Review

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Emerging cardiovascular indications of mineralocorticoid receptor antagonists

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Mineralocorticoid receptor (MR) antagonism is a well-established treatment modality for patients with hypertension, heart failure, and left ventricular systolic dysfunction (LVSD) post-myocardial infarction (MI). There are emerging data showing potential benefits of MR antagonists in other cardiovascular conditions. Studies have shown association between MR activation and the development of myocardial fibrosis, coronary artery disease, metabolic syndrome, and cerebrovascular diseases. This review examines the preclinical and clinical data of MR antagonists for novel indications including heart failure with preserved ejection fraction (HFPEF), pulmonary arterial hypertension (PAH), arrhythmia, sudden cardiac death, valvular heart disease, metabolic syndrome, renal disease, and stroke. MR antagonists are not licensed for these conditions yet; however, emerging data suggest that indication for MR antagonists are likely to broaden; further studies are warranted.

Introduction

The mineralocorticoid receptor (MR; see Glossary) is a cytosolic steroid receptor that binds mineralocorticoids and glucocorticoids [1]. MR is expressed in many tissues including kidney and heart. In epithelial tissues, MR activation and nuclear translocation results in increased expression of proteins that regulate sodium/potassium homeostasis, with concomitant sodium reabsorption and increase in extracellular volume, increased blood pressure, and potassium excretion. Inhibition of MR results in reduced sodium resorption in the kidneys and reduced urinary potassium excretion [1].

Landmark trials including RALES (Randomized ALdactone Evaluation Study), EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), and EMPHASIS-HF (Eplerenone in Mild

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Glossary

Acute myocardial infarction (AMI): necrosis of heart muscles usually caused by lack of blood supply due to occlusion of a coronary artery. It is further divided into ST elevation MI (STEMI) and non-ST elevation MI (NSTEMI) based on presence or absence of ST segment elevation on electrocardiogram (ECG).
ALBATROSS: Aldosterone blockade early after acute myocardial infarction clinical trial.
Angiotensin converting enzyme (ACE) inhibitors: pharmaceutical drugs that are used to treat hypertension and congestive heart failure. Their mode of action is via the inhibition of the angiotensin-converting enzyme of the RAAS.
Angiotensin receptor blockers (ARBs): pharmaceutical drugs that are used to treat hypertension and heart failure.
Aldo-DHF: Aldosterone Receptor Blockade in Diastolic Heart Failure clinical trial.
ARIES: Ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy study.
ALCHEMIST: ALdosterone Antagonist Chronic HEModialysis Interventional Survival trial.
Brain natriuretic peptide (BNP): a peptide secreted by the heart in response to changes in pressure that occur during heart failure and used for diagnosis of heart failure. The N terminus of prohormone BNP (NT-proBNP) may have higher sensitivity and specificity for diagnosing heart failure.
DOHAS: Dialysis Outcomes Heart Failure Aldactone Study.
EPHESUS Trial: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study.
EMPHASIS-HF Trial: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure.
Heart failure with preserved ejection fraction (HFPEF): symptoms and signs of heart failure with normal or preserved ejection fraction. This is also known as diastolic dysfunction.
Left ventricular systolic dysfunction (LVSD): defined as an ejection fraction less than 40% in the EPHESUS trial.
Mineralocorticoid receptor (MR): also known as the aldosterone receptor, is a receptor that binds mineralocorticoids and glucocorticoids with equal affinity. Activation of the receptor results in signal transduction and target gene expression.
MiREnDa: Mineralocorticoid Receptor Antagonists in End Stage Renal Disease study.
OPTIMIZE-HF: Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure study.
Pulmonary arterial hypertension (PAH): a condition whereby the blood pressure in the arteries of the lungs is abnormally high, affecting the function of the right side of the heart.
Renin–angiotensin–aldosterone system (RAAS): an endocrine system and signaling pathway that is responsible for regulating blood pressure and systemic vascular resistance.
RALES Trial: Randomized ALdactone Evaluation Study.
REMINDER Trial: impact of eplerenone on cardiovascular outcomes in patients post myocardial infarction.
SPIR AF: Effect of combined spironolactone-β-blocker ± enalapril treatment on occurrence of symptomatic atrial fibrillation (AF) episodes in patients with a history of paroxysmal AF.
Sudden Cardiac Death (SCD): Unexpected death which is presumed to be cardiac in origin and usually secondary to ventricular arrhythmias
TOPCAT Trial: Treatment of Preserved Cardiac function with an Aldosterone antagonist trial.

Patients Hospitalization and Survival Study in Heart Failure) have demonstrated that MR antagonists (spironolactone or eplerenone) have beneficial effects in patients with heart failure and LVSD. However, MR antagonists also have potential effects on vascular inflammation, macrophage activation, oxygen free radical formation, endothelial dysfunction, and myocardial fibrosis, and hence may provide more widespread benefits on cardiovascular disease states. These effects are mediated by a variety of signaling mechanisms and mediators, outlined in Figure 1 and reviewed in detail elsewhere [2]. This review briefly describes the existing indications of MR antagonists and critically evaluates potential indications of MR antagonists for the treatment of HF-PEF, PAH, cardiac arrhythmias, valvular heart disease, metabolic syndrome, renovascular diseases, and cerebrovascular diseases.

