



Mineralocorticoid receptor antagonist in heart failure: Past, present and future perspectives



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ABSTRACT

Aldosterone is involved in various deleterious effects on the cardiovascular system, including sodium and fluid retention, myocardial fibrosis, vascular stiffening, endothelial dysfunction, catecholamine release and stimulation of cardiac arrhythmias. Therefore, aldosterone receptor blockade may have several potential benefits in patients with cardiovascular disease. Mineralocorticoid receptor antagonists (MRAs) have been shown to prevent many of the maladaptive effects of aldosterone, in particular among patients with heart failure (HF). Randomized controlled trials have demonstrated efficacy of MRA in heart failure with reduced ejection fraction, both in patients with NYHA functional classes III and IV and in asymptomatic and mildly symptomatic patients (NYHA classes I and II). Recent data in patients with heart failure with preserved ejection fraction are encouraging. MRA could also have anti-arrhythmic effects on atrial and ventricular arrhythmias and may be helpful in patient ischemic heart disease through prevention of myocardial fibrosis and vascular damage. This article aims to discuss the pathophysiological effects of aldosterone in patients with cardiovascular disease and to review the current data that support the use of MRA in heart failure.

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1. Aldosterone in the pathophysiology of heart failure

Aldosterone is a mineralocorticoid hormone produced in response to angiotensin II release, hyperkalemia, and corticotropin mainly by the adrenal cortex. In addition to this pathway, recent evidences suggest local, extra-adrenal production of aldosterone by endothelial cells and vascular smooth muscle cells in the blood vessels and myocardium [1,2].

Aldosterone binding to mineralocorticoid receptor results in reabsorption of sodium and water in exchange for potassium in various sites including the distal tubule and collecting duct of the nephron, causing an increased intravascular fluid retention and volume overload. In addition to these classical epithelial effects, aldosterone has a variety of negative non-epithelial effects including induction of inflammation, vascular stiffening, collagen formation, myocardial necrosis and stimulation of fibrosis [1].

Aldosterone has an important role in the pathogenesis of heart failure. Increased levels of aldosterone tend to promote myocardial hypertrophy and remodeling, induce fibrosis and apoptosis, contribute to endothelial dysfunction and reduce myocardial perfusion, thus increasing the incidence of cardiovascular events [3]. In patients with

HF, plasma aldosterone may reach levels of 300 ng/dL, which is up to 60-fold the levels measured in normal subjects (5–15 ng/dL) [1].

Aldosterone has well-known effects in sodium and fluid retention that could account for an undesired impact in fluid balance in patients with CHF, causing hypervolemia and promoting congestion. In addition to its role in sodium balance, aldosterone stimulates cardiac fibrosis, which is one of the principal mechanisms involved in cardiac remodeling and progression of heart failure. In experimental models stimulation of mineralocorticoid receptor has been found to increase cardiac levels of the matrix cellular protein osteopontin, leading to increased fibrosis, and diastolic dysfunction [4].

Other studies have shown an increase of collagen and fibrosis in myocardial tissue in subjects treated with aldosterone [5–7]. Mechanisms at the basis of this action are various. Lijnen et al. proposed an involvement of angiotensin II acting through up-regulation of angiotensin receptor subtype 1 induced by aldosterone [8]. At a molecular level, Nakamura et al. demonstrated a critical role of apoptosis signal-regulating kinase 1 (ASK1) in the mechanism underlying aldosterone-induced cardiac injury. ASK1 is implicated in aldosterone/salt-induced cardiac inflammation and fibrosis through the enhancement of NADPH oxidase-mediated oxidative stress and the up-regulation of the cardiac renin-angiotensin system [9]. Aldosterone also enhances the gene expression of profibrotic molecules, including collagen, transforming growth factor-beta (TGF-beta) and plasminogen activator inhibitor,

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type 1 (PAI1). Aldosterone can also exert rapid, non-genomic effects, which involve transactivation of the epithelial growth-factor receptor (EGFR) and the phosphorylation of extracellular-signal-regulated kinase 1 (ERK)1/ERK2, thereby up-regulating the expression of pro-inflammatory transcription factors and related molecules. In the myocardium and in the kidney, the net effect of aldosterone-induced inflammation and extracellular matrix accumulation is tissue fibrosis and, ultimately, myocardial and renal scarring [10].

Another consequence of aldosterone/MR activation and cardiac remodeling is electrical remodeling. Myocardial fibrosis induced by aldosterone has an arrhythmogenic role in heart failure [11–13]. Some studies confirm that aldosterone and MR activation have also direct effects on cardiomyocyte calcium-handling that may predispose to arrhythmias [14].

Aldosterone is also involved in endothelial dysfunction, mainly by decreasing the bioavailability of nitric oxide and promoting oxidative stress [16].

Other negative effects of aldosterone are activation of the sympathetic nervous system, reduction of baroreceptor sensitivity, and activation of myocyte apoptosis [2].

