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Supplement Copy on

Mineralocorticoid Receptor Antagonist in Heart Failure: Evolution, Present Insights, and Future Directions

Contents

Guest Editorial

Sandeep Bansal*

Heart failure (HF) is now widely recognized as a heterogeneous syndrome, classified into three distinct phenotypes based on left ventricular ejection fraction (LVEF)—heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF). Among the therapeutic options available, mineralocorticoid receptor antagonists (MRAs) have emerged as a cornerstone in the management of HF across all phenotypes.[1] Their clinical utility is most extensively validated in HFrEF, where robust evidence supports their role in reducing cardiovascular mortality and hospitalizations.[2]

Evidence has shown that when MRAs are administered to all eligible HF patients, the magnitude of quantum clinical benefit, particularly in terms of reducing mortality rate, cardiovascular events, and hospitalizations, can rival that achieved through device-based therapies. Yet their real-world utilization, particularly in the Indian context, remains suboptimal.

This special supplement issue will focus on the long-standing and well-established role of MRAs in HFrEF, highlighting key trials and evolving insights that continue to shape contemporary HF management. It offers a timely, in-depth, evidence-based exploration of MRAs in current Indian medical practice. From tracing their pharmacological development and elucidating mechanisms of action to comparing safety profiles and highlighting the need for early initiation and careful dose titration, this collection of chapters seeks to provide a comprehensive perspective. Importantly, this supplement does not limit itself to the theoretical or scientific. It ventures into the realities of clinical practice, where therapeutic inertia, safety concerns, and limited awareness continue to hinder optimal use. The content shines a light on the tangible impact of delayed or inconsistent therapy and provides actionable strategies to overcome these barriers. By synthesizing robust evidence with clinical acumen, this supplement aims to close the gap between what we know and what we do. It serves not only as a clinical resource but as a call to action to move beyond hesitation and adopt MRA therapy with the consistency and confidence it merits.

Ultimately, this initiative is about more than improving prescription patterns; it is about elevating the standard of care for patients with HF across India. We hope the insights presented herein will empower clinicians, spark further research, and contribute to a future where evidence-based, patient-centered care becomes the norm.

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Preface

Jaideep Gogtay*

The concept of guideline-directed medical therapy (GDMT) witnessed a significant advancement in heart failure (HF) management in recent years. Mineralocorticoid receptor antagonists (MRAs), both spironolactone and eplerenone, are part of the four-pillar drugs strategy in HF, especially in heart failure with reduced ejection fraction (HFrEF).

Despite the availability of strong (level A) evidence for MRAs in HF, the overall uptake has been reported to be around 45% in India.[1–3] This special supplement aims to provide a comprehensive overview of the role of MRAs in contemporary medical practice. The chapters compiled in this supplement are designed to offer healthcare professionals an in-depth understanding of the historical evolution, mechanisms of action, comparative pharmacological properties, efficacy, and safety profiles of MRA therapy in HF.

The supplement also touches upon therapeutic inertia in adopting MRAs and addresses some of the reasons for therapeutic inertia. Through critical analysis and evidence-based discussions, this supplement shall be a valuable resource for clinicians, researchers, and students alike, fostering informed decision-making, optimal patient care, and contributing significantly to the ongoing discourse on MRA therapy.

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REVIEW ARTICLE

Mineralocorticoid Receptor Antagonists: An Overview of History and Evolution

BC Kalmath[1*], Mangesh Tiwaskar[2], Gattu R Kumar[3], Hemant Khemani[4], Amit Singh[5], Rajeev Kishore[6], Arvind Chouhan[7], Harikrishnan BL[8], Sarita Choudhary[9], Manish Goyal[10], Arun Pradhan[11], Febin Francis[12], Amarnath Sugumaran[13], Senthilnathan Mohanasundaram[14]

Abstract

Mineralocorticoid receptor antagonists (MRAs) have significantly evolved since the introduction of the first steroidal MRA, spironolactone, in the 1950s. Initially discovered for treating hypertension and heart failure (HF), the clinical applications of MRAs have been expanded to chronic kidney disease (CKD) and diabetic nephropathy. Steroidal MRAs, such as spironolactone and eplerenone, effectively suppress mineralocorticoid receptor activation but are associated with side effects like hyperkalemia and endocrine abnormalities. Current research aims to optimize MRAs further for broader therapeutic applications, including nondiabetic kidney and cardiovascular diseases, and to improve safety profiles. In this review, we reflect on the historical development, classification, evolution, major clinical trials, and future prospects of MRAs.

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Historical Background and Discovery

The mineralocorticoid receptor (MR) and its principal ligand, aldosterone, are primarily recognized as significant regulators of Na^+ reabsorption and K^+ excretion in the renal epithelial tissues. The sodium-to-potassium ratio in the urine was identified as a biomarker for mineralocorticoid activity and has been used in evaluating various steroid compounds similar in structure to progesterone, a weak partial MR agonist, to determine their efficacy as mineralocorticoid receptor antagonist (MRA).[1] Until the 1970s, deoxycorticosterone acetate (DOCA) synthesis was pivotal in understanding the physiology and pharmacology of MR agonists. During this period, progesterone was identified as a natural MRA, leading to the development of both parenteral and oral MRAs.[2] The history of MRAs started in the 1950s when Dr John Cella from Searle and his colleagues developed the 1st effective oral steroid-based MRA, spironolactone, in 1959, serving as the benchmark MR antagonist in clinical practice for nearly 6 decades.[1,3,4] The evolution of MRAs can be divided into 3 major waves: the initial phase, led by Searle Laboratories, which discovered spironolactone as the 1st MRA soon after aldosterone's purification; the second wave aimed at creating more specific steroidal MRAs, with companies such as Ciba-Geigy and Schering AG participating in this effort before the cloning of the MR; and the third wave, which emerged following the cloning of MR coding DNA (cDNA), leading to the discovery of nonsteroidal MRAs through the high-throughput screening of millions of compounds. The cloning of MR cDNA facilitated focused drug discovery, leading to the development of second-generation MRAs like eplerenone, which was launched in 2003.[3] Both spironolactone and eplerenone are used to treat chronic heart failure (CHF), resistant arterial hypertension, and hyperaldosteronism.[4] Despite the demonstrated effectiveness of MRAs in reducing morbidity and mortality in HF and resistant hypertension, their broader application has been limited by side effects, particularly hyperkalemia.[5,6] This limitation led to the development of novel nonsteroidal MRAs like finerenone and esaxerenone, which selectively inhibit the harmful effects of mineralocorticoid receptors while preserving their physiological roles.[3,7] The timeline for the discovery of MRAs is provided in Fig. 1.[2,8,9]

Classification of Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists are classified into steroidal and nonsteroidal MRAs, based on their chemical structure and mechanism of action.[2,3,10] The classification of MRAs and their pharmacological properties are provided in Table 1.[2,3,10]

Evolution of Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists have progressed significantly over the past 60 years, transitioning from steroidal to nonsteroidal MRAs and offering improved efficacy and safety profiles for treating cardiorenal diseases.[2,3] The 1st synthetic steroid-based MRA, spironolactone, entered clinical practice in the 1950s. In the years following, more specific steroidal MRAs were developed, with eplerenone being a notable example launched in 2003.[3] For many years, these compounds have been widely utilized in clinical settings, demonstrating their

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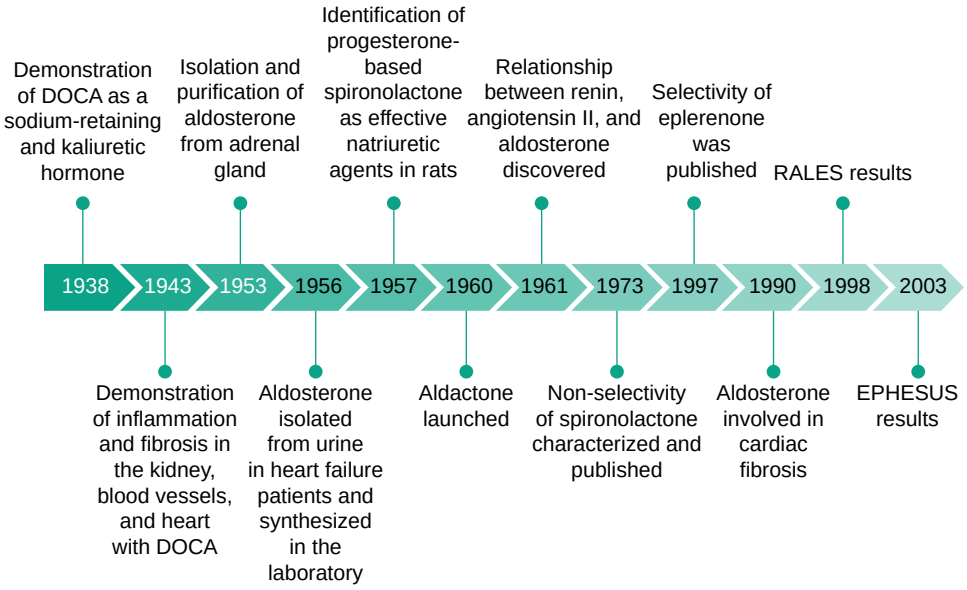