Current and emerging MR antagonists

Eplerenone and spironolactone (and its metabolite, potassium canrenoate) are the currently licensed MR antagonists for clinical use. Spironolactone is a high affinity but nonspecific MR antagonist and, due to its structural similarity to progesterone, binds also to progesterone, androgen, and glucocorticoid receptors, but with reduced affinity [3]. Eplerenone is also a steroidal compound with greater selectivity for MR and minimal binding to progesterone and androgen receptors [3]. Spironolactone and eplerenone differ in their metabolism and half-life [3,4]. There are also a few non-steroidal MR antagonists (e.g., Finerone, BR-4628) at various stages of development [5–7]. These emerging MR antagonists have the potential to deliver similar efficacy, but with less endocrine side effects, such as estrogenic side effects, including impotence and gynecomastia in men and menstrual irregularity in women, due to their non-steroidal structure. These compounds may also have higher affinity for cardiac MR, rather than renal MR, and therefore, potentially a reduced tendency for hyperkalemia than currently licensed agents. A comparison of MR antagonists is given in Table 1.

Currently licensed cardiovascular indications of MR antagonists

Chronic heart failure due to LVSD

RALES and EMPHASIS-HF trials have proven the efficacy of MR antagonists in chronic heart failure due to LVSD. In the RALES study, spironolactone showed a 30% relative reduction in mortality at 24-month follow-up [8]. In EMPHASIS-HF, there was a 24% reduction in cardiovascular death, and a 42% reduction in hospitalization for heart failure [9]. However, both spironolactone and eplerenone can potentially cause hyperkalemia, raising concerns about use of MR antagonist in patients with renal impairment [8,10]. It is worth noting that in patients with LVSD and moderate renal impairment, a newer non-steroidal MR antagonist, Finerenone (BAY 94-8862), decreased biomarkers of hemodynamic stress equivalent to spironolactone, but with lower incidence of hyperkalemia and worsening renal function [11]. Such newer compounds could potentially be safer alternatives to current MR antagonists for the existing cardiovascular indications.

LVSD after MI

In the EPHESUS trial, eplerenone administered 3–4 days after an acute myocardial infraction (AMI) in patients with clinical heart failure and LVSD, produced a 15% reduction in all-cause mortality, a 17% reduction in cardiovascular mortality and a 21% reduction in sudden cardiac death [10]. It was recently reported in the REMINDER trial that early administration of eplerenone within 24 hours of symptom onset can improve the outcome of patients with ST segment elevation myocardial infarction (STEMI), a type of heart attack, without clinical heart failure [12]. Eplerenone produced a significant reduction in the primary endpoint [composite of cardiovascular mortality,

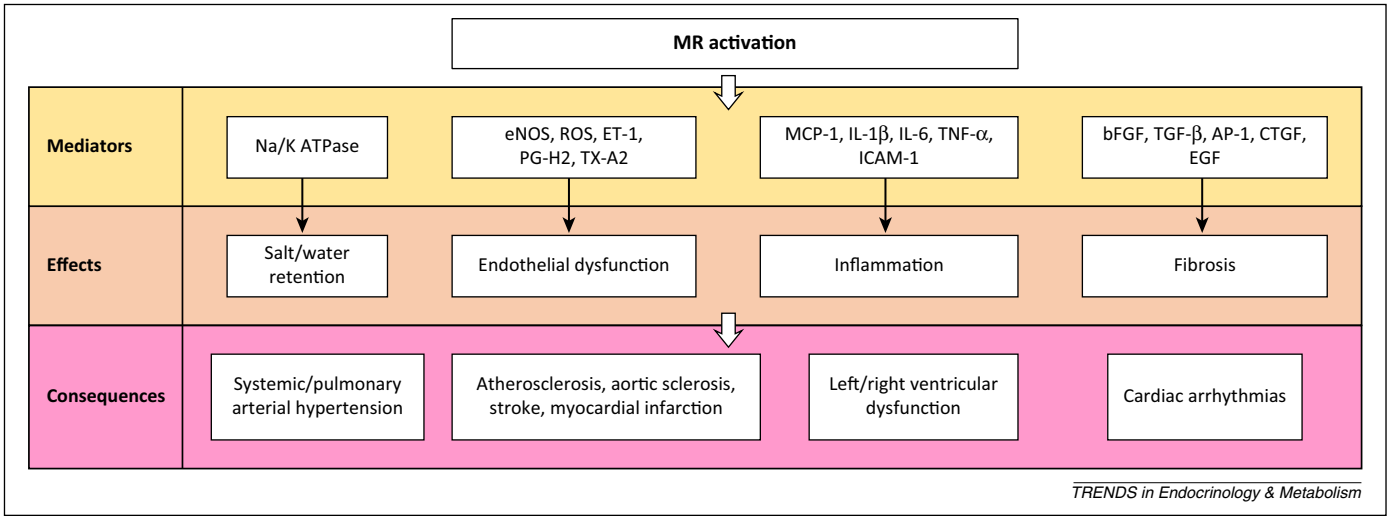
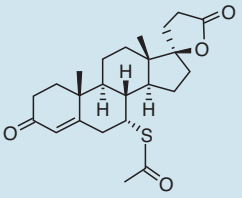
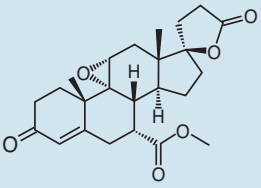
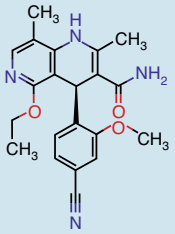


