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STATE-OF-THE-ART REVIEW

Aldosterone-Related Cardiovascular Disease and Benefits of Mineralocorticoid Receptor Antagonists in Clinical Practice

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ABSTRACT

High levels of aldosterone are associated with vascular and cardiac remodeling, myocardial fibrosis, and endothelial dysfunction with consequent increased risk of cardiovascular events and cardiovascular mortality. Indeed, mineralcorticoid receptor antagonists (MRAs) are recommended in the treatment of arterial hypertension, heart failure, alone or associated with chronic kidney disease. Nevertheless, molecular pathways underlying aldosterone-induced cardiac remodeling are poorly investigated. High levels of aldosterone induce reactive oxygen species with consequent oxidative stress and mitochondrial dysfunction. Moreover, aldosterone induces myocardial hypertrophy through increase of sarcomere mass mediated by pro-hypertrophic effect mediated by a G protein-coupled receptor kinase 5 cytosolic signaling and retention of ions and water regulated by aquaporins. Aim of this review is to report the data from the literature regarding excessive aldosterone signaling in mediating cardiovascular disease, also highlighting the morphostructural and molecular pathways correlated to myocardial damage and the role of MRAs in clinical practice. (JACC Adv. 2025;4:101762) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Aldosterone is the main mineralocorticoid hormone produced by the zona glomerulosa of the adrenal cortex. It is implicated in blood volume and pressure control through regulation of sodium and potassium homeostasis. The effects of aldosterone secretion are mediated by genomic and nongenomic mechanisms. The genomic effects are linked to the binding of aldosterone to intracellular receptors with consequent transcriptions of genes involved in the regulation of vascular tone and in hydro-electrolyte balance; nongenomic effects are due to the direct binding of aldosterone to specific membrane receptors in heart, vessels, and kidney tissues.[1] Aldosterone excess is caused by renin-independent production due to primary aldosteronism (PA) or hyperactivation of the renin-angiotensin-aldosterone system (RAAS) as in heart failure (HF) in the context of secondary aldosteronism. In both cases, fluid and sodium retention result in volume expansion, vasoconstriction, and consequent potassium depletion that are related to the development of hypertension. Moreover, aldosterone induces oxidative stress and decreased nitric oxide bioavailability,[2] leading to reduced vascular compliance, accentuated by aldosterone-mediated vascular fibrosis. Mineralocorticoid receptors (MRs)

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ACS = acute coronary syndrome(s)

AF = atrial fibrillation

AQ = aquaporin

CAMKII = calmodulin kinase II

EMB = endomyocardial biopsy

GRKs = G protein-coupled receptor kinases

HF = heart failure

HFrEF = HF and reduced ejection fraction

LV = left ventricular

LVEF = left ventricular ejection fraction

MI = myocardial infarction

miRNA = micro-RNA

MMP = matrix metalloproteinase

MR = mineralocorticoid receptor

MRA = mineralocorticoid receptor antagonist

NADPH = nicotinamide adenine dinucleotide phosphate

PA = primary aldosteronism

RAAS = renin-angiotensin-aldosterone system

ROS = reactive oxygen species

RV = right ventricular

SGLT2 = sodium-glucose cotransporter type 2

T2DM = type 2 diabetes mellitus

are present in coronary artery smooth muscle cells.[2] Hypersecretion of aldosterone is associated with vascular and cardiac remodeling, myocardial fibrosis, endothelial dysfunction with consequent increased risk of cardiovascular events and cardiovascular mortality.[3-5] Several trials have demonstrated the benefits of aldosterone inhibition.[6-9] Therefore, aldosterone inhibitors are recommended in the treatment of HF with reduced ejection fraction.[10-12]

In this review, we report the data from the literature regarding excessive aldosterone signaling in mediating cardiovascular disease, also highlighting the morphostructural and molecular pathways correlated to myocardial damage and the role of MRAs in clinical practice (**Central Illustration**).

HIGHLIGHTS

- High levels of aldosterone are associated with vascular and cardiac remodeling leading to increased risk of cardiovascular events and cardiovascular mortality.
- MRAs are well-established therapeutic agents in several clinical disease correlated to hyperactivation of RAAS such as arterial hypertension, acute coronary syndrome, heart failure, and pulmonary arterial hypertension.
- Nonsteroidal MRA such as finerenone reduces renal and cardiovascular disease progression in patients with heart failure and chronic kidney disease and diabetes mellitus.