Fig. 1: Timeline for the discovery of MRAs

Table 1: Classification of MRAs and their pharmacological characteristics[2,3,10]

MRA type	*Drug*	*MR affinity*	*Tissue distribution*	*Potency*	*Primary use*
Steroidal MRA	Spironolactone	High	Higher in kidneys	High (antiandrogenic)	Hypertension, heart failure
Steroidal MRA	Eplerenone	Moderate	Higher in kidneys	Moderate (40× less potent than spironolactone)	Hypertension, heart failure
Nonsteroidal MRA	Finerenone	High	Equal in heart and kidney	Equivalent to spironolactone	Heart failure, CKD, diabetes
Nonsteroidal MRA	Esaxerenone	High	Equal in heart and kidney	Greater than spironolactone	Hypertension, heart failure
Nonsteroidal MRA	Apararenone	Moderate	–	Weaker than spironolactone	Hypertension, CKD
Nonsteroidal MRA	AZD9977	Moderate	–	Comparable to eplerenone	Hypertension, heart failure
Nonsteroidal MRA	KBP-5074	High	–	Greater than spironolactone	Hypertension, CKD

efficacy in lowering the incidence of morbidity and mortality associated with CHF.[11] Steroidal MRAs have reported risk of hyperkalemia and sex hormone-related side effects, which led to the search for nonsteroidal alternatives.[10,12] The development of nonsteroidal MRAs marked substantial progress in treating cardiorenal disease.[13] The timeline for the evolution of MRAs is provided in Figure 2.[2,8,9]

Table 2: Major trials on steroidal and nonsteroidal MRAs[15,16]

Trial	*Patient population*	*MRA used*
RALES	Severe heart failure	Spironolactone
TOPCAT	HFpEF	Spironolactone
EPHESUS	HF with systolic LV dysfunction	Eplerenone
EMPHASIS-HF	LV systolic dysfunction	Eplerenone
ESAX-HTN	Essential hypertension	Esaxerenone
ESAX-DN	T2D with microalbuminuria	Esaxerenone
FIDELIO-DKD	T2D with CKD	Finerenone
FIGARO-DKD	T2D with CKD	Finerenone
FINEARTS-HF	Patients with preserved ejection fraction >40%	Finerenone
BLOCK-CKD	Advanced CKD 3B/4	Ocedurenone

Major Trials of Mineralocorticoid Receptor Antagonists

MRAs have been studied widely in various clinical trials (Table 2), demonstrating their efficacy in treating cardiovascular and renal diseases. In a recent meta-analysis of pivotal MRA trials—RALES (spironolactone) and EMPHASIS-HF (eplerenone) in patients with heart failure with reduced ejection fraction (HFrEF), and TOPCAT (spironolactone) and FINEARTS-HF (finerenone) trials in patients with heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF)—steroidal MRAs reduce the risk of cardiovascular death or HF hospitalization in patients with HFrEF, while nonsteroidal MRAs lower this risk in patients with HFmrEF or HFpEF.[14] Similarly, the EPHESUS trial demonstrated a significant reduction of total cardiovascular mortality

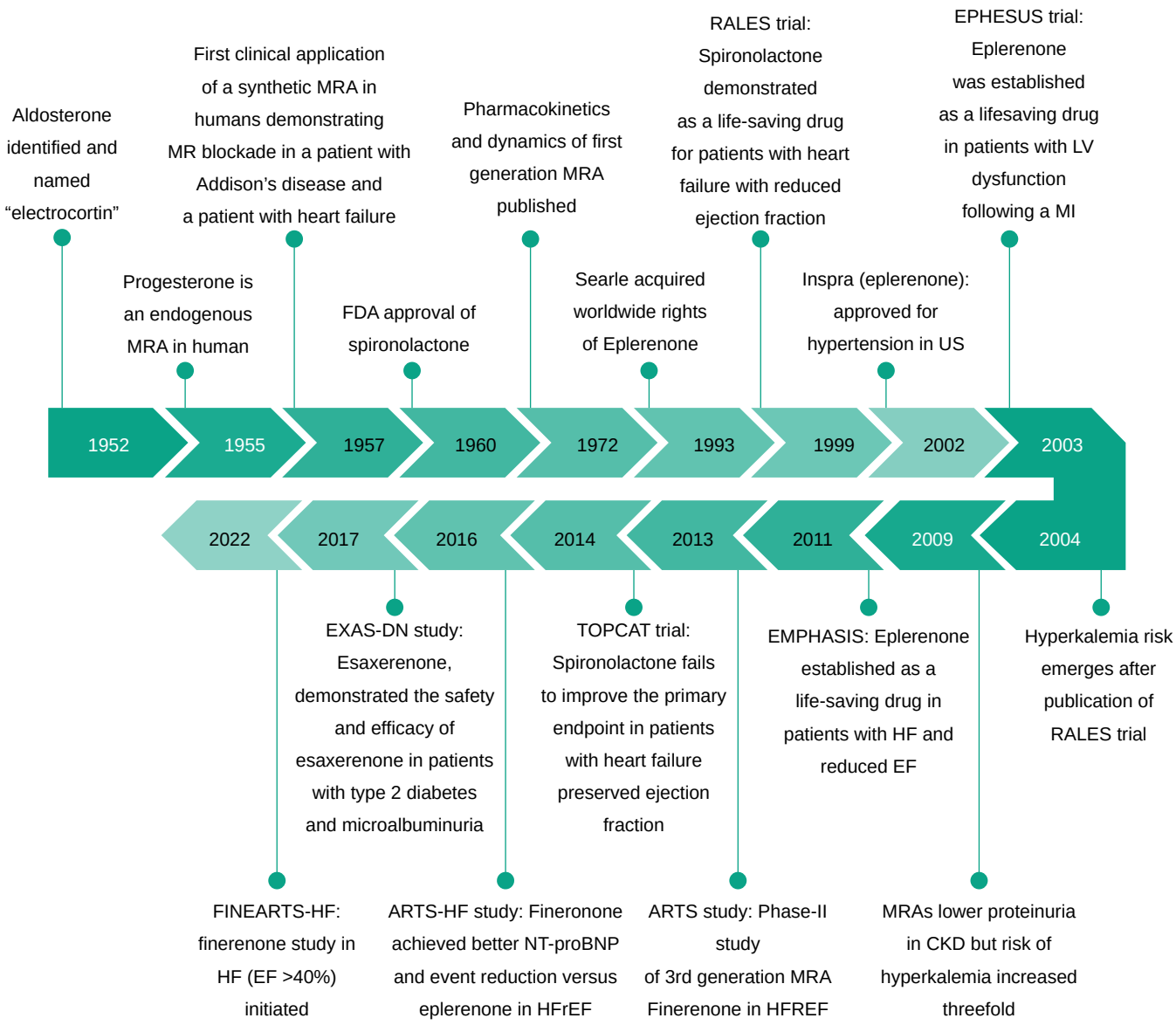

Fig. 2: Timeline for evolution of MRAs[15]

and hospitalization rates with eplerenone in patients with acute myocardial infarction complicated by left ventricular dysfunction.[2,12]

Conclusion

In conclusion, the evolution of MRAs from the initial introduction of spironolactone in the 1950s to the development of newer nonsteroidal MRAs represents significant progress in treating cardiovascular and renal diseases. While steroidal MRAs have effectively managed conditions such as heart failure and hypertension, issues like hyperkalemia and endocrine side effects have necessitated the search for better alternatives. As the therapeutic landscape continues evolving, ongoing research is essential to optimize MRAs for broader applications, including nondiabetic kidney and cardiovascular diseases. The continued refinement of these agents holds promise to improve patient outcomes and address unmet medical needs. Ultimately, the journey of MRAs underscores their growing importance in modern healthcare, and further innovation in this field will be instrumental in maximizing their clinical utility.