Figure 1. Mineralocorticoid receptor (MR) activation: pathophysiological effects and cardiovascular disease association. MR activation can lead to adverse cardiovascular outcomes via a number of potential pathways and mediators affecting electrolyte balance, inflammation, endothelial function, and fibrosis. Abbreviations: Na/K ATPase sodium/potassium adenosine triphosphatase; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; ET-1, endothelin-1; PG-H2, prostaglandin H2; TX-A2, thromboxane A2; MCP-1, monocyte chemotactic protein-1; IL-1β, interleukin 1-beta; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; ICAM-1, intercellular adhesion molecule 1; bFGF, basic fibroblast growth factor; TGF-β, transforming growth factor-beta; AP-1, activator protein 1; CTGF, connective tissue growth factor; EGF, epidermal growth factor.

Table 1. Comparison of current and emerging MR antagonists

	Spironolactone	Eplerenone	Finerenone (BAY 94-8862)
Chemical structure			
Chemical group	Steroid	Steroid	Non-steroidal
Mode of action	Competitive MR antagonism	Competitive MR antagonism	Competitive MR antagonism
MR affinity	+++	+	+++
MR selectivity	±	+++	+++
Inhibition of nongenomic MR effects	No	Yes	Unknown
Onset/offset of action	Slow	Quicker	Unknown
Bioavailability	60–90%	Absolute bioavailability unknown	Unknown (94% in rats)
Volume of distribution	Unknown	43–90 liters	Unknown
Protein binding	90% bound to plasma proteins	50% bound to plasma proteins	Unknown
Metabolism	Hepatic metabolism to active metabolites	Hepatic metabolism by CYP3A4 to inactive metabolites	Unknown
Half-life of drug	1–2 hours	4–6 hours	Unknown (8.5 hours in rats)
Active metabolites	Yes	No	Activity of metabolites not known
Elimination half-life of drug and metabolites	10–35 hours	4–6 hours	Unknown

ventricular arrhythmia, clinical or subclinical heart failure at 1 month, as determined by an ejection fraction less than 40% or elevation in brain natriuretic peptide (BNP) or N terminus of prohormone BNP (NT-BNP); heart rate (HR) 0.58, 95% confidence interval (CI) 0.45–0.75, $P < 0.0001$], at a mean follow-up of 10.5 months [12]. This improvement in primary endpoint was driven by a reduction in brain natriuretic peptide (BNP) levels (HR 0.58, 95% CI 0.44–0.77, $P < 0.0001$); the study was not able/powered to demonstrate effects on cardiac mortality (HR 0.52, 95% CI 0.05–5.99, P = ns), hospitalization (HR 0.56, 95% CI 0.20–1.54, P = ns), and ejection fraction (HR 1.08, 95% CI 0.58–2.00, P = ns) [12]. Spironolactone has not been assessed for this indication. However, ALBATROSS (Aldosterone blockade early after acute myocardial infarction; NCT-01059136) is an ongoing multicenter, open-labelled, randomized trial to assess the effects of MR blockade. The trial will assess a 200-mg intravenous bolus of potassium canrenoate followed by 25 mg/day spironolactone for 6 months, in 1600 patients with STEMI or high-risk NSTEMI [13]. In summary, the best current available evidence supports eplerenone in the treatment of LVSD after MI [4].

Systemic hypertension

MR antagonists are used as monotherapy and as an add-on therapy for hypertension [14,15]. These agents are as effective in lowering blood pressure as the currently recommended first-line anti-hypertensive agents – angiotensin converting enzyme (ACE) inhibitors [16] or angiotensin receptor blockers (ARBs) [17]. Eplerenone is better tolerated than amlodipine, a widely used calcium channel blocker, with similar reduction in systolic blood pressure [18]. MR antagonists have also been shown to prevent hypertension-induced end organ damage in both preclinical [19] and clinical studies [16,20]. However, MR antagonists are still used infrequently and considered as fourth-line therapy (for patients with resistant hypertension), in national and international guidelines [21]. The underuse of MR antagonists is due to relative paucity of long-term clinical outcome data, compared with other antihypertensive drugs. Therefore, potential future roles of MR antagonists in hypertension will be guided by further population-level data, but there is scope for wider acceptance in the treatment of hypertension.