Given these assumptions, it is clear that aldosterone receptor blockade could be beneficial in patients with cardiovascular disease in a variety of ways. Aldosterone receptor antagonists have been shown to prevent many of the maladaptive effects of aldosterone on the cardiovascular system. For instance, spironolactone prevents the aldosterone-mediated collagen synthesis that contributes to adverse left ventricular remodeling [7]. Rats with post-infarction heart failure treated with aldosterone receptor antagonists have improved left ventricular (LV) diastolic and systolic functions, a reduction of reactive fibrosis, and reduced myocardial norepinephrine content [17]. Eplerenone inhibits superoxide formation and enhances nitric oxide-dependent relaxation in experimental studies [18].

2. Aldosterone receptor antagonists

2.1. Spironolactone

Spironolactone is a widely used, non-selective aldosterone receptor antagonist marketed since the early 60s that is metabolized extensively in the liver to its active metabolites. Its plasma half-life is 1.4 h, although in CHF patients with hepatic congestion, this duration may increase 5-fold. A maximal drug response is seen 48 h after the first dose. Spironolactone is structurally similar to progesterone, thereby allowing sex-steroid receptor cross-reactivity. This phenomenon accounts for the anti-progesterone and anti-androgen effects observed in some patients treated with spironolactone. Gynecomastia or breast pain is the most frequent side-effect of spironolactone, occurring in about 10% of patients in chronic treatment [19].

2.2. Canrenone

Canrenone is the principal active metabolite of spironolactone, devoid of first-pass effect, and has a long half-life (of 16.5 h). As spironolactone, canrenone is a non-selective MRA, but a lower incidence of anti-androgen side effects has been reported [20]. It is frequently used as an alternative to spironolactone mainly in European countries. Canrenone is also derived from the rapid conversion *in vivo* of the salt potassium canrenoate, which has shown important anti-remodeling effects in post-infarction LV remodeling [21].

2.3. Eplerenone

Eplerenone is a selective aldosterone receptor antagonist derived from spironolactone but with lower affinity for the progesterone and androgen receptors so it lacks sex-related adverse side effects. Eplerenone is metabolized in the liver by cytochrome P450 (isoenzyme

CYP3A4); plasma levels of eplerenone are influenced by concomitant use of inhibitors of CYP3A4, including ketoconazole, itraconazole, ribonavir, and clarithromycin, that are associated with significant increases in its peak levels, whereas inducers of CYP3A4 such as phenobarbital decrease it. Eplerenone has a plasma half-life of 4 to 6 h, and steady-state drug levels are usually achieved 48 h after the first dose.

2.4. Side effects

A serious class side effect of MRAs is represented by hyperkalemia. Aldosterone, by binding its receptor, stimulates the apical Na–K-ATPase pump and luminal potassium channel activity into the late distal convoluted tubules and the distal collecting ducts, thus promoting luminal potassium excretion. Therefore, antagonism of the aldosterone receptor decreases luminal K excretion, promoting accretion of potassium in the body. When severe, hyperkalemia may precipitate cardiomyocyte membrane potential destabilization and unstable ventricular arrhythmias [17]. Although serious hyperkalemia occurred in about 2–3% of MRA treated patients in randomized clinical trial, [19,22] rates as high as 10% in the community have been reported [18]. The risk of serious hyperkalemia is minimized by routine serum potassium and renal function monitoring, and avoidance of concurrent pharmacotherapies associated with potassium retention or diet and dietary supplements containing high levels of potassium. Of particular interest, a novel therapeutic agent called RLY5016 (oral, a non-absorbed, potassium-binding polymer) prevented hyperkalemia in patients with HF receiving standard therapy and spironolactone [23].

Other important side-effects are linked to spironolactone cross-reaction with androgen-receptors. The incidence of spironolactone-associated breast tenderness and gynecomastia reported in clinical trials is 6.9% to 10% for men and typically occurs at doses 50 mg/d [19]. Generally, these side effects resolve with drug cessation. Spironolactone may also lower testosterone levels, causing erectile dysfunction in male and menstrual irregularities in female; when present, these side effects increase rates of medication noncompliance [7]. In contrast to spironolactone, eplerenone has 100–1000 lower affinity to testosterone and progesterone receptors, meaning less pronounced, placebo-equivalent, sexual side effects [22].