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REVIEW ARTICLE

The Mechanism of Action of Mineralocorticoid Receptor Antagonists in Heart Failure with Reduced Ejection Fraction

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Abstract

Mineralocorticoid receptor antagonists (MRAs) are one of the guideline-directed medical therapies for patients with heart failure and chronic kidney disease due to their anti-inflammatory and antifibrotic effects. MRAs regulate mineralocorticoid receptor (MR) signaling by inhibiting aldosterone binding to MR. MRAs are classified into steroidal and nonsteroidal categories based on their molecular interactions and clinical applications. Steroidal MRAs have been widely used in clinical practice and have demonstrated significant efficacy. Continuous advancements in the field have led to the development of nonsteroidal MRAs with greater receptor selectivity and better safety profile.

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Introduction

Mineralocorticoid receptor antagonists (MRAs), or aldosterone antagonists, have been a foundational therapy recommended as part of guideline-directed medical therapy (GDMT) for heart failure (HF).[1] MRAs are one of the renin-angiotensin-aldosterone system (RAAS) inhibitors widely used in clinical practice. RAAS is a neurohormonal homeostasis pathway and serves an important role in the regulation of renal sodium handling, osmolarity, fluid balance, renal blood flow, and blood pressure.[2] The RAAS pathway activation triggers the production of aldosterone, a mineralocorticoid hormone synthesized by the adrenal cortex, which acts on mineralocorticoid receptors (MR) in the distal and collecting tubules of the nephron, promoting sodium reabsorption and potassium excretion. Dysregulation and chronic activation of the RAAS can lead to chronic HF, arterial hypertension, endothelial dysfunction, and the progression of CKD.[3] MRAs inhibit the RAAS at its most distal part. Clinical trials have provided evidence that MRA treatment improves clinical outcomes in HF and CKD, leading to a class IA guideline recommendation.[4] This review focuses on the unique mechanism of action of MRAs and their role in the management of HF and CKD.

Role of Aldosterone in Heart Failure and Chronic Kidney Disease

Aldosterone is mediated by the activation of RAAS in response to low blood pressure, low cardiac output, hyperkalemia, and hyponatremia.[5,6] In renal epithelial cells, the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD2) converts cortisol into cortisone, which has low affinity for MR and therefore makes aldosterone its primary ligand.[7] In the distal nephron, MR activation promotes transcription and epithelial sodium channel (ENaC), which increases sodium and fluid retention and potassium excretion.[5,8] The MR is also expressed in multiple cell types in the heart, including cardiomyocytes, coronary endothelial and vascular smooth muscle cells, fibroblasts, and inflammatory cells.

The principal functional role of the MR in the kidney is to control sodium reabsorption and potassium secretion,[9] whereas its role in the heart is not fully understood but may include regulation of cardiomyocyte growth and cardiac electrophysiology.[10,11] However, overactivation of MR induces inflammation and fibrosis in organ tissues, contributing to CKD and cardiovascular disease (CVD) progression. Indeed, aldosterone-MR binding promotes cardiac and renal remodeling by inducing myocardial fibrosis and glomerular and tubular sclerosis. The relationship between falling glomerular filtration rate (GFR) and increasing aldosterone levels may predispose individuals with CKD to MR activation.[12] Moreover, aldosterone causes endothelial dysfunction and vasoconstriction, sympathetic activation, and oxidative stress (Fig. 1).[13]

Key evidence for the role of the MR in cardiac and renal disease comes from cell-specific overexpression and deletion studies showing that MR deletion in mouse models of myocardial infarction (MI) reduces ventricular remodeling, hypertrophy, and heart failure progression, whereas overexpression induces these changes.[14–17] Both MR and 11β-HSD2 expression are upregulated post-MI in response to high salt intake, in HF, and atrial fibrillation.[18,19] In renal disease, MR expression is increased 5-fold, especially in patients with high albuminuria.[20]

Direct deleterious effects of aldosterone in the heart include development of ventricular remodeling, myocardial hypertrophy, proarrhythmogenic effects, reduced coronary blood flow, myocardial injury, and myocardial ischemia.[21] The effects of aldosterone on the kidney include glomerulosclerosis, glomerular hypertrophy, proteinuria, renal injury, and reduced renal blood flow.[22] Aldosterone-induced inflammation, fibrosis, and oxidative stress are evident in several animal models of cardiac and renal disease.[18,23–25]

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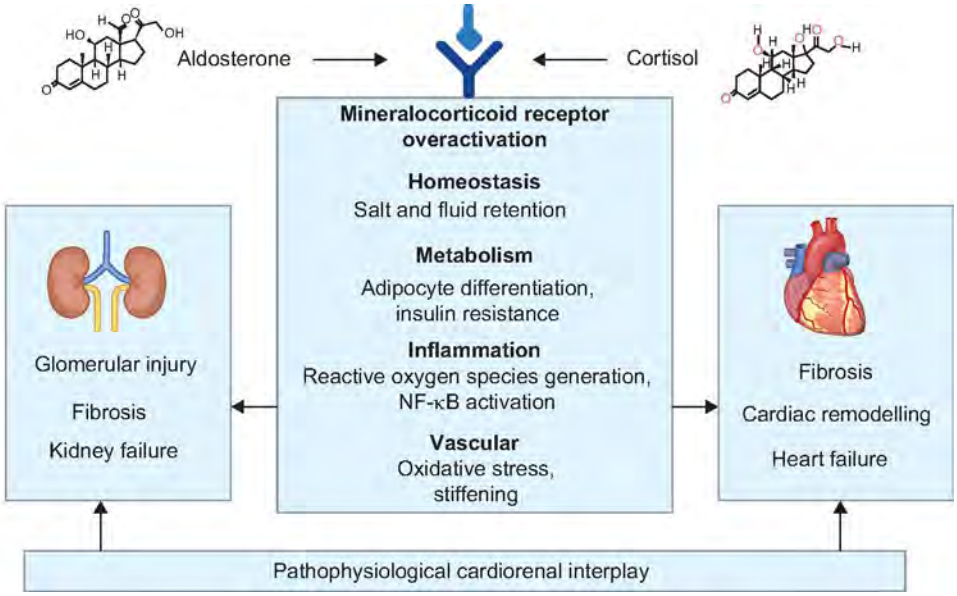

Fig. 1: Role of MR overactivation in cardiorenal disease[26]

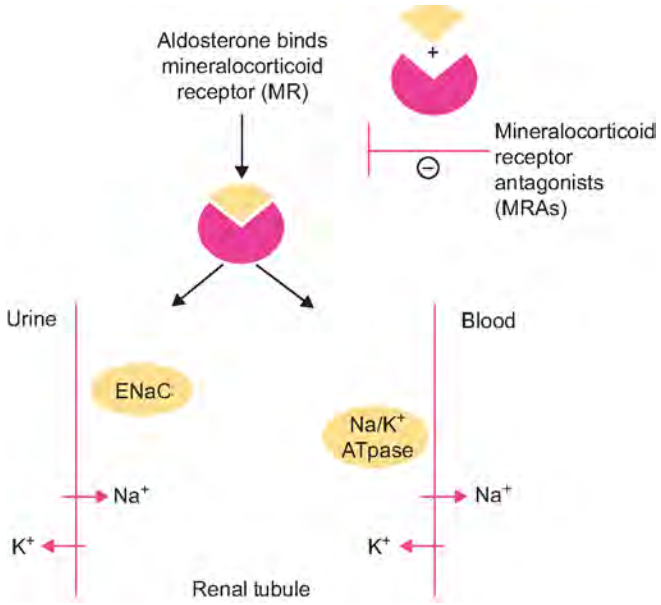

Fig. 2: Mechanism of action of MRAs[27]; ENaC, epithelial sodium channel; MRA, mineralocorticoid receptor antagonist

Mode of Action of Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists directly bind to and block MR, restricting aldosterone or 11-deoxycorticosterone from activating it, thereby reducing the degree of inflammation and remodeling in the heart (Fig. 2). MRAs are distinguished as steroidal and nonsteroidal based on their chemical class. The steroidal class includes spironolactone and eplerenone, whereas the nonsteroidal class includes finerenone.

