especially when two are used in combination. These adverse effects appear to be inherent to the pharmacological effect of RAAS blockade.[88,89]

Predicting, preventing, and managing renal and potassium safety issues

In a *post hoc* analysis of EPHESUS, independent predictors of serum potassium ≥6 mEq/L were eGFR <60 mL/min/1.73 m^2, history of diabetes mellitus, baseline serum potassium >4.3 mEq/L, and prior antiarrhythmic use. Statistically significant between-group differences in the proportion of patients with hyperkalaemia were only observed in the subgroup of patients with baseline eGFR < 60 mL/min/1.73 m^2.[76] One small study identified that the presence of the 215G allele in the gene for the NR3C2 (or mineralocorticoid) receptor was associated with a higher risk for potassium increases >0.5 mEq/L after initiation of spironolactone.[90]

Strict adherence to the dosing and monitoring regimens used in clinical trials should be used in clinical practice (*Table 7*). In a retrospective cohort study among patients managed by health maintenance organizations, appropriate potassium and serum creatinine monitoring were not performed in 28% of patients.[91]

The risk of hyperkalaemia can be further reduced by ensuring dietary and other pharmacologic sources of potassium are minimized. Salt substitutes are common sources of dietary potassium in patients with heart failure. Patients receiving MRAs should be educated to avoid salt substitutes and encouraged to season foods with non-sodium- and non-potassium-based spices. Select high potassium containing foods are shown in *Table 8*. A comprehensive listing of the potassium content of many common foods can be found at http://www.ars.usda.gov/ba/bhnrc/ndl. Nutritional supplement drinks are also generally high in potassium, and should be used cautiously in combination with an MRA. However, it is unknown to what extent dietary potassium intake should be limited in patients treated with an MRA, and further research is needed to clarify this issue.

In addition to foods, other drugs can raise serum potassium levels and should be avoided whenever possible. These include, but are not limited to potassium-sparing diuretics, potassium salts or supplements, non-steroidal anti-inflammatory drugs (NSAIDs), pentamidine, drospirenone, trimethoprim,[92] heparin, penicillin G potassium (IV), potassium iodide, tolvaptan, cyclosporine, and tacrolimus. Current guidelines recommend avoiding triple therapy with an ACE-inhibitor, ARB, and an MRA because of the unclear clinical benefit and the incremental risk of hyperkalaemia.[8,9,93] A *post hoc* analysis of the CHARM-added study showed that the reduction in cardiovascular death or heart

Table 8 Select dietary sources of potassium

Source	Weight (g)	Common measure[a]	Potassium content per measure (mg)
Tomato paste, canned	262	1 cup	2657
Orange juice, frozen concentrate	213	6 fl. oz. can	1436
Beet greens, boiled	144	1 cup	1309
White beans, canned	262	1 cup	1189
Dates, deglet noor	178	1 cup	1168
Milk, canned, condensed	306	1 cup	1135
Tomato puree, canned	250	1 cup	1098
Raisins	145	1 cup	1086
Potato, baked	202	1 potato	1081
Grapefruit juice, white, frozen concentrate	207	6 fl. oz. can	1002
Soybeans, cooked	180	1 cup	970
Lima beans, boiled	188	1 cup	955
Plantains, raw	179	1 medium	893
Refried beans, canned	252	1 cup	847
Halibut	159	$\frac{1}{2}$ fillet	840
Spinach, cooked	180	1 cup	839
Tomato sauce	245	1 cup	811
Prunes	240	1 cup	796
Sweet potato, canned	255	1 cup	796
Beans, pinto	171	1 cup	746
Carrot juice, canned	236	1 cup	689
Salmon	155	$\frac{1}{2}$ fillet	632
Black beans	172	1 cup	611
Yogurt	227	8 oz	579
Mushrooms	156	1 cup	555
Bananas	150	1 cup	537
Broccoli	156	1 cup	457
Brussels sprouts	155	1 cup	450
Cucumber, with peel	301	1 large	442
Cantaloupe	160	1 cup	427
Turkey, roasted	140	1 cup	417
Strawberries, raw	166	1 cup	254
Carbonated beverage, cola		12 fl oz	7
Licorice			Can be a cause of hypokalaemia