ALDOSTERONE AND CARDIAC REMODELING

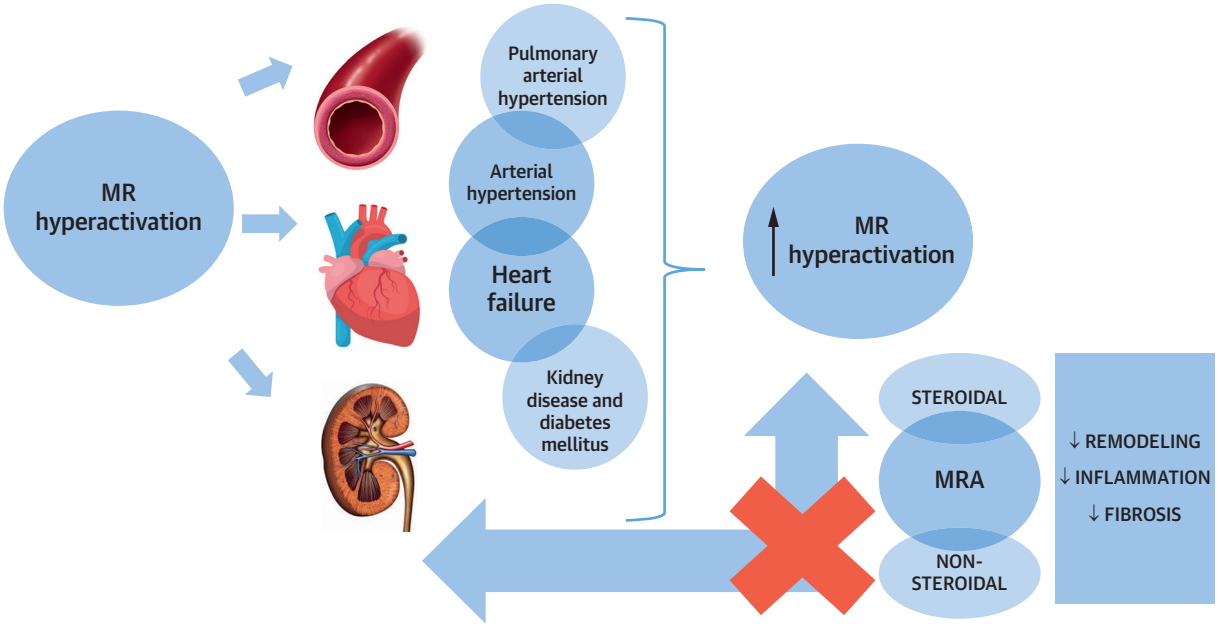
High levels of aldosterone can induce myocardial hypertrophy. In neonatal rat ventricular myocytes, aldosterone infusion can directly stimulate hypertrophy through the activation of the MR and related transcriptional factors.[13] Cesari et al[14] demonstrated that patients with primary and secondary hyperaldosteronism show high prevalence of left ventricular (LV) hypertrophy (61% and 39%, respectively) and diastolic dysfunction (35% and 36%, respectively) than healthy subjects; furthermore, in PA patients, there is a subclinical systolic dysfunction with peak systolic septal strain and midwall fractional shortening lower than in secondary aldosteronism patients (20% vs 23%; $P \leq 0.001$ and 15.9% vs 16.7%; $P = 0.001$, respectively). Chen et al[15] reported a major reduction of global longitudinal strain in the patients with PA than in patients with essential hypertension (-17.84 ± 2.36 vs -20.13 ± 2.32; $P < 0.001$). Global longitudinal strain was significantly correlated with serum potassium level ($r = -0.261$, $P = 0.033$), LV mass index ($r = 0.299$; $P = 0.014$) log-transformed plasma renin activity ($r = -0.302$; $P = 0.013$), log-transformed aldosterone/renin ratio ($r = 0.329$; $P = 0.007$), and log-transformed 24-hour urinary aldosterone levels ($r = 0.326$; $P = 0.007$). This suggests that high levels of aldosterone may cause subclinical systolic dysfunction.

In PA patients, myocardial fibrosis is increased as suggested by magnetic resonance imaging. Freel et al found a significant increase in the prevalence of noninfarct late gadolinium enhancement in PA patients (16/23, 70%) compared with patients with essential hypertension (5/39, 13%; $P < 0.0001$);[16] moreover, PA patients have significantly higher levels of superoxide and C-reactive protein levels. Regression of cardiac remodeling has been documented after adrenalectomy in surgically treated patients[17] as well as decrease in myocardial fibrosis.[18]

ALDOSTERONE AND MOLECULAR MECHANISMS OF MYOCARDIAL DAMAGE

Molecular mechanisms of myocardial dysfunction related to elevated aldosterone plasma concentration are not completely understood. Aldosterone can activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase with consequent reactive oxygen species (ROS) production that cause myocyte apoptosis and fibrosis.[19] Cannavo et al[20] have showed that pro-hypertrophic effects of aldosterone on the heart are mediated by MR-dependent mitochondrial G protein-coupled receptor kinases (GRKs). In particular, GRK2 moves into mitochondria promoting cell death and GRK5 translocates in the nucleus activating pro-hypertrophic gene transcriptions. In the study of Cannavo et al,[20] ventricular myocytes isolated from neonatal rats chronically exposed to high levels of aldosterone have GRK2 overexpression dependent on activation of both MR and angiotensin type 1 receptor (AT1R) and correlated to ROS generation, mitochondrial dysfunction, and apoptosis; in addition, activation of MR-AT1R signaling induces translocation of GRK5 in the nucleus with transcription of the myocyte enhancer factor-2 involved in the