MRAs suppress MR overactivation and reduce pro-inflammatory and profibrotic responses. Treatment with MRAs demonstrated decreased expression of mediators such as TGF-β, connective tissue growth factor, and matrix metalloproteinase-2, which are induced by aldosterone/salt high concentrations.[28] MRAs, such as eplerenone, effectively reduce renal inflammation, fibrosis, and oxidative stress markers. These effects have been endorsed in patients with chronic kidney disease and proteinuria, where MRAs improved renal function and reduced albuminuria.[29]

In addition to these effects, coronary and renal blood flow are also improved by MRAs by enhancing endothelial nitric oxide synthase activity, which has been observed to mitigate endothelial dysfunction.[30] They suppress aldosterone-mediated inflammation and fibrosis, which are key factors in cardiac remodeling and renal damage. These effects have been supported by trials like FIDELIO-DKD and FIGARO-DKD, which showed significant cardiorenal protection with finerenone.[31–33]

Clinical trials have shown that MRAs lower cardiovascular mortality and improve outcomes in heart failure with reduced ejection fraction (HFrEF). For example, spironolactone has demonstrated reductions in cardiac remodelling and fibrosis.[34,35] The beneficial effects of MRAs in preventing or attenuating cardiac and renal diseases are largely independent of systemic hemodynamic changes, suggesting they result from blocking the direct deleterious effects of MR activation in the heart and kidneys.

Steroidal Mineralocorticoid Receptor Antagonists: Spironolactone and Eplerenone

Spironolactone and eplerenone are MRAs that block the effects of aldosterone, but they differ in their mechanisms of action at a molecular level (Table 1). MRAs such as spironolactone and eplerenone block the MR and have been demonstrated in randomized clinical trials to provide substantial clinical benefit in the treatment of patients with HFrEF.[35–37]

Table 1: Comparison of spironolactone and eplerenone[35–37]

	Spironolactone	*Eplerenone*
Structure		
Formula	$C_{24}H_{32}O_4S$	$C_{24}H_{30}O_6$
Structural properties	Steroidal	Steroidal
Oral bioavailability	80–90%	69%
MR affinity	24.2 (high)	990 (low)
MR selectivity	Low	Medium
Plasma protein binding	88% (bound to albumin)[41]	49% (bound to a1-acid glycoprotein)[42]
Tissue distribution	Kidney >> heart, >6-fold	Kidney > heart, ≈ 3-fold
Half-life (hours)	>20	3–6
Hyperkalemia	High	Moderate
BP-lowering effect	Strong	Weak
Antifibrotic effect	Moderate	Moderate
Inhibitory concentration (IC50)		
Androgen receptor	77	21,200
Progesterone receptor	740	31,200
Metabolic pathways	Hepatic, deacetylation, and dethiolation	Hepatic, 6b-hydroxylation, and 3-keto reduction
Use	Heart failure, hypertension, nephrotic syndrome, ascites, antiandrogenic	Hypertension, heart failure, central serous retinopathy

Spironolactone

Spironolactone is a steroidal MRA that binds not only to MRs in the distal nephron. By inhibiting aldosterone, it prevents sodium reabsorption and potassium excretion, promoting diuresis. It also binds nonselectively to progesterone and androgen receptors, which often leads to progestogenic and antiandrogenic side effects, such as gynecomastia and sexual dysfunction.[38] The drug undergoes extensive metabolism, producing active metabolites with prolonged half-lives. While this contributes to a longer duration of action, it can also lead to drug accumulation and an increased risk of hyperkalemia. Spironolactone effectively blocks aldosterone's genomic effects, such as transcriptional regulation, over a period of hours to days. However, its ability to inhibit aldosterone's nongenomic effects, such as vasoconstriction, is less consistent compared to eplerenone.[39] Despite these drawbacks, spironolactone's prolonged metabolite activity allows for less frequent dosing, making it a convenient option for long-term therapy in certain conditions.

Eplerenone

Eplerenone is also a steroidal MRA that primarily binds to MRs and has lower interactions with progesterone and androgen receptors than spironolactone, thereby making it more selective for MRs than spironolactone. The minimal off-target binding to androgen and progesterone receptors significantly reduces hormonal side effects, such as gynecomastia and sexual dysfunction, commonly associated with nonselective agents like spironolactone.[38] Unlike spironolactone, eplerenone's metabolites are inactive, and it has a shorter half-life, resulting in faster drug clearance and a lower risk of hyperkalemia. Eplerenone effectively blocks aldosterone's genomic effects, similar to spironolactone, while demonstrating more consistent inhibition of aldosterone's nongenomic effects, such as vasoconstriction and improved vascular function.[40] Although its shorter half-life necessitates more frequent dosing, the reduced risk of side effects and improved safety profile make it a favorable option for patients requiring mineralocorticoid receptor antagonism.

Conclusion

Mineralocorticoid receptor antagonists have evolved into crucial therapeutic agents in the treatment of cardiovascular and renal diseases. By blocking the overactivation of MRs mediated by aldosterone, these agents reduce significant pathological processes such as inflammation, fibrosis, and oxidative stress, leading to better outcomes in conditions such as CKD and HF. Spironolactone and eplerenone present unique therapeutic advantages and safety considerations, allowing for tailored treatment strategies.

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REVIEW ARTICLE

The Pharmacological Properties and Safety Profile of Mineralocorticoid Receptor Antagonists in Heart Failure with Reduced Ejection Fraction

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Abstract

Among the established mineralocorticoid receptor antagonists (MRAs), spironolactone and eplerenone have demonstrated significant clinical utility in managing conditions such as chronic heart failure, resistant hypertension, and hyperaldosteronism. Spironolactone, the first steroidal MRA, is known for its broad receptor affinity, contributing to both therapeutic benefits and endocrine-related side effects. Eplerenone, a more selective agent, offers improved tolerability with reduced hormonal adverse effects. This review explores the pharmacokinetic and pharmacodynamic profiles of these agents, highlighting their mechanisms of action, receptor-binding characteristics, and clinical implications. The safety considerations associated with long-term use, particularly hyperkalemia and renal function impairment, are also discussed to provide a comprehensive understanding of their therapeutic roles.

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Introduction

Mineralocorticoid receptor antagonists (MRAs) are previously recognized as potassium-sparing diuretics, as they inhibit the action of aldosterone in renal epithelial tissues. Beyond their diuretic effects, MRAs also offer significant benefits in the management of heart failure, largely through their actions in nonepithelial tissues.[1] MRAs are part of the broader class of renin–angiotensin–aldosterone system (RAAS) inhibitors, commonly used in clinical practice.[2]

Spironolactone and eplerenone have long been established in this category. Spironolactone was the first steroidal MRA to be launched >60 years ago. About 40 years later, eplerenone, a newer drug from the same class, showed clinical efficacy with fewer adverse effects owing to its higher mineralocorticoid receptor specificity. Both drugs are often recommended for diseases like chronic heart failure, treatment-resistant hypertension, and hyperaldosteronism. Though both drugs have their advantages, their use is still restricted because of negative consequences, including reduced renal function and high potassium levels, particularly with long-term use.[1]

Mechanism of Action and Receptor Binding of Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists inhibit aldosterone from binding to MRs, particularly in the kidney, heart, and vasculature.