Adapted from US Department of Agriculture, Agricultural Research Service. 2011. USDA National Nutrient Database for Standard Reference, Release 24. Nutrient Data Laboratory Home Page, http://www.ars.usda.gov/ba/bhnrc/ndl.[a]1 cup ~8 oz ~240 mL.

failure hospitalization among the subgroup of patients receiving spironolactone at baseline was similar to that observed in the overall population. The proportion of patients who discontinued study drug (candesartan) because of increased serum creatinine or hyperkalaemia appeared to be the greatest in the subgroup of patients also treated with spironolactone.[94]

Achieving evidence-based clinical practice: are we there yet?

Strong recommendations from international guidelines support the use of MRAs in heart failure patients with reduced ejection fraction similar to those studied in the large randomized MRA trials.[8–10,93,95] It has been projected from national statistics and registry data in the USA that 603 014 patients with heart failure are eligible for treatment with an MRA, but only 36.1% receive the therapy.[96] It was further estimated that an additional 21 407 lives could be saved each year in the USA, if an MRA was used in appropriate patients.[96] These figures were based on existing indications for MRA prior to the publication of EMPHASIS-HF, and therefore underestimate the number of patients with mild heart failure symptoms who will also likely be considered eligible in future guidelines.

In an analysis of data from the Get With the Guidelines Heart Failure quality improvement registry, only 32.5% of 12 565 eligible patients were prescribed an MRA at the time of discharge from a heart failure hospitalization.[97] These data were collected from January 2005 through December 2007, 6–8 years after the publication of RALES. The widespread adoption of this therapy continues to lag significantly behind the evidence.

An MRA was prescribed to 43.7% of 3226 outpatients enrolled in the EURObservational Research Programme Heart Failure Pilot Survey, conducted from October 2009 to May 2010; however, a large proportion of patients in the survey had LVEF >30%.[98] Among patients hospitalized for heart failure in this survey, approximately 35% were receiving an MRA on admission. This proportion increased to approximately 55% during the hospitalization.[98] In the IMPROVE-HF registry (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) conducted in outpatient cardiology practices, the use of an MRA in patients with an appropriate indication was 34.5% at baseline and had improved to 60.3% at 24 months.[99] Focused process of care initiatives and clinician education can be effective measures to improve the use of MRAs in appropriate patients.

Conclusion

Mineralocorticoid receptor antagonists confer important clinical benefits to heart failure patients with mild-to-severe symptoms. They reduce total mortality and hospitalizations on top of ACE-inhibitors and beta-blockers.[100] Several possible mechanisms have been postulated to explain the observed clinical benefits. Antifibrotic and reverse remodelling effects are of particular interest, but remodelling studies in humans have been inconclusive. The exact mechanism of benefit has yet to be determined. Other methods of interfering with the deleterious effects of aldosterone, such as aldosterone synthase inhibition which decreases the production of aldosterone, are also under development.[101,102] However, the regulation of aldosterone is complex, and because MRAs and aldosterone synthase inhibitors address different pathways (receptor blockade vs. ligand production), these drug classes will not be interchangeable. Whether aldosterone synthase inhibitors will be a safe and effective treatment modality for patients with heart failure remains to be determined in clinical trials.

Importantly, both eplerenone and spironolactone improve survival and reduce hospitalizations. Pharmacologic differences between the agents may be useful to inform drug selection for individual patients. Mineralocorticoid receptor antagonists are being evaluated in several new patient populations, including heart failure with preserved systolic function,[33] ST segment elevation MI without heart failure, end stage renal disease on haemodialysis, atrial fibrillation, diabetic nephropathy, and other diseases where aldosterone contributes to disease pathology. As the totality of evidence grows, new strategies are needed to ensure the uptake of clinical trial evidence into clinical practice, from appropriate patient selection to optimal monitoring practices. The expansion of guideline recommendations for MRAs to include less sick patients may serve as a stimulus to develop such strategies or processes of care. These steps will lead to improved outcomes for patients with heart failure, left ventricular systolic dysfunction, and heart failure after AMI, and potentially additional diseases in the future.

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