2.5. Future research on aldosterone antagonists and synthase inhibitors

There is an active research for novel aldosterone antagonists with similar potency as spironolactone and even higher specificity than eplerenone such as SM-368229 from Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan) [24]. A novel approach is to move from receptor blockade to the inhibition of aldosterone synthesis [25]. At least three compounds with this mechanism of action were identified: FAD286 (Novartis, Basel, Switzerland), LCI699 (Novartis, Basel, Switzerland) and SPP2745 (Novartis, Basel, Switzerland) [26]. FAD286, an enantiomer of fadrazole with an inhibitory effect on aldosterone synthase, has been shown to reduce blood pressure, attenuate myocardial and renal injury [27,28] and normalize redox status in rats after myocardial infarction [29]. SPP2745 suppressed aldosterone levels and also provided cardiac, renal and vascular protective effects when administered on top of conventional therapy [26]. Finally, LCI699 suppressed aldosterone levels and lowered blood pressure by 4.1 mm Hg in 14 hypertensive patients, but also latently inhibited cortisone formation [30]. Inhibition of aldosterone synthase should prevent reactive increase in aldosterone levels and adverse androgen receptor-related effects, since these new drugs do not have a steroid structure. On the other hand, mineralocorticoid receptors are also stimulated by cortisol and other ligands that are released in conditions of augmented oxidative stress [31]. Aldosterone synthase inhibitors will not oppose these aldosterone-independent mechanisms that might be blocked by spironolactone or eplerenone. Future studies will show whether what these theoretical concerns will have as clinical implications.

Table 1
Effects of MRA therapy on LV remodeling, NYHA class and diastolic function in patients with heart failure and reduced ejection fraction.
LVEF (left ventricular ejection fraction), LVESVI (left ventricular end-systolic volume index), LVEDVI (left ventricular end-diastolic volume index), E (peak velocities of early mitral inflow), DT (E wave deceleration time). WMD indicates weighted mean difference.

Author	Time	LVEF (%) (WMD)	NYHA functional class (WMD)	LVESVI (mL/mq) (WMD)	LVEDVI (mL/mq) (WMD)	E (cm/s) (WMD)	DT (ms) (WMD)
Barr et al. [95]	8 weeks	20 ± 6 → 19 ± 6 (P = NS)	-	-	-	57 ± 4 → 51 ± 6 (P = NS)	-
Tsutamoto et al. [96]	4 months	32.2 ± 2.2 → 35.0 ± 1.9 (P < 0.05)	2.3 ± 0.1 → 1.9 ± 0.1 (P = 0.002)	-	192 ± 11 → 178 ± 10 (P < 0.05)	-	-
Cicoira et al. [97]	12 months	33 ± 7 → 36 ± 9 (P < 0.01)	-	188 ± 94 → 171 ± 97 (P < 0.01) (not indexed)	275 ± 104 → 251 ± 105 (P < 0.01) (not indexed)	62 ± 21 → 59 ± 21 (P = NS)	217 ± 93 → 219 ± 67 (P = NS)
Akbulut et al. [98]	12 weeks	28.9 ± 6.1 → 36.3 ± 8.3 (P < 0.01)	-	-	-	-	-
Kasama et al. [88]	6 months	33 ± 6 → 39 ± 6 (P < 0.005)	2.8 ± 0.4 → 1.7 ± 0.5 (P < 0.0005)	-	187 ± 26 → 154 ± 41 (P < 0.005) (not indexed)	-	-
Ozkara et al. [99]	-	-	-	-	-	-	-
Kasama et al. [100]	6 months	32 ± 6 → 43 ± 11 (P < 0.001)	2.6 ± 0.5 → 1.9 ± 0.7 (P < 0.001)	131 ± 30 → 95 ± 29 (P < 0.001) (not indexed)	192 ± 32 → 165 ± 30 (P < 0.001) (not indexed)	-	-
Gao et al. [86]	6 months	42 ± 11 → 46 ± 13	-	-	-	-	-
Chan et al. [47]	52 weeks	26 ± 2 → 35 ± 3 (P < 0.01)	2.0 ± 0.6 → 1.5 ± 0.5 (P < 0.001)	120.30 ± 14.74 → 88.14 ± 17.10 (P < 0.01)	154.68 ± 14.21 → 121.10 ± 15.76 (P < 0.01)	77 ± 6 → 62 ± 4 (P < 0.05)	216.87 ± 21.81 → 251.89 ± 15.71 (P = NS)
Boccanelli et al. [20]	12 months	39.9 ± 8.6 → 45.1 ± 9.6 (P < 0.05)	-	-	156.8 ± 54.5 → 128.2 ± 44.6 (P < 0.05) (not indexed)	-	-
Taheri et al. [101]	6 months	31.3 ± 8.8 → 41.2 ± 9.6 (P = 0.01)	-	-	-	-	-
Udelson et al. [46]	36 weeks	P = NS	P = NS	P = NS	P = NS	-	-
Vizzardi et al. [45]	6 months	34.6 ± 9.8 → 38.4 ± 6.3 (P < 0.001)	-	114.5 ± 5.6 → 96.9 ± 9.0 (P < 0.001) (not indexed)	173.2 ± 28.9 → 155.9 ± 4.2 (P < 0.001) (not indexed)	57 ± 54 → 37 ± 14 (P < 0.001)	236 ± 106 → 273 ± 70 (P = 0.001)
Kimura et al. [102]	12 months	34 ± 6 → 37 ± 8 (P = NS)	-	-	61 ± 4 → 59 ± 5 (P < 0.05)	-	-

Table 2
 Summary of RCT evaluating effects of MRA on mortality and HF hospitalizations in patients with HF and reduced LVEF.
 RCT: randomized controlled trial, LVEF: left ventricular ejection fraction, MI: myocardial infarction, NYHA: New York Heart Association, HF: heart failure, HR: hazard ratio, CI: confidence interval, CV: cardiovascular.