CENTRAL ILLUSTRATION **MRAs Have Favorable Effects on the Kidney, Heart, and Vessels by Reducing Inflammation, Remodeling, and Fibrosis**



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High levels of aldosterone lead to hyperactivation of the MR with consequent negative effects on the kidney, heart, and vessels. Both steroid and nonsteroid MRAs block the vicious cycle, with beneficial effects in terms of reduced fibrosis, remodeling, and inflammation. Abbreviations as in Figure 2.

development of maladaptive hypertrophy. Pretreatment of cells with losartan or spironolactone inhibits GRK2 and GRK5 activation. Despite aldosterone overproduction, myocardial dysfunction is totally prevented in GRK2 knockout mice and attenuated in GRK5 knockout mice; furthermore, GRK5 knockout mice do not develop myocardial hypertrophy. So, GRKs are associated with MR-AT1R signaling responsible of cardiac dysfunction and may be possible target of HF therapy.

He et al[21] documented in mice that high levels of aldosterone after myocardial infarction (MI) induce activation of NADPH oxidase, production of ROS, and oxidative activation of Ca2+/calmodulin kinase II (CAMKII) in cardiomyocytes with overexpression of matrix metalloproteinase (MMP)-9 causing cardiac rupture. The same authors showed that inhibition of myocardial CAMKII in the post-MI mouse model correlates with reduced MMP9 activation and cardiac rupture. This suggests that CaMKII oxidative activation promotes cardiotoxic effects of aldosterone after MI.[21] Moreover, activation of CAMKII induces hyperphosphorylation of cardiac voltage-gated Na+ channels and ryanodine receptor 2 with proarrhythmic effects.[22]

The association between aldosterone and atherosclerosis is well established. Patients with PA have an increased risk of cardiovascular complications, coronary artery disease, and MI compared to patients with essential hypertension.[23] In a retrospective study of Mulatero et al, [24] patients with PA had a higher rate of cardiovascular and cerebrovascular events than patients with essential hypertension both at baseline (14.1% vs 8.4%; $P = 0.007$) and at follow-up (8.5% vs 4.3%; $P = 0.008$). Inoue et al[25] showed that elevated levels of aldosterone are correlated with increased risk of subclinical atherosclerosis (evaluated by coronary artery calcium score) and all-cause mortality in patients with suppressed plasma renin activity. McGraw et al[26] demonstrated in mice that aldosterone infusion increases atherosclerosis in regions of turbulent blood flow and induces plaque inflammation through activation of a pro-inflammatory placental growth factor promoting smooth muscle cell proliferation and monocyte chemotaxis. Proarrhythmic effects of aldosterone can be related to

activation of L-type Ca2+ channels cardiomyocytes and reduction of the activity of the rapidly activating delayed rectifier potassium current Ikr and transient outward K+ currents.[27] Moreover, aldosterone increases Ca2+ release from the sarcoplasmic reticulum through activation of ryanodine receptors leading to Ca2+ overload.[28] Detrimental effects of aldosterone on arrhythmias are reduced by MRAs. In the RALES trial, patients with HF treated with spironolactone showed 31% reduction in the risk of death from cardiac causes than placebo group ($P < 0.001$) due to both the reduction of advanced HF and sudden death by preventing myocardial fibrosis and remodeling.[7] Stambler et al[29] showed that eplerenone reduced ventricular electrical remodeling and tachyarrhythmia vulnerability in rapid ventricular pacing-induced HF dogs.

Micro-RNAs (miRNAs) are endogenous, small, noncoding RNAs that regulate the post-transcriptional gene expression. In recent years, miRNAs have achieved considerable interest and have been studied in the pathogenesis of cardiovascular disease.[30] MiR-21 upregulation has been documented in a rat experimental model of aldosterone-mediated cardiac dysfunction in PA[31] and in end-stage HF.[32,33] On the contrary, Syed et al[34] demonstrated the protective role of miR-21 in aldosterone-mediated cardiac injury. They treated miR-21 knockout mice with aldosterone and salt in drinking water for 2 or 8 weeks; miR-21 genetic ablation enhanced aldosterone/salt-mediated LV dysfunction and myocardial hypertrophy and fibrosis at histological examination with increase of inflammation markers. MiR-21 target is the Sprouty 2 gene that codifies for a negative regulator of the extracellular signal-regulated kinase intracellular signaling pathway that modulates proliferation, differentiation, motility, and survival;[35] miR-21 may be a protective role in aldosterone-mediated cardiac remodeling. These contradictory findings suggest that miR-21 may have multiple roles in the heart. While it has been shown that miR-21 promotes cardiac fibrosis, its upregulation also attenuates cardiac injury.[36] Further studies are needed to clarify its role in cardiac disease.