Emerging cardiovascular indications of MR antagonists

HF-PEF

MR activation may cause left ventricular hypertrophy (LVH) and collagen deposition, which reduces LV compliance, a characteristic of HF-PEF. MR antagonists have therefore been investigated as potential therapeutic agents (Table 2). Although eplerenone has been shown to attenuate collagen turnover in patients with HF-PEF [22,23] and improve echocardiographic measures of diastolic function, this did not correlate with functional improvement [23]. After 6 months of treatment, no differences in 6-minute walk distance were noted in the eplerenone and placebo groups. However, this small study (n = 40) was underpowered to demonstrate functional outcomes. A sub-study of the OPTIMIZE-HF trial compared 492 patients with HF-PEF receiving MR antagonists with 487 propensity matched patients not receiving MR antagonists [24]. During the mean follow-up of 2.4 years, the primary composite endpoint of all-cause mortality or HF hospitalization occurred in 392 (81%) and 393 (81%)

Table 2. Summary of studies investigating MR antagonists for HF PEF

Study name	Study design	Drug (dose)	No. of patients	Eligibility criteria[a]	Primary endpoints	Follow-up	Outcomes	Refs
RAAM-PEF	Single-center, randomized, double blind, placebo-controlled trial	Eplerenone (50 mg/day)	44	Clinical HF with NYHA Class II or III symptoms, EF $\geq$ 50% and BNP levels $\geq$ 100 pg/ml	6-minute walk distance	6 months	No significant difference in the change in 6-minute walk test between the eplerenone and placebo arms; however, improvement in diastolic function and reduced collagen turnover	[23]
OPTIMIZE-HF	Matched patients from a registry	Any MR antagonist	974	EF $>$ 40%, no renal impairment, not using ACE-I/ARB	All-cause mortality, HF hospitalization, all-cause hospitalization	2.4 years	No impact on all-cause mortality or HF hospitalization	[24]
Kosmala *et al.*	Prospective, blinded, parallel-group, placebo-controlled trial	Spironolactone (25 mg/day)	80	Patients with DHF and metabolic syndrome already receiving ACE-I/ARB	Echocardiographic indices of LV systolic and diastolic function, and serum markers of collagen turnover	6 months	Spironolactone improved LV function and reduced markers of collagen turnover	[25]
Aldo-DHF	A multicenter, prospective, randomized, double-blind, placebo-controlled trial	Spironolactone (25 mg/day)	422	HF symptoms with NYHA class II or III or evidence of diastolic heart failure (grade $\geq$ I) on echocardiography	Exercise capacity, peak VO_2, diastolic function	1 year	No improvement in exercise capacity or quality of life; however, improved myocardial function, reduced LVH, and reduced markers of collagen turnover	[26]
TOPCAT	Multicenter, randomized, double blind, placebo-controlled trial	Spironolactone (15–45 mg/day)	3445	HF with EF $\geq$ 45%, controlled BP, serum $K^+ < 5.0$	CV mortality, aborted cardiac arrest, HF hospitalizations	3.4 years	No reduction in primary end-points but reduction in HF hospitalization	[27]

[a]Abbreviations: HF, heart failure; NYHA, New York Heart Association; EF, ejection fraction; BNP, brain natriuretic peptide; MR antagonist, mineralocorticoid receptor antagonist; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DHF, diastolic heart failure; LVH, left ventricular hypertrophy; BP, blood pressure.

patients receiving and not receiving MR antagonists, respectively (HR 0.97, 95% CI 0.84–1.11, $P = 0.63$).

Kosmala *et al.* ($n = 80$) have shown that spironolactone improved myocardial function and reduced markers of collagen turnover at 6 months, compared to placebo, in patients with metabolic syndrome already receiving ACE inhibitors [25]. The Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trial ($n = 422$) also demonstrated an improvement in left ventricular diastolic function on echocardiography with spironolactone, but failed to show any significant benefit on exercise capacity or quality of life at 1-year follow-up [26]. TOPCAT (Treatment of Preserved Cardiac function with an Aldosterone antagonisT), the largest trial so far for this indication, randomized 3345 patients with HF-PEF to spironolactone or placebo, and failed to show any significant effect on the primary composite endpoint of cardiovascular mortality, aborted cardiac arrest, and heart failure hospitalization (HR 0.89, 95% CI 0.77–1.04, $P = 0.14$), at 3.3 year follow-up [27] (Table 2). However, there was a significant reduction in HF hospitalization (HR 0.83, 95% CI 0.69–0.99, $P = 0.042$). Moreover, subgroup analyses suggested that spironolactone appeared to have beneficial effects in patients enrolled in the trial, based on high baseline BNP, rather than those included on the basis of a hospitalization for heart failure symptoms. Furthermore, a post-hoc analysis suggested that there might be geographic differences in the outcomes [27]. These hypothesis-generating analyses suggest there may be merit in further investigations in high-risk patients with more stringent diagnostic criteria for HF-PEF.

PAH

Pulmonary hypertension is a condition with raised blood pressure in the pulmonary vasculature leading to strain on the right side of the heart and consequent right heart failure.

Elevated plasma aldosterone levels have been associated with the progression of PAH [28]. MR blockade reduces the proliferation of pulmonary arterial smooth muscle cells [29]. Both spironolactone and eplerenone have been shown to prevent or reverse pulmonary vascular remodeling, and improve cardiopulmonary hemodynamics in murine models of PAH [30].

The data from ARIES (Ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy study) evaluated ambrisentan (an endothelin receptor antagonist) against a placebo. A sub-analysis identified 21 patients (out of the 67 randomized to ambrisentan alone) with a combination of ambrisentan and spironolactone for the treatment of PAH. The results showed that combination treatment resulted in an improvement in World Health Organization (WHO) functional class by ≥ 1 ($P = 0.08$), 6-minute walking distance by 94% ($P = 0.11$), with a drop in BNP levels ($P = 0.08$) [31].