RCT	Drug	n	LVEF	NYHA class	Etiology of HF	Primary end-point (CV deaths and HF hospitalizations)	HR (95% CI) P value	Death for any cause, HR (95% CI), P value
RALES	Spironolactone	1663	≤35%	III to IV	Ischemic and non-ischemic	38.1% vs. 50.5%	0.68 (0.59–0.78) <0.001	0.70 (0.60–0.82) P < 0.001
EPHESUS	Eplerenone	6642	≤40	II to IV, even class I if diabetes is present	Post-MI (2 weeks)	26.6% vs 30.0%	0.87 (0.79–0.95) 0.002	0.85 (0.75–0.96) P = 0.008
EMPHASIS	Eplerenone	2737	≤30%, ≤35% if QRS > 130 ms	II	Ischemic and non-ischemic	18.3% vs 25.9%	0.63 (0.54–0.74) <0.001	0.76 (0.62–0.93) P = 0.008

3. Aldosterone receptor antagonists in heart failure

3.1. Heart failure with reduced ejection fraction (HF-REF)

As previously discussed, aldosterone is regarded as a potent mediator of cardiac remodeling in left ventricular dysfunction and therapy with MRA has a role in preventing these maladaptive effects in patients with CHF and left ventricular (LV) systolic dysfunction. A number of large randomized controlled trials (RCTs) investigating the benefit of aldosterone antagonists in patients with systolic heart failure have demonstrated a clear reduction in death and cardiovascular morbidity [19,22,32], as well as benefits in systolic and diastolic patterns (Table 1).

Three landmark randomized controlled clinical trials have shown the benefits of MRA therapy with reduction of morbidity and mortality among patients with reduced LV ejection fraction (LVEF), Table 2. Randomized ALDactone Evaluation Study (RALES) published in 1999 was the first large, randomized, double-blind, placebo-controlled trial on a mineralocorticoid receptor antagonist in patients with heart failure (HF) [19]. RALES evaluated the benefits of spironolactone in a total of 1663 patients with severe heart failure (functional class New York Heart Association III and IV) and decreased LVEF (EF ≤ 35%) who were being treated with standard therapy for heart failure. Patients were randomly assigned to receive spironolactone (25–50 mg daily, mean daily study dose 26 mg) or placebo for a mean follow-up period of 24 months. The primary end-point was all-cause mortality. Patients randomized to spironolactone had a significantly lower risk of death from any cause when compared with placebo (35% vs 46%, RR 0.70, P < 0.001). Spironolactone also reduced cause-specific mortality. Sudden death was reduced by 29% and death due to progressive heart failure was reduced by 36% (RR 0.64). In the spironolactone treated group hospitalization for worsening heart failure was 35% lower. In addition, patients who received spironolactone had a significant improvement in their symptoms of heart failure assessed using NYHA functional class. Safety of spironolactone was acceptable: patients randomized to spironolactone had an increase in median potassium concentration of 0.3 mEq/L, but the incidence of severe hyperkalemia (serum potassium ≥ 6 mEq/L) in the treatment group was only 2% and not significantly different from placebo group, (P = 0.42). A recent post-hoc analysis showed that African American (AA) subjects with HF enrolled in this study exhibited less hyperkalemia and more hypokalemia with spironolactone compared with non-AA and seemed to derive less clinical benefit: in non-AA participants, spironolactone was associated with a 30% reduction in the risk for all-cause mortality (adjusted hazard ratio, 0.70) and a 36% reduction in the risk for the composite outcome of death or hospitalization for HF (adjusted hazard ratio); in the AA participants, spironolactone use was associated with no effect on mortality (adjusted hazard ratio, 0.84) or death or hospitalizations for HF (adjusted hazard ratio, 1.18). These findings suggest that safety and efficacy of mineralocorticoid receptor antagonists may differ by race but mechanisms underlying this difference are unclear at this moment so further study will be necessary [33]. Additional insights from RALES suggest that spironolactone limited the excessive extracellular matrix turnover in the heart, which may contribute to prevention of adverse cardiac remodeling in patients with HF [34].