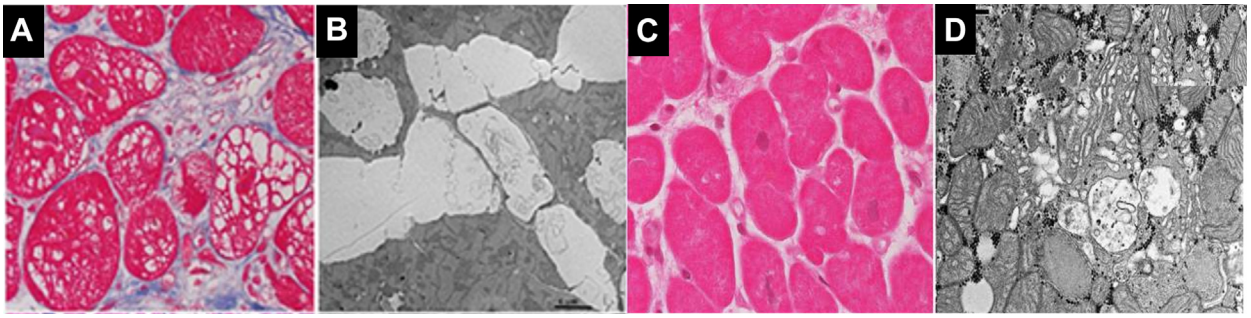
Mitochondrial dysfunction has been described in the pathogenesis of HF[37] and high levels of aldosterone induce ROS production with consequent oxidative stress and mitochondrial damage.[38] Tsai et al[39] evaluated the effects of aldosterone excess on cardiac mitochondrial function in a mouse model. In their study, aldosterone excess in mouse cardiomyocytes suppressed mitochondrial DNA, cytochrome-C oxidase subunit IV and superoxide dismutase 2 (that are 2 mitochondrial proteins involved in oxidative phosphorylation) and ATP production and induced ROS generation through MR and p38/mitogen-activated protein kinase[40] signaling pathways; this observation was confirmed in vivo after infusion of aldosterone in mice. Conversely, treatment with eplerenone and an antioxidant reduced these effects. Hung et al[41] also demonstrated that aldosterone excess reduced mitochondrial DNA and superoxide dismutase 2 protein expression through activation of NADPH oxidase 2 and generation of ROS first in vitro in mouse cardiomyocytes and then in vivo in a mouse model. Administration of eplerenone and N-acetylcysteine prevented cardiac mitochondrial damage in vivo.

ALDOSTERONE AND MORPHOSTRUCTURAL EVIDENCE OF MYOCARDIAL DAMAGE

The negative effects of high levels of aldosterone in mediating cardiovascular damage is recognized. However, molecular pathways underlying aldosterone-induced cardiac remodeling are poorly investigated. In a recent study,[42] histological and ultrastructural myocardial changes in 4 patients with PA-associated cardiomyopathy admitted because of worsening dyspnea have been reported. At histology, all patients showed prominent myocardial hypertrophy and fibrosis, with increased volume of cardiomyocytes for large intracellular vacuoles. At ultrastructural examination, vacuoles were filled of an electron-clear homogeneous content, suggesting ion and water accumulation. At western blot analysis, myocardial expression of MR and aquaporin (AQ)-1 showed a 2.8- and a 3-fold increase in protein expression compared to patients with essential hypertension. Aquaporins are a group of proteins with high-selective permeability for water, expressed in many organs and tissue; AQ-1 is highly expressed in the cytoplasm of cardiomyocytes, smooth muscle cells, and endothelial cells.[43] At control endomyocardial biopsy (EMB) after adrenalectomy, cardiomyocytes appeared smaller, intracellular vacuoles were no more detectable in the cytoplasm, mitochondria and lysosomes recovered their normal volume and the electron density, the extracellular spaces appeared reduced and myofibrillolysis was no more visible.

In a subsequent study,[44] the authors investigated the morphomolecular changes of cardiomyocytes in HF and in subsequent recovery of cardiac function. Twenty-six consecutive patients with HF and reduced ejection fraction (HFrEF) and normal coronaries and valves underwent EMB for evaluation of myocardial substrate. In all patients, histology showed an increased volume of cardiomyocytes,

FIGURE 1 Histologic and Ultrastructural Changes of Cardiomyocytes in a Patient With Heart Failure Caused by Myocarditis and After Cardiac Recovery by Immunosuppression



LV EMB showing vacuolar degeneration of myocytes (A) corresponding at electron microscopy to water accumulation in clear cisternae in the endoplasmic reticulum (B). Optical microscopy shows reduction of cardiomyocytes with disappearance of vacuoles and decrease of extracellular spaces following cardiac recovery (C), hypertrophic/hyperfunctioning Golgi apparatus with enlarged vesicles for water/ion extrusion at electron microscopy (D). Adapted from Frustaci et al.[44]
EMB = endomyocardial biopsy; LV = left ventricular.

