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,

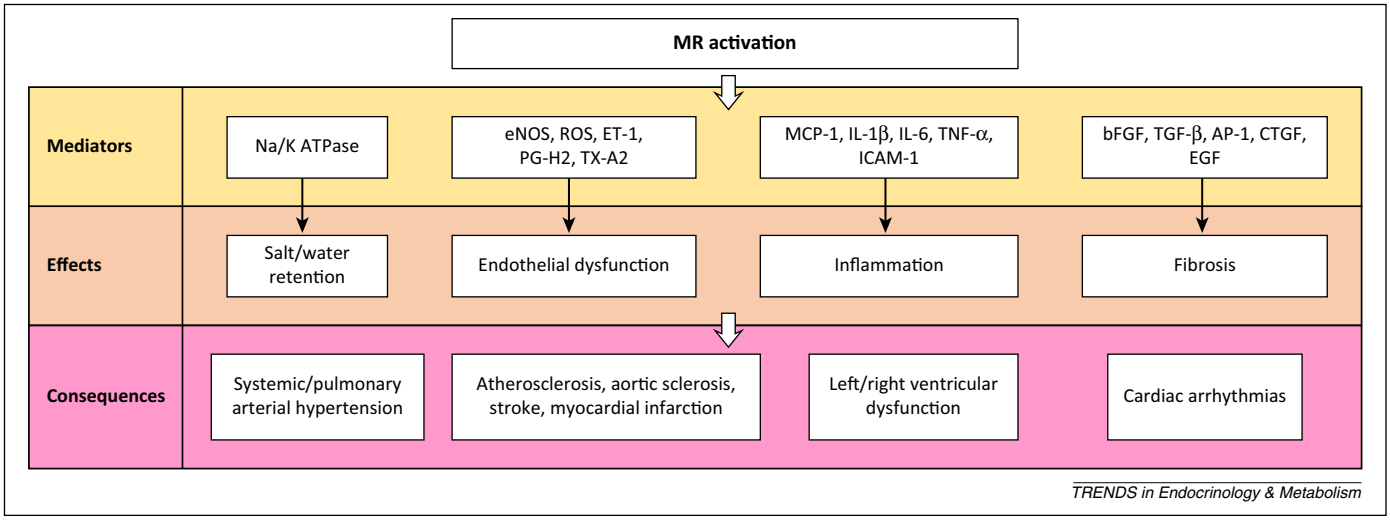

Figure 1. Mineralocorticoid receptor (MR) activation: pathophysiological effects and cardiovascular disease association. MR activation can lead to adverse cardiovascular outcomes via a number of potential pathways and mediators affecting electrolyte balance, inflammation, endothelial function, and fibrosis. 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.