The use of MR antagonists in the treatment of PAH and right heart failure is not licensed currently (except as part of diuretic therapy in patients with right-sided heart failure). There are minimal clinical data at present, but preclinical data appear promising and have led to a number of clinical studies, which will address this indication more definitively (Table 3).

Atrial arrhythmias/fibrillation

There are emerging data, mainly from preclinical studies, on the role of MR antagonists in atrial arrhythmias. MR activation may have direct effects (changes in myocyte electrical properties, abnormal repolarization, ion channel abnormalities, nitric oxide availability, atrial dysfunction, and myocardial fibrosis), and indirect effects mediated by control of hypertension and heart failure and prevention of hypokalemia.

Increased MR expression and associated fibrosis of the left atrial tissue has been reported in human atrial fibrillation (AF) and a cellular model of AF [32,33]. MR activation is a potential substrate for atrial arrhythmias characterized by atrial fibrosis, myocyte hypertrophy, and conduction disturbances [34]. Plasma aldosterone levels are raised in patients with AF [35] and patients with primary aldosteronism have a 12-fold higher risk of developing AF compared with blood pressure-matched controls [36].

Spironolactone has been shown to prevent atrial fibrosis in preclinical studies [36]. Pre-treatment with spironolactone in a ventricular tachy-pacing AF model in dogs reduced the amount of atrial fibrosis and inducibility of AF [37]. Spironolactone also prevented AF-related changes in atrial structure and function *in vivo* in a canine model of persistent AF; reduced apoptotic cell death, myolysis, and mitochondrial swelling; and maintained left atrial ejection fraction [38]. Eplerenone has also been shown to suppress fibrosis and inducible AF in a canine model [39].

The clinical data also suggest that MR antagonists may have a beneficial effect in patients with AF. A small retrospective study in 83 patients with AF, including 23 who were treated with spironolactone for ≥ 3 months, has shown that the spironolactone group had significantly fewer AF-related hospitalizations or need for electrical cardioversion [40]. MR antagonism has also been shown to improve maintenance of sinus rhythm after radiofrequency catheter ablation in patients with persistent AF. In a study examining 161 patients with persistent AF who underwent ablation, eplerenone was used in 55 patients and not used in the remaining 106 patients [41]. Other conventional pharmacologic agents, including ACE inhibitors or ARBs, were used equally in the two groups. After 24 months of follow-up, the rate of freedom from AF recurrence was significantly greater in the eplerenone group (60%) than in the non-eplerenone group (40%) ($P = 0.011$). In a multivariate cox regression analysis, eplerenone therapy was an independent predictor of maintenance of sinus rhythm [41]. New onset AF was an adjudicated, pre-specified secondary endpoint in the EMPHASIS-HF trial and was significantly reduced by eplerenone [42]. At the mean follow-up of 2 years, new onset AF occurred in 25/911 (2.7%) of the patients in the group randomized to eplerenone, versus 40/883 (4.5%) in the group randomized to placebo (HR 0.58, 95% CI 0.35–0.96, $P = 0.034$). Similar findings were reported in SPIR-AF trial ($n = 164$ patients); at the 12-month follow-up,

Table 3. Summary of ongoing studies investigating MR antagonists for newer indications[a]