containing large intracellular vacuoles and a typical cell swelling (Figure 1A). At electron microscopy, these large vacuoles contained an electron-clear material mostly corresponding to the enlarged cisternae of endoplasmic/sarcoplasmic reticulum (Figure 1B), Golgi apparatus, and other subcellular compartments; cytosol also appeared electron-clearly diluted with large regions of myofibrillolysis; mitochondria were uniformly swollen with disorganized cristae; nuclear changes included swelling of nucleoplasma, chromatolysis, nucleolar disorganization, and nuclear membrane alterations. At western blot analysis, myocardial expression of MR and AQ-1 showed, respectively, a 2.6- and a 2.7-fold increase in protein expression compared to controls. Patients with virus-negative inflammatory cardiomyopathy treated with immunosuppression according to tailored immunosuppression in virus-negative inflammatory cardiomyopathy protocol[45] showed at control EMB healed myocarditis with reduced volume of cardiomyocytes and disappearance of large vacuoles (Figure 1C). In particular, electron microscopy documented an advanced reorganization of the swollen altered myocardiocytes with a general recovery from swelling and vacuolar degeneration (Figure 1D), an almost normal columnar distribution among myofibrils of mitochondria, recovering from swelling and vesiculation; MR and AQ-1 that were both equally overexpressed in HF, normalized after cardiac recovery. HF is associated with secondary states of hyperaldosteronism leading to overactivation of myocyte MR and AQ-1 that independently from etiology of cardiac dysfunction determines intracellular water overloading. Water overloading causes cardiomyocyte swelling and negatively influences cardiomyocyte relaxation and contraction contributing to impairment of diastolic and systolic cardiac function. Conversely, cardiac recovery is accompanied by downregulation of hormonal receptors and normalization of cell structure and water composition. High levels of aldosterone induce myocardial hypertrophy through 2 different mechanisms: increase of sarcomere mass by a pro-hypertrophic effect mediated by a G protein-coupled receptor kinase 5 cytosolic signaling[20] and retention of ions and water regulated by aquaporins.

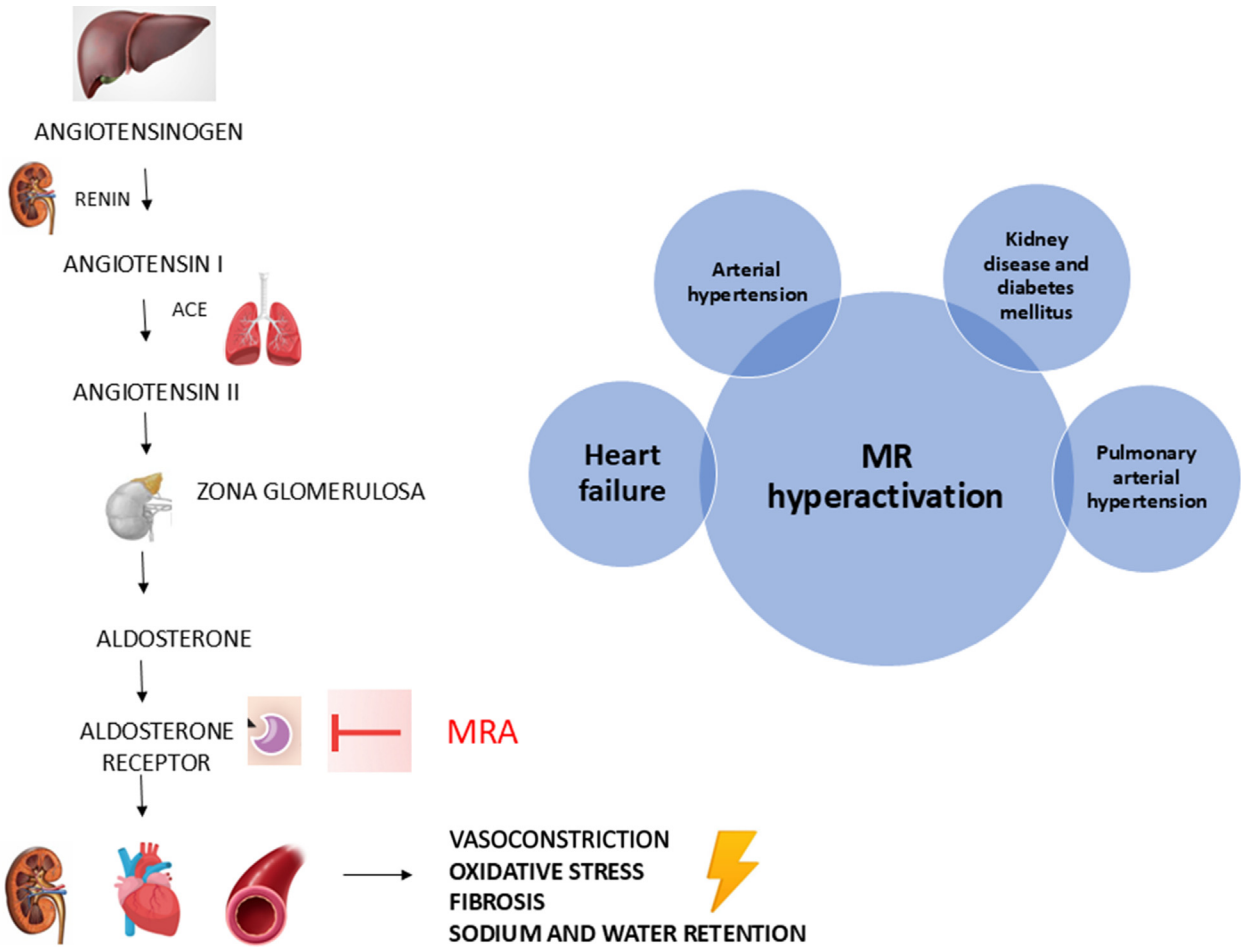
ROLE OF MRAs IN CLINICAL PRACTICE

In this section, the role of MRAs in clinical practice is discussed. Figure 2 schematically illustrates the RAAS and the effects on the heart, kidney, and vessels resulting from its hyperactivation and the diseases in which hyperactivation of the MR is implicated.