The knowledge about aldosterone as a mediator of myocardial remodeling and fibrosis is the rationale at the basis of a second important trial on patients with LVEF and heart failure, which evaluated patients with recent acute myocardial infarction: the Eplerenone Post-myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS). This trial demonstrated the benefit of aldosterone receptor antagonists in patients with LVEF <40% after MI. Patients (n = 6642) included those post-MI who had left ventricular dysfunction and either diabetes or clinical evidence of HF and they were randomized to eplerenone 25 mg/d or placebo for 4 weeks, after which the dose of eplerenone was increased to a maximum of 50 mg/die. Patients were followed for an average of 16 months. In EPHESUS, MRA therapy

significantly reduced mortality and morbidity. Eplerenone reduced the risk of death from any cause and death from cardiovascular causes by 15% and 13%, respectively. Eplerenone also reduced time to death from any cause (RR 0.85, $P = 0.008$) and the composite of time to cardiovascular death or first cardiovascular hospitalization (RR 0.87, $P = 0.02$) when compared with placebo. Serious hyperkalemia (≥ 6 mEq/L) was reported more often in the eplerenone group. However, drug discontinuation was similar between the two (4.5% vs 4.4%). An interesting result in EPHEUS was that the survival advantage with eplerenone treatment was seen as early as 30 days after initiation of therapy. In a similar study evaluating MRA therapy on post-infarction LV remodeling, in patients with first acute anterior MI after revascularization, it was found that combination of spironolactone and ACE-inhibitors prevented post-infarction LV remodeling better than ACE-inhibitors alone [35].

These findings are in line with reports that high plasma levels of aldosterone discovered during hospitalization for an acute ST-segment elevation myocardial infarction are an independent prognostic marker for future CHF, ventricular arrhythmia, and cardiac death [36,37].

About Acute HF, the usefulness of aldosterone receptor antagonists in the setting of acute decompensated heart failure has not been determined. Current evidence from RALES and EPHEUS supporting the use of aldosterone receptor antagonists is based on long-term clinical outcome data, but the acute effects of these agents are less established. Evidence suggests that aldosterone antagonists may improve cardiac vagal control (including heart rate variability and baroreflex sensitivity) immediately after intravenous administration, an effect that may be beneficial in decompensated heart failure and MI [38].

RALES only evaluated patients with HF in class NYHA classes III to IV. Recently, evidence from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study suggests that also patients with mild heart failure benefit substantially from aldosterone receptor antagonist therapy [22]. This study enrolled 2737 patients with NYHA class II systolic heart failure and left ventricular ejection fraction $\leq 35\%$ (patients with LVEF $> 30\%$ but $< 35\%$ could be included if QRS complex was > 130 ms on ECG) randomly assigned to receive eplerenone (up to 50 mg daily) or placebo. The addition of eplerenone to optimal therapy reduced the risk of cardiovascular death or hospitalization for HF (18.3% vs 25.9%, HR 0.63, $P < 0.001$). Benefits of eplerenone therapy were also observed in several secondary outcomes including all-cause mortality (HR 0.76, $P = 0.008$). Focusing on hospitalization, post-hoc analyses of the EMPHASIS-HF data suggested that patients with mild HF and treated with eplerenone had significantly fewer HF hospitalizations especially within the first year. In addition, eplerenone not only reduces the risk of first admissions but also decreases the likelihood of second and subsequent admissions for heart failure (and, therefore, the overall number of patients hospitalized and the total number of admissions for any reason) [39]. Eplerenone was generally well tolerated in EMPHASIS-HF with the most frequent adverse event being hyperkalemia, but the incidence of severe hyperkalemia (defined as serum potassium > 6 mEq/L) was not different among eplerenone and placebo-treated patients (2.5 vs. 1.9%, $P = 0.29$). Sexual adverse events (e.g. gynecomastia) occurred in $< 1\%$ of eplerenone recipients, reflecting the selectivity of eplerenone for mineralocorticoid receptors. A recent analysis of EMPHASIS-HF confirms that benefits of eplerenone therapy were evident even in the sub-group of patients receiving high doses of standard background therapies (ACE-i, or angiotensin receptor blocker, β -blocker, or both drug classes) [40]. Finally, another recent post-hoc analysis from EMPHASIS-HF, categorized subjects enrolled in this trial into three groups of low-, medium-, and high-risk based on strong independent risk factors identified using multivariable analysis: age, sex, systolic blood pressure, estimated glomerular filtration rate, diabetes, BMI, hemoglobin, prior HF, prior myocardial infarction, and heart rate. Rates (per 100 patient-years) of the primary outcome in patients

treated with were 7.6, 19.0, and 39.4 in the low, medium and high risk group, respectively. Among patients treated with eplerenone, these rates were 5.6, 12.2, and 24.2, respectively. Therefore, eplerenone was beneficial across all risk categories. The benefit derived from treatment was greatest among those at highest risk [41].

Based on the data of these three trials, current European Society of Cardiology (ESC) Guidelines and American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines are coherent in strongly recommending the use of ARA with a high level of evidence in patients with reduced LVEF and symptoms of HF (Table 3) [42–44]. Guidelines warn that, although in clinical trials hyperkalemia and worsening renal function were uncommon, they may occur more frequently in ordinary clinical practice, especially in the elderly. Therefore, an important limitation of the use of MRA is represented by an impaired renal function (i.e. serum creatinine is greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women or estimated glomerular filtration rate < 30 mL/min/1.73 m²), and/or potassium greater than 5.0 mEq/L.