Study	NCT	Design	Phase	*n*	Condition	Study drug (dose)	Eligibility criteria	Primary endpoints	Secondary endpoints	Expected results
Aldosterone Antagonism and Microvascular Function	01887119	Randomized, double blind trial	4	60	Metabolic syndrome	Eplerenone (50 mg/day)	40–65 years, Caucasian with metabolic syndrome	Change in capillary recruitment	Microvascular blood volume in skeletal muscle of the forearm	2015
Comparison of Effects of Eplerenone Versus Spironolactone in Heart Failure Patients With Glucose Intolerance or Type 2 Diabetes (SNOW)	01586442	Randomized double blind trial	3	62	Metabolic syndrome	Eplerenone (25–50 mg/day) vs. Spironolactone (12.5–25 mg/day)	Patients > 18 years with NYHA class II–IV, impaired glucose tolerance or type 2 diabetes, LVEF ≤ 40%, on ACE inhibitor (or ARB) and beta-blockers	HbA_{1C}	Fasting glucose, lipid profile, insulin, cortical, adiponectin, NT-proBNP levels	2014
Early Mineralocorticoid Receptor Antagonist Treatment to Reduce Myocardial Infarct Size (MINIMISE STEMI)	01882179	Randomized double blind trial	3	150	Myocardial infarction	Potassium Canrenoate, followed by Spironolactone 25–50 mg/day	Patients > 18 years with acute STEMI and K^+< 5 mmol/l	Myocardial infarct size, as assessed by cardiac MRI	Cardiac biomarkers, TIMI flow, ST resolution, microvascular obstruction	2015
ALdosterone Antagonist Chronic Hemodialysis Interventional Survival Trial (ALCHEMIST)	01848639	Randomized, double blind trial	3	825	Chronic kidney disease	Spironolactone (25 mg/day)	Age > 18 years old, on hemodialysis for at least 6 months for end-stage renal disease regardless of the etiology	Time to onset of the first incident: nonfatal MI or HF hospitalization or nonfatal stroke or cardiovascular death	Cumulate rate of nonfatal MI, hospitalization for heart failure, nonfatal stroke or CV death	2018
Mineralocorticoid Receptor Antagonist in End Stage Renal Disease (MiREnDa)	01691053	Randomized, double blind trial	2	120	Chronic kidney disease	Spironolactone (50 mg/day)	Age > 18 years, on hemodialysis for 3+ months, and having 3 dialysis sessions per week	Left Ventricular Mass Index as assessed by cardiac MRI	Cardiac function, 24-hour BP, NYHA class, 6-minute walk test, vascular function assessment	2014
MR Antagonist and Kidney Allograft Histology	01510795	Open label, non-randomized study	4	40	Chronic kidney disease	Spironolactone (25-50 mg/day)	Renal transplant, K^+ < 5 mmol/l, eGFR > 30 ml/min and not on ACE inhibitor or ARB	Changes in chronic Banff scores	eGFR, urinary protein/creatinine ratio and urinary albumin/creatinine ratio	Unknown
EPLErenone in CsA-Treated Recipients (EpleCsAT)	01834768	Open label, single-group assignment study	2	Not stated	Chronic kidney disease	Eplerenone (25 mg/day)	Patient >18 years with a functional kidney allograft, on cyclosporine A, GFR 30–50 ml/min/1.73 m^2	Adverse event requiring discontinuation of eplerenone	–	2014
Mineralocorticoid Antagonism and Endothelial Dysfunction in Autosomal Dominant Polycystic Kidney Disease (ADPKD)	01853553	Randomized, double blind trial	4	60	Chronic kidney disease	Spironolactone (25 mg/day)	Age 60–79 years, with ADPKD, eGFR ≥ 60 ml/min, BP > 130/80 on ACE inhibitor or ARB, free from antioxidants and alcohol dependence	Flow-mediated dilation at 6 months	Vascular stiffness, aortic pulse wave velocity, carotid compliance at 6 months	2016
Spironolactone for Pulmonary Arterial Hypertension	01712620	Randomized, double blind trial	1–2	70	PAH	Spironolactone (25 mg/day)	WHO Group 1 PH patients	6-minute walk distance	VO_2 max, right heart function, biomarkers of vascular inflammation	2015
Effects of Spironolactone on Collagen Metabolism	01468571	Randomized, double-blind,	4	50	PAH	Spironolactone (50 mg/day)	WHO Group 1 PH patients	Biomarker level	Adverse events, 6-minute walk test,	2015/16

Table 3 (*Continued*)

Study	NCT	Design	Phase	*n*	Condition	Study drug (dose)	Eligibility criteria	Primary endpoints	Secondary endpoints	Expected results
in Patients With Pulmonary Arterial Hypertension		cross-over study							functional class, clinical worsening	
Safety and Efficacy Study of BAY94-8862 in Subjects With Worsening Chronic Heart Failure and Left Ventricular Systolic Dysfunction and Either Type 2 Diabetes Mellitus With or Without Chronic Kidney Disease or Chronic Kidney Disease Alone (ARTS-HF)	01807221	Randomized, double blind trial	2b	1060	Heart Failure	Finerenone (BAY 94-8862)	Worsening Chronic Heart Failure and Left Ventricular Systolic Dysfunction and Either Type 2 Diabetes Mellitus With or Without Chronic Kidney Disease or Chronic Kidney Disease Alone	NT-proBNP	Potassium levels, heart rate, BP	2015

[a]Abbreviations: STEMI, ST segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; PPCI, primary percutaneous coronary intervention; ADPKD, autosomal dominant polycystic kidney disease; PAH, pulmonary arterial hypertension; HF, heart failure; NYHA, New York Heart Association; EF, ejection fraction; BNP, brain natriuretic peptide; MR antagonist, mineralocorticoid receptor antagonist; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DHF, diastolic heart failure; LVH, left ventricular hypertrophy; BP, blood pressure; MVO, microvascular obstruction.

spironolactone-treated groups had a significant ($P < 0.001$) reduction in the incidence of AF episodes compared to the comparator non-spironolactone groups [43].

In summary, MR antagonists may have a role in the prevention of atrial arrhythmias, especially AF, and further randomized controlled trials are warranted.

Ventricular arrhythmias and sudden cardiac death

Mineralocorticoids may play a potential role in ventricular arrhythmias and sudden cardiac death (SCD). Overexpression of cardiac MR in murine models has been shown to result in severe ventricular arrhythmias and death [44]. This conditional cardiac-specific MR overexpression resulted in ion channel remodeling and prolonged ventricular repolarization, without systemic aldosterone access. Conversely, MR blockade, in addition to the standard therapy, reduced the incidence of sudden cardiac death in the RALES, EPHESUS, and EMPHASIS-HF trials [8–10]. A recent meta-analysis has shown that MR antagonists reduce the risk of SCD in patients with LVSD [45]. Both spironolactone and eplerenone significantly reduced ventricular premature complexes, ventricular tachycardia, and SCD [45]. Additionally, spironolactone in combination with ACE inhibitors reduced arrhythmias in post-MI patients [46].