MRAs IN ARTERIAL HYPERTENSION

The hyperactivation of RAAS plays a key role in the pathogenesis of hypertension and cardiovascular and renal diseases. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARBs) are the pillars in the treatment of arterial hypertension as well as beta-blockers, diuretics, and calcium-channel blockers. According to the 2024 European Society of Cardiology (ESC) guidelines for the management of elevated blood pressure and hypertension,[46] 10% to 20% of patients show resistant hypertension that is characterized by the failure to reach optimal blood pressure values despite lifestyle

FIGURE 2 Schematic Representation of the RAA Axis and the Effects on the Heart, Kidney, and Vessels Resulting From Its Hyperactivation



On the right are represented the diseases in which hyperactivation of the MR is implicated. MR = mineralocorticoid receptor; MRA = MR antagonist.

measures and treatment with the maximum tolerated doses of multiple drugs, including a diuretic, a renin-angiotensin system blocker and a calcium-channel blocker and by the exclusion of causes of misdiagnosis (nonadherence to prescribed treatment or mismeasurement). Resistant hypertension is not a disease per se, but an indicator of patients at high risk for cardiovascular disease, in which secondary hypertension is also frequent.[46] Patients with resistant hypertension have higher risk of cardiovascular events (MI, stroke, end-stage renal disease, and death) compared with patients with hypertension and optimized blood pressure values.[47]

MRAs are indicated in this context. In a metanalysis[48] of 12 randomized clinical trials including 1,655 patients, spironolactone significantly reduced office and 24-hour ambulatory blood pressures values compared both to placebo and other drugs, confirming the result of PATHWAY-2[49] that had showed spironolactone was the most effective drug in resistant hypertension because of more significantly lowering systolic blood pressure values when compared to placebo (−8.7 mm Hg; 95% CI: −9.72 to −7.69 mm Hg; $P < 0.0001$), to simultaneous administration of doxazosin and bisoprolol (−4.26 mm Hg; 95% CI: −5.13 to −3.38; $P < 0.0001$), to doxazosin alone (−4.03 mm Hg; 95% CI: −5.04 to −3.02 mm Hg; $P < 0.0001$), and to bisoprolol alone (−4.48 mm Hg; 95% CI: 5.50-3.46 mm Hg; $P < 0.0001$). Main adverse events are hyperkalemia and gynecomastia in men and menstrual irregularities and postmenopausal bleeding in women (mainly due to blockade of steroid hormone receptors by aldosterone) that often require discontinuation of the drug.

MRAs IN ACUTE CORONARY SYNDROMES

High levels of aldosterone are associated with collagen deposition and interstitial fibrosis leading to vascular remodeling and cardiac hypertrophy. In patients with MI, early administration of MRAs has been shown to prevent cardiac remodeling.[50] Previous randomized controlled trials investigated the benefit of early MRAs administration in patients with MI. In the REMINDER (Early Eplerenone Treatment In Patients With Acute ST-Elevation Myocardial Infarction Without Heart Failure) trial,[51] the addition of eplerenone to standard therapy within 24 hours of the onset of symptoms in patients with ST-segment elevation myocardial infarction without evidence of HF reduced the primary composite endpoint of cardiovascular mortality, rehospitalization or extended initial hospital stay due to diagnosis of HF, sustained ventricular tachycardia or fibrillation, left ventricular ejection fraction (LVEF) ≤40%, or elevated B-type natriuretic peptide (BNP)/N-terminal pro-B-type natriuretic peptide after 1 month and a mean follow-up of 10.5 months; the effect was primarily driven by a decrease of BNP levels. The ALBATROSS (Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up) trial[52] failed to demonstrate the efficacy of early administration of a single intravenous bolus of 200 mg potassium canrenoate followed by oral 25 mg spironolactone once daily for 6 months in addition to standard therapy or standard therapy alone in acute MI irrespective of the presence of HF or LV dysfunction; the primary composite outcome of death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for implantable defibrillator, or new or worsening HF at 6-month follow-up, occurred in similar rate in both the treatment (11.8%) and control (12.2%) groups. The authors suggested that the benefit of MRA in acute coronary syndrome (ACS) patients was driven by HF. In the EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study),[8] the addition of 25 mg per day initially titrated to a maximum of 50 mg per day in patients with acute MI complicated by HF reduced cardiovascular morbidity (relative risk: 0.87; 95% CI: 0.79-0.95; $P = 0.002$) and mortality (relative risk: 0.83; 95% CI: 0.72-0.94; $P = 0.005$) with a safety profile. The 2023 ESC guidelines for the management of ACS recommend MRA in ACS patients with an LVEF ≤40% and HF.[53]