Since MRAs have been shown to reduce fibrosis and remodeling among patients with reduced LVEF [20,34,45–47], there could be a rationale in treating even asymptomatic patients with low LVEF for preventing the progression of chronic HF. Some small studies suggested that MRA could be beneficial among asymptomatic patients with dilated cardiomyopathy, at least in reducing the risk of hospitalization [48]. However, to date there is insufficient evidence to recommend MRA among asymptomatic patients and further studies (i.e. large RCTs) are needed.

3.2. Heart failure with preserved ejection fraction (HFpEF)

Given the clear benefit of aldosterone antagonists in patients with reduced LVEF, an important question is whether there could be a role for MRA in patients with HF and preserved ejection fraction (HFpEF). HFpEF is defined as the clinical syndrome of HF, but with preserved systolic function and abnormalities in diastolic function. Patients with HFpEF have a slightly lower mortality than patients with reduced LVEF [49], however absolute mortality is still high in these patients (i.e. 12–13%/year) highlighting the need for a treatment to improve prognosis. No treatment has yet been shown, convincingly, to reduce morbidity and mortality in these patients and MRAs represent a promising class of drugs.

Various physiologic mechanisms have been implicated in the pathogenesis of HFpEF and diastolic dysfunction including increased passive ventricular stiffness due to enhanced extracellular collagen deposition and intrinsic alterations in myocyte cytoskeletal proteins [50], impaired active myocardial relaxation related to altered myocyte calcium handling and reduced myocardial energy reserve [1], 10,11 abnormal ventricular–vascular coupling and pulsatile load as a consequence of diminished aortic compliance [51], and impaired renal handling of salt and water because of increased neurohormonal activation. Since aldosterone is involved in many of these mechanisms, MRA may be useful in preventing many of the pathologic alterations in HFpEF.

Aldosterone antagonism has been shown to improve echocardiographic measurements of myocardial relaxation in patients with paroxysmal dyspnea and abnormal LV filling patterns [52]. A recent meta-analysis showed that MRA treatment brought benefits on early mitral inflow (E) and E wave deceleration time (DT), which may serve as surrogates for diastolic dysfunction [53]. This benefit in HFpEF is likely independent of the antihypertensive effects of these agents, because improvement in diastolic parameters have been demonstrated independent of blood pressure effect: in a randomized, double-blinded, placebo-controlled study of 30 hypertensive patients with HFpEF, spironolactone therapy (25 mg/day) over 6 months improved LV relaxation and filling patterns independent of changes in BP when compared with placebo [54]. The Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial showed the benefits of spironolactone on diastolic function in patients with HFpEF [55]. The Aldo-DHF trial was

Table 3
Comparison between guideline recommendations about the use of mineral corticoid receptor antagonist.

	ESC Guidelines	ACC/AHA Guidelines
Chronic HF	An MRA is recommended for all patients with persisting symptoms (NYHA classes II–IV) and an EF $\leq 35\%$, 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).	MRA are recommended in patients with NYHA class II–IV HF and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate > 30 mL/min/1.73 m ²), and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize the risk of hyperkalemia and renal insufficiency (class I, level of evidence A).
Post-MI HF	Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction $\leq 40\%$ and heart failure or diabetes, provided no renal failure or hyperkalemia (class I, level of evidence B).	Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated (class I, level of evidence B).

a multicenter, randomized, double-blind, placebo-controlled trial of 422 patients with chronic NYHA class II or III symptoms, preserved LVEF of $\geq 50\%$, and echocardiographic evidence of diastolic dysfunction, who were randomly assigned to spironolactone 25 mg once daily ($n = 213$) or placebo ($n = 209$). Co-primary endpoints were changes in diastolic function (E/e') on echocardiography and maximal exercise capacity (peak VO_2) on cardiopulmonary exercise testing at 12 months. MRA improved diastolic function (E/e' decreased from 12.7 to 12.1 with spironolactone and increased from 12.8 to 13.6 with placebo) but therapy with spironolactone failed to improve maximal exercise capacity or symptoms. Therefore it is not clear whether improvements of surrogate end-point (such as diastolic function) may have clinical relevance in patients with HFpEF.