Spironolactone is a nonselective antagonist MRA that has affinity for both androgen and progesterone receptors. Aldosterone in the RAAS works on receptors in the distal tubules and collecting ducts of the nephron, therefore facilitating sodium reabsorption, potassium excretion, vascular stiffness, and structural remodeling. Aldosterone additionally leads to remodeling, fibrosis, and heart inflammation. Spironolactone exerts its therapeutic benefits by competitively inhibiting aldosterone at its receptor sites, preventing aldosterone-induced water and salt retention and promoting potassium conservation.[3] Spironolactone reduces sebum production in the treatment of acne vulgaris by inhibiting the binding of dihydrotestosterone to androgen receptors, decreasing sebocyte growth.[4]

Eplerenone is a selective MRA that inhibits aldosterone binding to mineralocorticoid receptors, mainly in renal distal tubules and collecting ducts. This effect reduces potassium excretion and encourages natriuresis. Unlike spironolactone, eplerenone has a 100–1,000-fold lower binding affinity for androgen and progesterone receptors, subsequently minimizing the possibility of endocrine-related side effects. Along with its renal actions, eplerenone reduces aldosterone-mediated vascular inflammation, myocardial fibrosis, and remodeling, therefore supporting its cardioprotective qualities in the control of heart failure and hypertension.[5]

Pharmacological Properties of Mineralocorticoid Receptor Antagonists

Spironolactone

Pharmacokinetic Properties

Spironolactone is rapidly and extensively metabolized in the liver to produce a number of active metabolites, such as canrenone [which has a terminal half-life of 16.5 hours (ranges around 16–24 hours in healthy individuals)], 7α-thiomethylspirolactone (13.8 hours), and 6β-hydroxy-7α-thiomethylspirolactone (15 hours).[6–8] It is quickly absorbed when taken orally, and the peak plasma concentration (T_{max}) usually occurs 1–2 hours after the dosage.[9]

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Table 1: Pharmacokinetic differences between spironolactone and eplerenone[6–8,13–22]

	Spironolactone	*Eplerenone*
Structural features	Based on progesterone; g-lactone ring as substituent at C-17	17α-thoacetyl group of spironolactone replaced with carbomethoxy group; 9,11-epoxide added to lactone ring
Oral bioavailability	73%	69%
Plasma protein binding (SmPC)	88% (bound to albumin)	49% (bound to a1-acid glycoprotein)
Peak plasma level (hour)	1–2	1.5–2
Mean half-life (hour)	13–17	3–5
Metabolic pathways	Hepatic, deacetylation, and dethiolation	Hepatic, 6b-hydroxylation and 3-keto reduction
Active metabolites	7α-thiomethylspironolactone, 6β-hydroxy-7α-thiomethylspirolactone, and canrenone	None
T1/2 (h), active metabolites	16.5 (canrenone); 13.8 (7a-thiomethylspironolactone); 15.0 (6β-hydroxy-7a-thiomethyl spironolactone)	NA
CYP enzyme inducer	Yes	No
Tissue distribution (based on quantitative whole-body autoradiography in rodents)	Renal concentration sixfold higher than cardiac concentration	Renal concentration threefold higher than cardiac concentration

The absolute bioavailability was determined to be 73%,[9] and it may be improved by taking it with meals, which increases absorption and reduces first-pass metabolism.[10]

Additionally, it has been shown that individuals with cirrhotic ascites had a longer terminal half-life of spironolactone (canrenone up to 57.8 hours in cirrhotic patients) due to slower clearance rates in patients with hepatic impairments.[6]

Pharmacodynamic Properties

Spironolactone efficiently promotes diuresis and lowers blood pressure by blocking aldosterone receptors in the distal renal tubules, which reduces the reabsorption of sodium and water while conserving potassium. Adding spironolactone to regular antihypertensive medication lowers systolic/diastolic blood pressure in resistant hypertension by an average of 22/10 mm Hg.[11]

Its structural similarity to progesterone accounts for its mild antiandrogenic effect, which inhibits androgen receptors and explains its usage in hyperandrogenic conditions such as hirsutism and acne.[12]

Eplerenone

Pharmacokinetic Properties

The absorption of eplerenone is rapid upon oral administration, often reaching peak plasma levels (C_{max}) in 1.5–2 hours, and it has an oral bioavailability of approximately 69% following administration.[5,13] Plasma protein binding is 33–60% with no significant preferential segregation into red blood cells.[13]

Eplerenone undergoes significant CYP3A4 metabolism, mostly by hydroxylation, to produce inactive metabolites. The majority of its pharmacological action is attributed to its active form.[14,15] It has a short elimination half-life (about 3–5 hours), and about 66% of the dose is removed as metabolites, mostly in urine and feces.[16] Renal function has minimal impact on eplerenone clearance, since <2% is excreted unchanged, and no major dosage modifications are often required depending on pharmacokinetics.[17]

Pharmacodynamic Properties

Eplerenone lowers blood pressure and prevents cardiac remodeling by inhibiting aldosterone-mediated sodium retention, potassium excretion, and water reabsorption in epithelial tissues such as the kidney, heart, and vasculature *via* competitive binding to mineralocorticoid receptors.[18,19]

In individuals with heart failure and left ventricular dysfunction after myocardial infarction, eplerenone increases survival and lowers morbidity.[20] Its specific effect lowers vascular damage and aldosterone-driven heart fibrosis. In addition, it effectively decreases systolic and diastolic blood pressure and minimizes end-organ damage.[21]

Eplerenone significantly lowers the incidence of gynecomastia, which is often seen with spironolactone, because of its selectivity for mineralocorticoid receptors, indicating that it interacts minimally with androgen and progesterone receptors.[22]

The comparison of MRAs (spironolactone and eplerenone) is outlined in Table 1.[6–8,13–22]

Safety Profile of Mineralocorticoid Receptor Antagonists

Spironolactone

Spironolactone's nonselective receptor binding causes a comparatively high frequency of side effects, including hyperkalemia, gynecomastia, and other sex hormone-related disorders such as irregular menstruation.[23] In a long-term prospective study of 274 patients with resistant hypertension receiving spironolactone, Vaclavik et al. found that 26.3% of patients experienced adverse events, which resulted in 84.7% of the patients discontinuing the study. Gynecomastia (30.6%), hyperkalemia (30.6%), and symptomatic hypotension (26.4%) were the most frequently reported side effects.[24]

A randomized controlled trial conducted in patients with symptomatic heart failure and a left ventricular ejection fraction ≥45% receiving spironolactone vs placebo reported no significant reduction in deaths or hospitalization rates. In addition, the patient group receiving spironolactone was observed to be associated with elevated creatinine serum levels and increased rates of hyperkalemia (18.7 vs 9.1%). However, it was effective in reducing hypokalemia.[25]

Although spironolactone continues to be a significant therapeutic option for the management of resistant hypertension and heart failure,[3] these safety constraints limit its potential for broader clinical application.

Eplerenone

Eplerenone improves receptor selectivity over spironolactone, therefore lowering the incidence of sex hormone-related negative effects. Though these concerns are often less than those seen with spironolactone, it still increases hyperkalemia and possible renal function decline.[5] A safety review by Lainscak et al. compared both MRAs (spironolactone and eplerenone) and reported a decreased frequency of gynecomastia and menstrual disorders with eplerenone; however, hyperkalemia remained a significant safety concern.[26]

Conclusion

Spironolactone and eplerenone remain cornerstone therapies in the management of cardiovascular and renal disorders due to their ability to counteract aldosterone-mediated pathophysiology. While both

agents effectively promote natriuresis and reduce blood pressure, their pharmacological differences, particularly in receptor selectivity, significantly influence their safety profiles. Spironolactone's broader receptor activity accounts for its antiandrogenic effects, which can be beneficial in certain endocrine conditions but may lead to undesirable side effects. Eplerenone's enhanced specificity offers a more favorable safety profile, especially in patients at risk for hormonal disturbances. Despite their proven efficacy, careful patient selection and monitoring are essential to mitigate risks such as hyperkalemia and renal impairment. Continued research and clinical vigilance are necessary to optimize the use of these MRAs in diverse patient populations.

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REVIEW ARTICLE

Mineralocorticoid Receptor Antagonists: The Pillar Drug in Heart Failure

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Abstract

Mineralocorticoid receptor antagonists (MRAs) have emerged as a cornerstone in the pharmacological management of heart failure (HF), particularly in patients with reduced ejection fraction (HFrEF). By antagonizing the effects of aldosterone, MRAs mitigate fluid retention, myocardial fibrosis, and neurohormonal activation, key contributors to HF progression. Steroidal MRAs, including spironolactone and eplerenone, have demonstrated significant clinical efficacy in landmark trials such as Randomized Aldactone Evaluation Study (RALES), Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), showing reductions in mortality, hospitalizations, and symptomatic burden. Spironolactone, though potent, is associated with hormonal side effects due to its nonselective receptor binding, while eplerenone offers improved tolerability through greater receptor specificity. This review explores the pharmacological mechanisms, clinical trial evidence, and safety considerations of steroidal MRAs, underscoring their indispensable role in comprehensive HF therapy.