MRAs IN HF

Several trials have demonstrated the efficacy of MRAs administration in patients with HFrEF regardless of HF etiology. In the RALES (Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure) trial,[7] the addition of 25 mg of spironolactone daily to standard therapy in patients with HFrEF reduced by 35% the risk of both cardiovascular morbidity and death (the relative risk of death was 0.70; 95% CI: 0.60-0.82; $P < 0.001$. The relative risk of hospitalization was 0.65; 95% CI: 0.54-0.77; $P < 0.001$). The EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in HF)[9] demonstrated that addition of eplerenone (up to 50 mg daily) in patients with chronic systolic HF and mild symptoms reduced cardiovascular death and hospitalization for HF; the primary outcome was a composite of death from cardiovascular causes or hospitalization for HF and occurred in 18.3% in the eplerenone group vs 25.9% in the placebo group (HR: 0.63; 95% CI: 0.54-0.74; $P < 0.001$). The EPHESUS trial[8] showed the benefit of MRAs in ACS complicated by HF. In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With An Aldosterone Antagonist) trial[54] was evaluated the effects of spironolactone in patients with HF and preserved ejection fraction. The treatment with spironolactone did not reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest or hospitalization for HF; after a mean follow-up of 3.3 years, the primary outcome occurred in 18.6% of the spironolactone group vs 20.4% of the placebo group (HR: 0.89; 95% CI: 0.77-1.04; $P = 0.14$). However, there was a significant reduction in the hospitalization for HF (12.0% in the spironolactone group vs 14.2% in the placebo group; HR: 0.83; 95% CI: 0.69-0.99; $P = 0.04$). It should be noted that the incidence of hospitalization for HF was higher in the subgroup with elevated natriuretic peptide level within 60 days before than in the subgroup with previous hospitalization for HF.[55]

All these trials have demonstrated the benefit of aldosterone inhibition, so MRAs have been introduced in the American College of Cardiology/American Heart Association and ESC guidelines on HF with reduced ejection fraction.[10-12]

A recent study[56] on conventional therapy in patients with transthyretin cardiac amyloidosis has demonstrated that traditional HF drugs (ACE inhibitors and angiotensin receptor blockers) are often discontinued while MRAs are well tolerated and

TABLE 1 Main Characteristics of Steroidal (Spironolactone, Eplerenone) and Nonsteroidal (Finerenone) MRAs

	Steroidal MRA		Nonsteroidal MRA
	Spironolactone	Eplerenone	Finerenone
MR selectivity	+	++	+++
MR affinity	+++	+	+++
MR cofactor recruitment	Partial agonist	Partial agonist	Inverse agonist
Tissue distribution	Kidney > heart	Kidney > heart	Kidney = heart
Half-life	>20 h	4-6 h	2-3 h
Active metabolites	++	-	-
Sexual side effects	++	+	-
Hyperkalemia	++	++	+

MR = mineralocorticoid receptor; MRA = MR antagonist.

associated with reduced risk of mortality (HR: 0.82; 95% CI: 0.71-0.94; $P = 0.004$).