In summary, the larger studies of MR antagonists in LVSD have confirmed a reduction in ventricular arrhythmias and SCD; however, the role of MR antagonists in patients with risk of ventricular arrhythmias and SCD without LVSD needs further evaluation in clinical studies.

Reno-vascular and chronic kidney disease

The kidney and renal vasculature are potential targets of aldosterone-mediated pathology. The spontaneously hypertensive stroke-prone rats, characterized by activation of the renin–angiotensin–aldosterone system (RAAS), develop severe hypertension, cerebral hemorrhage, and renal pathology. Spironolactone has been shown to protect against the development of malignant nephrosclerotic and cerebrovascular lesions in this model, independent of its blood pressure lowering effect [47]. MR activation has also been implicated in the cardiac hypertrophy observed in uremic rats, and spironolactone has been shown to attenuate cardiac hypertrophy and prevented oxidative stress in this model [48].

In dialysis patients, the efficacy and safety of MR antagonists have been reported in a few small clinical studies, reviewed elsewhere [49]. DOHAS (Dialysis Outcomes Heart Failure Aldactone Study), a prospective, multicenter, randomized, controlled, open-label trial ($n = 309$), has shown that spironolactone (25 mg/day) may substantially reduce cardiovascular and cerebrovascular morbidity and mortality in patients on hemodialysis [50]. Spironolactone has also been reported to be safe in patients with early stages of chronic kidney disease with a strict monitoring of renal function and electrolytes over the first month of treatment, followed by standard surveillance [51]. However, further large-scale, multicenter, randomized, double-blind, placebo-controlled trials in patients with different stages of renal insufficiency are needed [52]. ALCHEMIST (ALdosterone Antagonist Chronic HEModialysis Interventional Survival

Trial; NCT01848639) and MiREnDa (Mineralocorticoid Receptor Antagonists in End Stage Renal Disease; NCT01691053) are currently ongoing (Table 3) and will provide further data needed before definitive treatment recommendations can be made. The non-steroidal MR antagonist, Finerenone (BAY 94-8862), is also being tested in clinical trials for heart failure patients with chronic kidney disease and in patients with diabetic nephropathy (Table 3).

Other possible cardiovascular indications of MR antagonists

Metabolic syndrome and coronary artery disease

Aldosterone plays a central role in linking obesity, dyslipidemia, insulin resistance, renal dysfunction, hypertension, and other features of metabolic syndrome. Obesity is known to be associated with a reduced level of adiponectin and increases in proinflammatory adipokines. Guo *et al.* have shown that in a diabetic mouse model, MR blockade reduces the expression of proinflammatory and prothrombotic factors in adipose tissue and increases expression of adiponectin in heart and adipose tissue [53]. Armani *et al.* have shown that spironolactone can prevent glucose impairment, body weight gain, and expansion of white fat in high-fat-fed mice [54]. MR blockade may also improve the detrimental endocrine and vascular abnormalities that characterize the metabolic syndrome by increasing pancreatic insulin release, improving utilization of glucose, as well as increasing vasorelaxation of the endothelium [55]. Therefore, it can be hypothesized that MR blockade might reduce the risk of coronary artery disease in patients with a metabolic syndrome. Aldosterone has been shown to accelerate atherosclerosis in preclinical studies and to promote a rupture-prone inflammatory plaque phenotype [56]. Plasma aldosterone is also associated with progression of atherosclerosis in humans [57]. However, there have been concerns that spironolactone may impair glycemic control and endothelial function in patients with type 2 diabetes [53,55,58]. Eplerenone may have no such adverse effects [58] and actually may improve coronary circulatory function (adenosine-stimulated myocardial perfusion reserve) and endothelial function in diabetic patients already receiving ACE inhibitors [59]. In the ongoing SNOW trail (comparison of Effects of Eplerenone Versus Spironolactone in Heart Failure Patients With Glucose Intolerance or Type 2 Diabetes; NCT01586442), investigators will examine whether the selectivity of eplerenone for the MR will translate into a better glucose and metabolic profile, compared to spironolactone in patients with heart failure, with glucose intolerance, or type 2 diabetes.

Aldosterone has also been linked to the development of prothrombotic conditions. Hypertensive subjects with an increased renin–sodium profile are at increased risk for MI [60]. It is plausible that this deleterious role of the RAAS system is via interaction with the homeostatic balance of prothrombotic and fibrinolytic systems. Brown *et al*. have reported that aldosterone correlates with plasminogen activator inhibitor-1 (PAI-1) levels in patients [61]. MR antagonism can also limit infarct size during AMI, and this potential role is currently being studied in MINIMISE-STEMI, a trial where patients with STEMI receive intravenous potassium canrenoate prior to coronary angioplasty followed by 3 months of oral spironolactone (Table 3).

In summary, there are encouraging early data and further clinical studies are needed to help elucidate the possible role of MR antagonists in primary or secondary prevention of coronary athero-thrombotic disease.