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Introduction

Mineralocorticoid receptor antagonists (MRAs) are one of the fundamental components of guideline-directed medical therapy (GDMT) in heart failure (HF). MRAs are particularly useful in heart failure with reduced ejection fraction (HFrEF). However, they have some role in heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF).[1]

Mineralocorticoid receptor antagonists can be steroidal (e.g., spironolactone and eplerenone) or nonsteroidal (e.g., finerenone and esaxerenone).[1] Though steroidal and nonsteroidal MRAs have similar modes of action, they have subtle differences in their distribution in the human body, mechanism of mineralocorticoid receptor (MR) binding, and subsequent gene expression.[1] Steroidal MRAs are distributed more in the kidneys than in the heart, while the nonsteroidal MRA is distributed equally in the kidneys and the heart.[1]

Pathophysiology of Heart Failure

Heart failure is a complex syndrome characterized by neurohormonal activation, fluid overload, ventricular remodeling, and progressive myocardial dysfunction.[2,3]

Role of Aldosterone

Low cardiac output in HF leads to renal hypoperfusion. This stimulates the overactivation of the renin-angiotensin-aldosterone system (RAAS), which leads to excessive aldosterone secretion. Aldosterone is a neurohormone that worsens HF progression through its action on MR present in the kidney, heart, central nervous system (CNS), and blood vessels (Fig. 1).[3–6]

Although aldosterone mainly causes electrolyte and fluid dysbalance in HF *via* its action on distal nephrons in the kidneys, it also disrupts broader cardiovascular (CV) function through its receptors on vascular smooth muscle cells, endothelial cells, and cardiomyocytes (Fig. 1).[3–6]

Role of Mineralocorticoid Antagonism

Mineralocorticoid receptor antagonists counteract the harmful effects of aldosterone in HF by blocking the MR.[3–6] MRAs decrease preload and edema and relieve symptoms by reducing sodium and water retention. MRAs improve cardiac function by preventing myocardial fibrosis and remodeling (left ventricular hypertrophy and diastolic dysfunction are reduced). By decreasing inflammation and oxidative stress, MRAs improve endothelial dysfunction, reduce arrhythmia, and prevent sudden cardiac deaths. MRAs improve hemodynamics by lowering blood pressure and afterload. Together, MRAs provide symptomatic relief and prevent disease progression in HF.[3–6]

Landmark Clinical Trials of MRA in Heart Failure

The outcomes of spironolactone from the landmark Randomized Aldactone Evaluation Study (RALES) (HFrEF) and Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial (HFpEF); that of eplerenone from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) (HFrEF) and Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) (post-MI HF) studies, and that of finerenone from the finerenone trial to investigate efficacy and safety superior to placebo in patients with heart failure (FINEARTS-HF) trial (HFpEF and HFmrEF) will be covered. The details of these trials are presented in Table 1.

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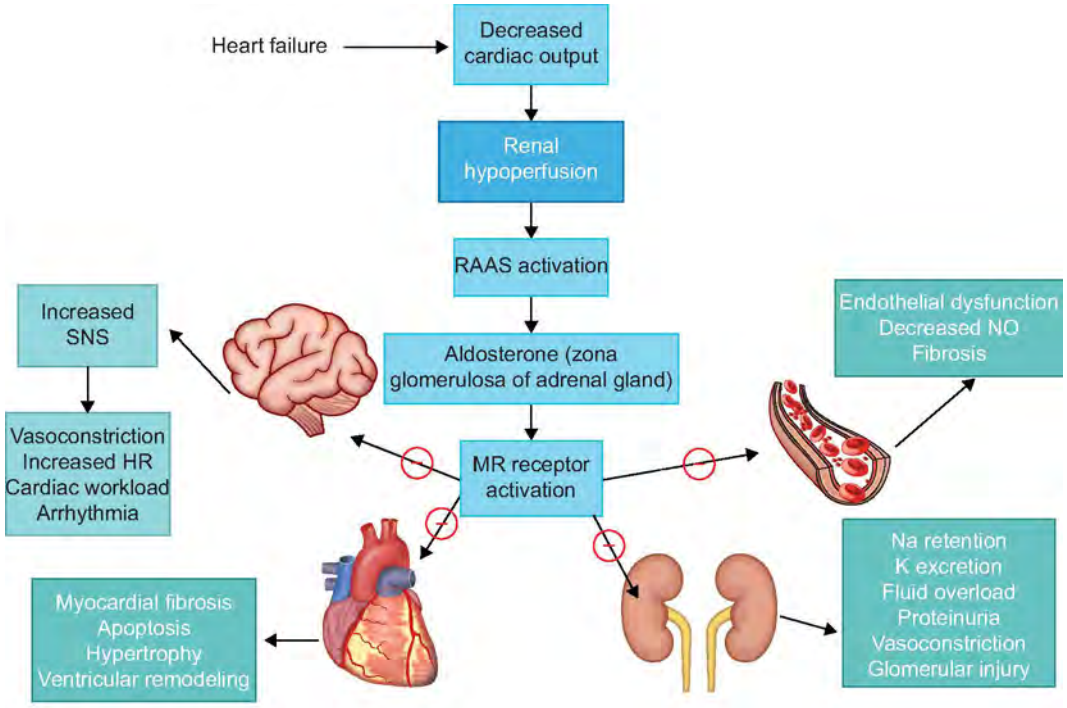

Fig. 1: Role of aldosterone in the pathophysiology of HF and mineralocorticoid antagonism; CKD, chronic kidney disease, HR, heart rate, MR, mineralocorticoid receptor, NO, nitric oxide, RAAS, renin-angiotensin-aldosterone system, SNS, sympathetic nervous system

Mineralocorticoid Receptor Antagonist in HFrEF

The "Randomized Aldactone Evaluation Study" was the pivotal trial that established the role of spironolactone in severe HFrEF in 1999 (Table 1).[5] The trial was discontinued early because an interim analysis established the efficacy of spironolactone after a mean follow-up of 24 months. Patients in the spironolactone group had a lower risk of death from progressive HF and sudden death from cardiac causes, which translated into a significantly lower risk of death compared to patients on placebo.[5] Further, the New York Heart Association (NYHA) symptom class improved in 41% of patients in the spironolactone group, remained the same in 21%, and worsened in 38%, with significant between-group differences ($p < 0.001$).[5] There was minimal risk of severe hyperkalemia with proper monitoring.[5]

Published in 2003, the "Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study" demonstrated the benefits of eplerenone in postmyocardial infarction HF in patients with left ventricular ejection fraction (LVEF) ≤40% (Table 1).[7] The rate of severe hyperkalemia was 5.5% in the eplerenone group vs 3.9% in the placebo group ($p = 0.002$).[7] Patients with serious hyperkalemia were more likely to have a baseline serum potassium concentration >5.5 mmol/L or calculated creatinine clearance <70 mL/minute than patients without serious hyperkalemia.[7] The EPHESUS trial supported the use of eplerenone as a life-saving therapy in post-MI HF.

In 2011, the "Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure" study expanded the role of eplerenone in patients with mild HFrEF (Table 1).[10] Eplerenone was well tolerated, with a modest increase in hyperkalemia risk.[8]

These trials established the role of MRA across the spectrum of HFrEF of different severity and etiology.[11] Early use of MRA in HFrEF reduced the risk of all-cause mortality, CV mortality, and hospitalizations for HF.[2,5,7,8]

Mineralocorticoid Receptor Antagonist in HFmrEF and HFpEF

The "Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist" trial (Table 1) is the largest randomized trial evaluating the role of spironolactone in HFpEF.[9] The trial showed no significant reduction in the primary outcome of the composite of CV death, HF hospitalization, or aborted cardiac arrest ($p = 0.14$). Despite no mortality benefit, spironolactone reduced HF hospitalizations by 17% ($p = 0.04$). Patients had a higher risk of hyperkalemia and worsening of renal function. Regional variations were seen, with patients from the United States, Canada, Argentina, and Brazil showing significant benefits, while those from Russia and Georgia did not experience significant benefits from spironolactone.[12]

Though steroidal MRA trials in HFmrEF are lacking, retrospective analysis of the TOPCAT trial showed a reduction in hospitalizations for HF and CV mortality in patients with LVEF ≥45 and <55%.[12,13]

The FINEARTS-HF trial (Table 1) showed that nonsteroidal MRA, finerenone, lowered the risk of the composite of worsening HF (WHF) and CV death than placebo in HFmrEF and HFpEF patients.[14] The risk of WHF was much lower in patients enrolled within 7 days of WHF [risk ratio (RR): 0.74] or between 7 days and 3 months of enrollment (RR: 0.79) than in patients who had WHF >3 months before enrollment or who never had WHF episode (RR: 0.99).[14]