CARDIORENAL BENEFITS OF FINERENONE

Upregulation of MR plays a key role in the worsening of kidney disease and cardiovascular (CV) damage promoting inflammation and fibrosis, especially in patients with type 2 diabetes mellitus (T2DM). The traditional blockade of the RAAS with ACE inhibitors, ARBs,[57] and MRAs is not sufficient to arrest the renal and cardiovascular disease. Recently, the sodium-glucose cotransporter type 2 (SGLT2) inhibitors[58] demonstrated to reduce kidney disease progression and cardiovascular complication. However, despite treatment with renin-angiotensin system blockers and SGLT2 inhibitors, patients with chronic kidney disease (CKD) and T2DM have high risk of CKD progression and CV complication.[59] Finerenone is a new selective nonsteroidal MRA indicated in patients with CKD (stage 3 and 4 with albuminuria) and T2DM. Three pivotal phase III clinical trials have evaluated finerenone in patients with CKD and T2DM on top of maximally tolerated RAAS inhibitor treatment: FIDELIO-DKD[60] (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease), FIGARO-DKD[61] (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease), and the prespecified pooled analysis FIDELITY[62] (Combined FIDELIO-DKD and FIGARO-DKD Trial program analysis). In the FIDELIO-DKD,[60] finerenone reduced the primary composite endpoint of kidney failure, sustained decrease of at least 40% in the estimated glomerular filtration rate from baseline, or death from renal causes by 18% (HR: 0.82; 95% CI: 0.73-0.93; $P = 0.001$) and the secondary endpoint of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for HF by 14% (HR: 0.86; 95% CI: 0.75-0.99) during a median follow-up of 2.6 years. In the FIGARO-DKD trial,[61] the primary outcome of CV death, nonfatal MI, nonfatal stroke, or HF hospitalization, after a median follow-up of 3.4 years (HR: 0.87; 95% CI: 0.76-0.98; $P = 0.03$). The benefit was driven by lower incidence of HF hospitalization in the finerenone group compared to placebo (3.2% vs 4.4%; HR: 0.71; 95% CI: 0.56-0.90). In both the FIDELIO-DKD and FIGARO-DKD trials, the occurrence of hyperkalemia was higher in patients treated with finerenone vs placebo. The prespecified pooled analysis FIDELITY[62] included 13,026 patients from both the FIDELIO-DKD and FIGARO-DKD trials. After a median follow-up of 3 years, finerenone significantly reduced the composite CV outcome including CV death, nonfatal stroke, nonfatal MI, and HF hospitalizations (HR: 0.86; 95% CI: 0.78-0.95; $P = 0.0018$) as well as hospitalization for HF alone (HR: 0.78; 95% CI: 0.66-0.92; $P = 0.003$). Based on the results of these trials, finerenone is recommended in patients with HF and with T2DM and CKD by 2023 Focused Update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF.[12] Since patients with HFrEF were excluded from these trials, the FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) trial has been developed to investigate the effect of finerenone in terms of cardiovascular deaths and HF events in patients with HF with LVEF greater or equal to 40% irrespectively from the presence of CKD or diabetes.[63] Finerenone reduced by 18% HF events (RR: 0.82; 95% CI: 0.71-0.94; $P = 0.006$); however, the difference in cardiovascular mortality was not significant (8.1% vs 8.7% deaths in the finerenone and placebo groups, respectively).[64] The risk of hyperkalemia (defined as serum potassium levels >5.5 mmol/L) was higher in the finerenone group (14.3% vs 6.9%), but there were no deaths and few hospitalizations resulting from hyperkalemia. Moreover, SGLT2 inhibitors and finerenone may have synergistic effects. The CONFIDENCE study (NCT05254002)[65] is an ongoing trial investigasting the effects of a simultaneous administration of empagliflozin with finerenone in patients with CKD and T2D.

Compared to steroidal MRAs spironolactone and eplerenone, finerenone has demonstrated to reduce renal and CV disease progression with a lower incidence of hyperkaliemia. **Table 1** shows the main characteristics of steroidal and nonsteroidal MRAs.

MRAs IN ATRIAL FIBRILLATION

Arterial hypertension is a major risk for atrial fibrillation (AF). Hyperaldosteronism determines cardiac remodeling and electrophysiological alterations

promoting the development of AF.[66] PA patients have a 3.52-fold higher risk for AF than patients with hypertension as estimated in a large metanalysis including 31 studies.[67] Prevalence of PA is 42% in patients with AF[68]; therefore, it is suggested to screen AF population for PA. Surgical removal of adenoma in PA patients reduces incidence risk of AF.[69] MRAs have been demonstrated to reduce incidence of new-onset AF and recurrent AF in 2 large metanalysis.[70,71] As a consequence, the current European Society of Cardiology guidelines on AF recommend MRAs for upstream therapy in AF patients.[72]

MRAs IN PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling with thickening of the small pulmonary arteries, progressive elevation of pulmonary vascular resistance and PA pressure and it is associated with adverse outcomes. In patients with PAH, plasma aldosterone values are elevated suggesting that MR hyperactivation could be involved in pulmonary vascular remodeling.[73] MR activation in cardiomyocytes, endothelial cells, and vascular smooth muscle cells induces inflammation and adverse remodeling of the heart and vascular system. Animal and in vitro studies have demonstrated that various factors, such as hypoxia, endotelin-1, and angiotensin II, can directly stimulate the production of aldosterone at the level of the pulmonary vasculature.[74,75] MR activation in pulmonary vascular cells alter NO signaling by promoting ROS production and activation of profibrotic factors including tissue growth factor, collagen 1, MMP-2, and MMP-9.[76] In a rat PAH model, MRA administration after the onset of right ventricular (RV) failure showed beneficial effect on cardiac function at magnetic resonance imaging imaging in terms of improved cardiac index, RV end-diastolic volume/LV end-diastolic volume ratio, and degree of septal displacement.[77] Clinical studies suggest beneficial effects of MRAs in PAH. In a retrospective analysis of ARIES (Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study)-1 and ARIES-2 trials, combination of spironolactone and ambrisentan in PAH patients was associated with an improvement of 6-minute walking distance and BNP levels compared to ambrisentan alone.[78] The 2022 ESC/European Respiratory Society guidelines for the diagnosis and treatment of pulmonary hypertension[79] suggest restricting fluid intake and using diuretics (loop diuretics, thiazides, and MRAs) in PAH patients with RV-HF.

CONCLUSIONS

High levels of aldosterone are associated with vascular and cardiac remodeling, myocardial fibrosis, endothelial dysfunction with consequent increased risk of cardiovascular events and cardiovascular mortality. MRAs are well-established therapeutic agents in several clinical disease correlated to hyperactivation of RAAS such as arterial hypertension, ACS, HF, and PAH. Nonsteroidal MRA such as finerenone reduces renal and cardiovascular disease progression with a lower incidence of hyperkaliemia in patients with HF, CKD, and T2DM.

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