Post-angioplasty remodeling

MR antagonists have a potentially beneficial impact on post-angioplasty constrictive remodeling. Eplerenone has been shown to attenuate constrictive remodeling and in-stent restenosis after coronary artery angioplasty in experimental animals [62]. This benefit seems to be due to reduction in collagen accumulation. Spironolactone has been shown to inhibit neointimal proliferation after balloon-angioplasty in rabbits [63]. However, these results could not be reproduced in a porcine coronary angioplasty model [62] or in a clinical trial [64]. Eplerenone has shown promising results in many preclinical models [62,65,66]. However, the efficacy of eplerenone for this indication has not been tested in a dedicated clinical trial. A post-hoc analysis of the EPHESUS trial studied 1580 EPHESUS patients treated with percutaneous coronary intervention (PCI). Eplerenone administration, compared with placebo, in the PCI-treated EPHESUS cohort did not affect PCI-related clinical outcomes, including recurrence of angina, the occurrence of acute coronary syndromes, or the need for further revascularization [67]. Therefore, use of an MR antagonist cannot be recommended to prevent restenosis in patients undergoing PCI who have no other indication for these drugs. However, further prospective studies to evaluate angiographic outcomes with eplerenone may provide a definitive answer.

Aortic valve disease

In theory, MR activation can promote aortic sclerosis and aortic stenosis, due to its effect on inflammation and fibrosis. Once aortic valve disease has been established, the pressure or volume overload may induce left ventricular dysfunction, which can be potentially prevented or treated with MR antagonists.

A clinical trial randomized 65 patients with asymptomatic moderate to severe aortic stenosis to eplerenone (100 mg) or a placebo, and followed up for an average of 19 months. Cardiac magnetic resonance imaging, echocardiography, and NT-proBNP were performed at baseline and follow-up. Eplerenone did not affect the progression of aortic stenosis (change in aortic valve area -0.11 ± 0.22 vs. -0.18 ± 0.24 cm^2 per year, $P = 0.2$), the development of left ventricular hypertrophy (change in LV mass index -0.3 ± 14.6 vs. $+5.1 \pm 15$ g/m^2 per year, $P = 0.3$), and the onset of systolic (change in LV ejection fraction $+0.0 \pm 5.7\%$ vs. $+0.8 \pm 5.7\%$ per year, $P = 0.9$) or diastolic dysfunction (change in E/E' $+0.49 \pm 0.7$ vs. $+1.32 \pm 2.0$ per year, $P = 0.4$) [68]. However, this study used a small patient group who were asymptomatic, and therefore further studies with a larger cohort of asymptomatic and symptomatic patients randomized to placebo, spironolactone, or eplerenone are needed

before completely ruling out any utility of MR antagonists for this indication.

There is currently no strong clinical evidence for the use of MR antagonists in medical management for aortic regurgitation. Preclinical data have suggested that the RAAS may play a role in mediating LV hypertrophy, and that MR blockade may maintain normal systolic function in aortic regurgitation. Zendaoui *et al.* looked at the effect of spironolactone in adult rats with severe aortic regurgitation compared to non-treated and sham-operated rats over 6 months [69]. Spironolactone decreased myocardial fibrosis with decreased heart weight and LV expression of atrial natriuretic peptide mRNA, resulting in a protective effect against volume-overload cardiomyopathy [69]. However, there has been no clinical study to date to investigate the effect of MR antagonism on the progression of aortic regurgitation or prevention of its consequences on LV function.

In summary, the data for use of MR antagonists for aortic valve disease is sparse and further clinical studies to confirm or refute this potential indication are needed.

Stroke

Cerebrovascular events, alongside other cardiovascular events, are more common in patients with primary aldosteronism, independent of hypertension [36]. Preclinical and clinical evidence suggest that MR activation leads to worse outcome after stroke [70]. Experimental data have shown that MR antagonism reduces the incidence/size of stroke, and improves survival in an experimental model of stroke-prone spontaneously hypertensive rats maintained on a 1% saline and stroke-prone diet [47,71]. It has also been shown that pre-treatment with eplerenone reduces stroke size in a mouse model of middle cerebral artery occlusion [72]. A study by Frieler *et al*. explored the mechanism of action of MR at the cellular level, and demonstrated that MR expressed in myeloid cells (i.e., non-lymphocytic leukocytes) is potentially involved in post stroke outcome, by showing that myeloid-specific MR knockout mice had 65% reduction in infarct volume ($P = 0.005$) after middle cerebral artery occlusion [73]. Clinical studies have shown a strong association of increased level of aldosterone with risk of stroke and death [74]. Further large-scale randomized control trials are required to explore the beneficial effects of MR antagonists in the prevention and treatment of stroke.

Concluding remarks and future perspectives

The beneficial effects of MR antagonism have been robustly demonstrated for patients with hypertension and heart failure due to LVSD. Recently, an MR antagonist was shown to reduce the hospitalization rate in patients with HF-PEF. However, the emerging data suggests that MR antagonists may also have a role in the treatment of other cardiac and vascular conditions including atrial fibrillation, pulmonary hypertension, renal failure, and stroke. The beneficial effects of MR antagonists in these conditions have been shown in pre-clinical or small-scale clinical studies; adequately powered randomized trials are warranted to confirm these findings. It is also prudent to highlight that the non-steroidal MR antagonists currently in development may have less endocrine side effects and hyperkalemia (due to their bio-distribution properties), thereby improving efficacy and reducing side effects. It is, therefore, plausible that the clinical indications for both novel and existing MR antagonists will be extended in the future.

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