The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial was the most recent and the largest RCT that evaluated MRA therapy in HFpEF population. The trial randomized 3445 patients with HF and LVEF $> 45\%$ to receive spironolactone or placebo. It was the first trial of MRA in HFpEF sufficiently powered to detect effects on morbidity and mortality [56]. Spironolactone failed to reduce the primary endpoint consisting in the composite of CV death, hospitalization for the management of HF, or aborted cardiac arrest (18.6% spironolactone vs. 20.4% placebo, HR = 0.89, 95% CI 0.77–1.04, $P = 0.14$). However, patients randomized to spironolactone were less likely to be hospitalized for HF compared to those on placebo (12.0% vs. 14.2%, HR 0.83, 95% CI 0.69–0.99, $P = 0.042$). There were no significant differences between the groups in deaths or hospitalizations from any cause. Hyperkalemia (18.7% vs. 9.1%, $P < 0.001$) and renal failure, defined as doubling of creatinine > 2 upper limit of normal, were both significantly higher in the spironolactone arm. Although the overall results of TOPCAT are negative, spironolactone is the first agent who reduced HF hospitalization rate in HFpEF population, with no increase in mortality. This is an encouraging finding since hospitalizations for HF represent a major burden in these patients, which impacts quality of life. Moreover a post-hoc analysis of patients enrolled in the Western regions suggested a potential efficacy of spironolactone in reducing primary end-point (HR 0.82 (95% CI 0.69–0.98)) [57]. This finding and the reduction in HF hospitalizations with spironolactone are hypothesis generating and deserve further study.

3.3. Effects on fibrosis, remodeling and arterial stiffening

The efficacy of MRA in reducing fibrosis has been first demonstrated in animal models. A study by Lacolley et al. on old normotensive rats showed that cardiac collagen density and carotid collagen and elastin densities and contents were significantly decreased in association with an increase of carotid distensibility in subjects after eight-week treatment with spironolactone compared with controls [58]. The same results were observed in a study conducted on rats in which spironolactone was demonstrated able to prevent the perivascular/interstitial fibrosis and scarring [59]. These observations in animal models encouraged to study MRA in humans [60]. The association between aldosterone and left ventricular remodeling has been shown previously in a community-based sample. In 2119 participants in the Framingham Offspring Study, the aldosterone–renin ratio was positively associated with both concentric and eccentric left ventricular hypertrophy [61]. A follow-up study performed in the same community-based sample related elevated levels of pro-collagen type III aminoterminal peptide (PIIINP), a marker of matrix synthesis, or tissue inhibitor of matrix metalloproteinase-1 (TIMP1) for mortality risk [15]. Several studies suggest that MRAs are effective in reducing myocardial fibrosis. Preclinical studies have shown that these changes in extracellular matrix turnover are not solely the result of fibroblast aldosterone and MR activation, and that cardiomyocytes themselves do participate in extracellular matrix remodeling [62]. Serum levels of collagen markers have been proposed as noninvasive indicators of

myocardial collagen content, and they are well correlated [63]. A subgroup analysis from the RALES trial revealed a highly significant decrease in the serum levels of PIIINP among patients treated with spironolactone [34]. Moreover, a sub-study of EPHEsus involving 476 patients showed that by 6 months and persisting at 9 months, procollagen type I and III amino-terminal peptide (PINP and PIIINP) levels were significantly lower among patients randomized to eplerenone, suggesting a positive anti-fibrotic and anti-remodeling action of eplerenone [64]. MRA therapy has been shown to prevent a progressive increase in markers of collagen turnover and improved diastolic function also in patients with HFpEF [65,66]. Other studies documented a substantial regression of myocardial fibrosis and a significant amelioration of LV diastolic dysfunction in patients with an elevated serum marker of myocardial collagen accumulation [67]. A recent meta-analysis further confirmed that administration of MRA is correlated with a reduction in serum PIIINP for patients with HF or myocardial infarction [53]. Finally, recent randomized controlled trial on 113 obese patients impaired early diastolic mitral annular velocity, randomized to spironolactone 25 mg/day or placebo for 6 months, and showed significant improvements in myocardial deformation, peak early diastolic velocity (E_m) and E/e' with a simultaneous decrease in PICP and PIIINP in spironolactone group [68].

Previous epidemiological studies have demonstrated that increased pulse wave velocity (PWV), a marker of arterial stiffness, is associated with an increased risk of cardiovascular morbidity and mortality [69, 70]. Arterial stiffening is frequent in HF patients and has a negative impact on functional capacity and worsening of HF [71–73]. Elastic artery stiffening is due to degenerated elastic fibers, increased collagenous material, hypertrophied vascular smooth muscle layer, increased pro-inflammatory cytokines and increased calcium deposition resulting in a less compliant media layer [74]. Previous studies have revealed that aldosterone increases the collagen content and fibronectin accumulation in the arterial wall [75,76]. A study by Park et al. demonstrated that serum aldosterone is significantly associated with central aortic PWV in 438 hypertensive patients, suggesting a possible role for aldosterone in developing central aortic stiffness and increased PWV in hypertensive patients [77]. Studies on animal models showed a positive action of MRA on arterial and myocardial wall stiffness by reducing fibrosis [58,75,76,78]. Similar results have been showed in human subjects: PWV decreased significantly after six months spironolactone treatment in hypertensive elderly subjects [79]. Both spironolactone and eplerenone have been shown to decrease LV mass with a reduction in the prevalence of hypertrophy in treated patients from 30% to 7% [80]. These data suggest that MRA could be effective in reducing myocardial remodeling in hypertensive subjects and may slow down the progression from hypertensive heart disease to congestive heart failure.