Guideline Recommendations for MRA in Heart Failure

International and Indian guidelines strongly recommend the early use of MRA in HFrEF (Table 2).[12,13,15,16] In patients with HFrEF and NYHA II–IV symptoms, the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines state that MRA therapy provides high economic value.[11] The economic value of MRA in HFrEF has been demonstrated through the economic evaluation of RALES[17] and EPHESUS[18] trials. In the EPHESUS trial, the use of an MRA in patients taking both

Table 1: Landmark trials of MRAs in HF

Trial	*Population*	*Intervention*	*Primary outcome*	*Key results*
HFrEF				
RALES (1999)[5] (*N* = 1663)	Severe HFrEF (NYHA III–IV, LVEF ≤35%) from 15 countries; being treated with an ACEi and a loop diuretic*	Spironolactone 25 mg daily vs placebo	All-cause mortality	• 35% reduction in hospitalization for WHF ($p < 0.001$) • 32% reduction in the combined risk of death from cardiac causes and hospitalizations due to cardiac causes ($p < 0.001$) • 31% reduction in risk of death from cardiac causes ($p < 0.001$) • 30% reduction in risk of all-cause mortality ($p < 0.001$) • Risk of hospitalizations from cardiac causes ($p < 0.001$)
EPHESUS (2003)[7] (*N* = 6,632)	Postacute MI (within 3–14 days); LVEF ≤40%; HF symptoms; patients with diabetes even without HF symptoms; being treated with standard HF therapy (ACEi, ARB, diuretics, and beta-blockers)	Eplerenone 25 mg >> titrated to 50 mg daily vs placebo	All-cause mortality; CV death or HF hospitalization	• 23% fewer episodes of hospitalization for HF ($p = 0.002$) • 21% reduction in risk of sudden cardiac death ($p = 0.03$) • 17% reduction in CV mortality ($p = 0.005$) • 15% reduction in all-cause mortality ($p = 0.008$) • 15% reduction in risk of hospitalization for HF ($p = 0.03$) • 13% reduction in CV death or hospitalization for HF ($p = 0.002$) • 8% reduction in death from any cause or hospitalization for HF ($p = 0.02$)
EMPHASIS-HF (2011)[8] (*N* = 2,737)	Mild HFrEF; age ≥55 years; NYHA II, LVEF ≤30% (or >30–35% + QRS of >130 ms on ECG); being treated with standard HF therapy (ACEi, ARB, and beta-blockers)	Eplerenone 25 mg >> titrated to 50 mg daily vs placebo	CV death or HF hospitalization	• 42% reduction in HF hospitalizations ($p <0.001$) • 37% reduction in CV death or HF hospitalization ($p <0.001$) • 24% reduction in all-cause mortality ($p = 0.008$)
HFpEF and HFmrEF				
TOPCAT (2014)[9] (*N* = 3,445)	HFpEF (LVEF ≥45%); age ≥50 years; NYHA II–IV symptoms; either a history of HF hospitalization or elevated natriuretic peptide levels	Spironolactone 15–45 mg daily vs placebo	Composite of CV death, HF hospitalization, or aborted cardiac arrest	• No significant reduction in primary outcome ($p = 0.14$) • 17% reduction in HF hospitalizations ($p = 0.04$)
FINEARTS-HF (2024)[10]	HFmrEF or HFpEF (LVEF ≥40%)	Finerenone at a maximum dose of 20 mg or 40 mg once daily vs placebo	Composite of WHF** and CV death	Primary outcome (WHF and CV death): • Finerenone group: occurred in 624 of 3,003 patients • Placebo group: occurred in 719 of 2,998 patients in the placebo group (rate ratio, 0.84 ($p = 0.007$)WHF: 842 in the finerenone group and 1,024 in the placebo group [rate ratio, 0.82 ($p = 0.006$)] CV death (% of patients who died): 8.1 and 8.7%, (hazard ratio, 0.93)

*Digitalis and vasodilators permitted; potassium-sparing diuretics not permitted; **First or recurrent unplanned hospitalization or urgent visit for HF; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CV, cardiovascular; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; WHF, worsening heart failure

angiotensin-converting enzyme (ACE) inhibitors and beta-blockers was cost-effective in increasing years of life.[19]

However, based on the inconclusive results of the TOPCAT trial, MRAs carry a weak (class IIb or IIc) guideline recommendation in select HFmrEF and HFpEF patients (Table 2).[11,13,15] The 2023 ACC guidelines recommend adding MRA to female patients

Table 2: Guideline recommendations for MRA in HF

Indian guideline	*Defining HF patient type*	*Recommendation*	
CSI position statement[16]	HFrEF; LVEF <35%, NYHA II–IV symptoms on optimal tolerated doses of an ACEi (or ARB) and beta-blocker	Add either spironolactone or eplerenone	
	Postacute MI HF, LVEF <40%, symptoms of HF or history of diabetes mellitus	Add either spironolactone or eplerenone	
International guidelines	*Defining HF patient type*	*Class*	*Level*
2022 AHA/ACC/HFSA[11]	HFrEF (LVEF ≤35%); NYHA II–IV symptoms Only if eGFR >30 mL/minute/1.73 m^2 and K^+ <5.0 mmol/L	I	A
		To reduce morbidity and mortality	
2021 ESC[13]	HFrEF (LVEF ≤40%) NYHA II–IV symptoms	I	A
		To reduce risk of HF hospitalization and death	
2022 AHA/ACC/HFSA[11]	HFmrEF (LVEF: 41–49%)	II	B
2022 AHA/ACC/HFSA[11]	Symptomatic HFpEF (LVEF ≥50%) Select pts: LVEF ≥45%, elevated BNP level or HF admission within 1 year, eGFR >30 mL/minute/1.73 m^2, creatinine <2.5 mg/dL, and potassium <5.0 mEq/L	II	B
2021 ESC[13]	HFmrEF (LVEF: 41–49%)	II	C
		May be considered to reduce the risk of HF hospitalizations and death	
2021 ESC[13]	HFpEF (LVEF ≥50%) Select patient population: elevated natriuretic peptides and no severe renal impairment or hyperkalemia	No specific recommendations. May be considered based on subgroup analysis of TOPCAT trial	
2023 ESC focused update[15]	HF patients with type 2 diabetes and chronic kidney disease	I	A
		Finerenone recommended to reduce risk of hospitalization for HF	

ACEi, angiotensin-converting enzyme inhibitors; AHA/ACC/HFSA, American Heart Association/American College of Cardiology/Heart Failure Society of America; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association

receiving sodium-glucose cotransporter 2 inhibitors (SGLT2i) irrespective of LVEF.[20] For male patients, the ACC guidelines recommend adding MRA to SGLT2i if fluid retention and LVEF is <55–60%.[20]

Close monitoring of diuretic dosage, potassium levels, and renal function is necessary to reduce the risk of hyperkalemia and renal deterioration for all patients receiving MRA.[11,16,21]

Conclusion

The role of MRA in HF is supported by strong pathophysiological rationale and robust clinical evidence demonstrating significant mortality benefits and reduction in hospitalizations due to HF. While spironolactone offers potent therapeutic effects, its broader receptor activity necessitates careful monitoring for hormonal side effects. Eplerenone, with its greater receptor selectivity, provides a safer alternative in many patients. Thus, MRAs like spironolactone and eplerenone carry strong class IA recommendations as a GDMT in HFrEF. Careful renal and potassium monitoring allows for the safe and effective use of MRA in managing a broad spectrum of HFrEF severity with NYHA II–IV symptoms. Steroidal MRAs may have some place in the management of HFmrEF and HFpEF (class IIb/IIc recommendations). Nonsteroidal MRAs are proving to be effective in reducing HF hospitalizations and mortality in HFmrEF and HFpEF. Together, MRAs form a critical pillar of HF therapy, reinforcing the importance of individualized treatment strategies and vigilant monitoring to optimize outcomes.

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REVIEW ARTICLE

Real-world Utilization of Mineralocorticoid Receptor Antagonists in India and the Benefits of GDMT in Heart Failure

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Abstract

Early initiation of guideline-directed medical therapies (GDMTs) in heart failure (HF) and their uptitration to the target dose confer mortality benefits and reduce the risk of readmission. GDMT nonuse is a significant predictor of mortality in HF patients. However, GDMT prescription and adherence in India are low. Of the GDMTs, mineralocorticoid receptor antagonists (MRAs) are the least prescribed. There are multilevel gaps [healthcare professional (HCP)-related, patient-related] in the adoption and use of MRAs in HF. There is an unmet need to identify these gaps and formulate mitigation strategies to close them. This can improve or enhance GDMT adoption in the HF treatment paradigm.