3.4. Arrhythmias

Arrhythmias are frequent among patients with HF and sudden cardiac death (SCD) due to ventricular arrhythmias represents a major cause of death in CHF. Aldosterone has been suggested to have pro-arrhythmic effects and MRAs have been shown to have anti-arrhythmic action. Particularly, among patients with HF, MRA demonstrated to reduce the incidence of ventricular arrhythmias and SCD [81]. In both the RALES and EPHEsus trials aldosterone blockade was associated to a reduction of sudden death events. In the RALES trial, spironolactone reduced the incidence of sudden death by 29% (RR 0.71, $P = 0.02$) [19]. In EPHEsus, eplerenone significantly reduced sudden death by 21% (RR 0.79, $P = 0.03$) [32]. 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 SCD [82]. In a recent meta-analysis the therapy with MRA was associated with a 23% risk reduction of sudden cardiac death among patients with LV systolic dysfunction, with similar benefits for spironolactone and eplerenone [83]. Although the exact mechanism that underlies the anti-arrhythmic

properties of MRA is not known, many hypotheses have been proposed. Probably MRAs suppress the arrhythmogenic effects of aldosterone at multiple levels. First, MRAs contribute to modulation of renin-angiotensin-aldosterone system reducing ventricular remodeling in HF and in post-MI patients. At the tissue level, they limit potassium and magnesium loss and reduce myocardial fibrosis and hypertrophy [84–86]. At the cellular level, MRAs suppress the combined effect of aldosterone on select calcium and potassium currents, which prolongs the ventricular action potential duration and lowers the threshold for ventricular arrhythmias [81]. With whole-cell patch-clamp methods, exposure to aldosterone for 48 h was shown to increase delayed after-depolarizations in experimental models with cardiac overexpression of human MR. This finding was attributed to MR-mediated ion channel remodeling, especially the down-regulation of FK506-binding proteins, which regulate the ryanodine receptor macromolecular complex. The resulting increased activity of ryanodine receptor leads to long-lasting and broader calcium sparks and, consequently, to prolonged ventricular repolarization [14]. Thus, one effect of MR antagonism would be to decrease prolonged cardiomyocyte calcium sparks and potentially limit arrhythmias through this mechanism. Moreover, MRAs reduce the release of norepinephrine from sympathetic nerve terminals enhancing parasympathetic activity and promoting its direct reuptake into the myocyte reducing ventricular arrhythmias [87,88].

In addition to its potential role in the prevention of ventricular arrhythmias, aldosterone receptor antagonism has also a role in the prevention of atrial arrhythmias. Atrial fibrillation is the most common sustained arrhythmia in congestive heart failure. In rat models spironolactone reduces the adverse structural changes that occur in congestive heart failure, including atrial fibrosis and atrial remodeling [89]. Eplerenone has been shown to suppress the inducibility of atrial tachyarrhythmias in dog models [90]. Meta-analysis of several studies demonstrates that ARBs and ACE-inhibitors are associated with less atrial fibrillation [91]. It is possible that additional blockade of the RAAS system may also be particularly useful to prevent recurrence of atrial fibrillation after cardioversion as well [92]. In EMPHASIS-HF trial, the incidence of new onset atrial fibrillation or flutter was a secondary endpoint. A sub-analysis, which included 1794 patients without history of atrial fibrillation or flutter, showed that eplerenone reduced the incidence of new atrial fibrillation: 25 of 911 eplerenone-treated patients (2.7%) versus 40 of 883 patients (4.5%) in the placebo group (hazard ratio [HR]: 0.58, $P < 0.034$). Background use of ACE inhibitor or ARBs did not influence the results [93]. It has been proposed that aldosterone receptor blockade may serve as a primary prevention agent of sudden cardiac death in patient populations at risk, including long QT syndrome, Brugada syndrome, and hypertrophic cardiomyopathy [94]. Despite that potential antiarrhythmic mechanisms of MRA exist and the retrospective data from previous studies are encouraging, further prospective studies are necessary to prove the efficacy of these drugs in preventing arrhythmias.

4. Conclusions

Aldosterone receptor antagonists have been shown to be a highly efficacious pharmacologic intervention in the treatment of HF patients with reduced LVEF and mild to severe symptoms. In these patients current evidence clearly shows that MRAs reduce morbidity and mortality. MRAs have also several effects that prevent cardiac remodeling and fibrosis. These effects could potentially extend clinical utility of MRA to a broader cardiovascular patient population, such as asymptomatic patients with reduced LVEF, patients with HFpEF and patients at risk of cardiac arrhythmias. To date, randomized clinical trials have only evaluated the tip of the iceberg in terms of the patient population that may benefit from MRA. Results of ongoing and future prospective studies will hopefully upgrade the clinical indications of this class of medications.

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