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Introduction

The four main guideline-directed medical therapies (GDMTs) in heart failure (HF) consist of angiotensin receptor blocker (ARB) and neprilysin inhibitor (ARNI) or angiotensin-converting enzyme inhibitors (ACEi), beta blockers (BB), mineralocorticoid receptor antagonist (MRA), and sodium glucose cotransporter 2 inhibitor (SGLT2i).[1] These four GDMTs are used in HF with reduced ejection fraction (HFrEF) and select cases of HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF).[2–10]

Impact of GDMT on Heart Failure Outcomes

The optimal and correct use of GDMT can significantly reduce all-cause mortality, cardiovascular mortality, and hospitalization for HF.[11–16]

Using an India-specific HF (ISHF checklist) to optimize GDMT use in HF could significantly improve HF outcomes.[17] Over a 12-month period, there was a significant reduction in rehospitalizations for HF in the ISHF group by 49.6 vs 30.4% in the no ISHF group ($p \leq 0.001$).[17] The ISHF group also showed improvement in left ventricular ejection fraction (LVEF) from 29.1 ± 7.6 at the study start to 36.4 ± 8.1 at 12 months ($p = 0.05$). The ISHF group also had a lower mortality risk, with a hazard ratio (HR) of 0.57.[17]

The Trivandrum Heart Failure Registry (THFR) data showed that HF patients who did not receive GDMTs experienced significantly higher mortality compared to those who received GDMT (HR 0.28; $p < 0.001$).[18] Another Indian study showed that using renin–angiotensin–aldosterone system (RAAS) blockers was associated with a 40% lower mortality risk (HR = 0.60).[19] MRA use was associated with a 25% reduction in 5-year mortality risk (HR = 0.75; $p < 0.001$).[20] Not using a GDMT in HF was a significant predictor of 90-day, 6-month, 12-month, and 5-year mortality.[19–21]

These benefits are seen with early initiation of the GDMTs and uptitration to the target dose.[22,23] However, despite these benefits, Indian HF registry data show low uptake of GDMTs for HF in India (Box 1). Further, at 1 year, GDMTs are uptitrated to their optimal dose in only 15–27% of patients.[22]

The Current Landscape of Mineralocorticoid Receptor Antagonist Usage

Of the GDMTs, MRAs are generally the most underutilized GDMT for HF, globally and in India.[11,12,15–21,26–29]

The Trend in MRA Prescriptions (Global and India)

Mineralocorticoid receptor antagonists are the least prescribed GDMT globally (39–43% of patients).[12] A recent global study noted an increasing trend in the prescriptions of BBs, RAAS inhibitors, and MRAs over the last decade. Of the GDMT prescriptions, 80% were BB, 82% were RAAS, and 41% were MRAs. Despite the study noting an increasing trend in GDMT prescriptions, those for MRAs remained low. Another study in low- and middle-income countries (LMICs) noted no significant increase in MRA prescriptions over time (1990–2010) (by 0.67%; $p = 0.38$).[29]

Interestingly, a recent Indian study noted that BBs and MRAs were used in the majority of HF patients with NYHA class I–IV and LVEF ≤50%. In this study, 83% of patients were on BBs, 74% on MRA, and 35 and 34% on ARNI and SGLT2i, respectively.[1] However, this high MRA prescription rate should be viewed cautiously, as this was a small single-center

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study of 100 patients, of which only 7% received all four components of GDMT.

Mineralocorticoid Receptor Antagonist Use by Income Strata

Mineralocorticoid receptor antagonist adoption differed according to low- vs high-income countries and was higher in LMIC (50%) (range: 43–58%) than in high-income countries (39%) (37–41%).[12] The regional differences in MRA use were also evident in the 16 LMICs across Africa, Asia, and the Middle East included in the INTER-CHF study between 2012 and 2014. MRAs were prescribed in 48% of patients.[27]

Mineralocorticoid Receptor Antagonist Use by Inpatient/Outpatient/Acute and Nonacute Settings

Mineralocorticoid receptor antagonist adoption in the HF treatment paradigm is poor in both outpatient and hospital settings.[11,19,30–32] In a US study of >12,000 hospitalized HF patients who were candidates for an MRA as GDMT, only one-third received an MRA prescription at discharge.[11] A study conducted in LMICs and including HF patients managed in acute and nonacute settings noted that while 57% of patients were treated with ACEi, 34% received BB, and 32% received MRAs. This shows lower adoption of MRAs in LMICs.[29] The MRA use was slightly higher in nonacute settings globally (42%) (range: 39–44%) than in acute settings (40%) (range: 33–47%).[12]

Mineralocorticoid Receptor Antagonist Use in Asia

Among the LMICs, MRA use was lowest in Asia and much higher in Africa, the Middle East, and South America.[26] The ASIAN-HF study (2012–2015) with 5,276 HFrEF patients from 11 countries noted that BBs were prescribed in 79% of patients, RAS inhibitors in 77%, and MRAs in 58%. MRAs were the least prescribed GDMT.[28] The guideline-recommended MRA dose was achieved in only 29% of patients on MRAs.[28]

Mineralocorticoid Receptor Antagonist Use in India

Indian data shows low adoption of MRAs in the HF treatment paradigm. The Indian THFR data showed that 43.73% of the patients received MRAs at admission and 48.89% at discharge.[18] In patients with left ventricular systolic dysfunction, 47.09% received an aldosterone receptor antagonist (ARA) at admission and 49.66% at discharge.[18] A recent Indian study reported ARA use at discharge in 38.6% of patients.[21]

Indian data from the Cardiology Society of India-Kerala Acute Heart Failure Registry (CSI-KHFR) showed that inhospital prescription of an aldosterone inhibitor after stabilization was significantly higher in patients admitted with HFrEF (49.9%) compared to those admitted with HFmrEF (37.2%) and the HFpEF group (34.1%) ($p < 0.001$).[19] The aldosterone inhibitor prescription at discharge was also significantly higher for HFrEF (49.4%) as compared to HFmrEF (37.2%) and HFpEF (32.6%) ($p < 0.001$).[19]

Strategies to Enhance Mineralocorticoid Receptor Antagonist Adoption

Despite its many advantages, the adoption and use of GDMT in HF, including MRA, is low.[12] One Indian study reported that only 27.9% of hospitalized patients with HF receive GDMT.[19] Further, in another Indian study, all four GDMTs were prescribed in only 7% of HF patients.[1]

Hence, identifying the multilevel gaps in the adoption and use of GDMT in HF, including MRA, is an unmet need; mitigation strategies to close these gaps can improve or enhance GDMT adoption in the HF treatment paradigm.[12]

Addressing System-level Gaps in GDMT/MRA Adoption in India

Only three GDMT classes—RAAS inhibitors (excluding ARNI), BBs, and MRAs (spironolactone only)—are mentioned in the current Indian National List of Essential Medicines (NLEM) 2022.[33–36] However, these are not categorized correctly as GDMTs for HF.[34,35] Hence, it is important to correctly list all the GDMTs of HF as GDMTs for HF, including their correct use according to LVEF.[35] Further, even if the GDMTs are included correctly in the NLEM list, they are often unavailable to LMIC patients, including India.[12,35] Therefore, information on including GDMTs in essential medicine lists should be correctly disseminated across all healthcare levels (primary, secondary, and tertiary).

Other problems with GDMT adoption and use in HF include a lack of awareness and affordability and a lack of adequate medical specialists and programs to treat HF in overcrowded settings.[19,35] This should be tackled through government policies, including availability of low-cost, certified generic medications through various government schemes, HF awareness initiatives, patient education programs, and overcoming barriers at healthcare professional (HCP) and patient levels through adequate

Box 1: GDMT use in HF registry from India

Registry	*Proportion of patients receiving GDMT*
THFR	25.4% with HFrEF[20]
National Heart Failure Registry (NHFR)	47.5% of patients with HFrEF[24]
CSI-KHFR	28% of patients with HFrEF[19]
Indian College of Cardiology National Heart Failure Registry (ICCNHFR)	24.99% of patients with acute decompensated HF received GDMT at discharge and 23.72% adhered to the prescription until 30 days[25]

GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction

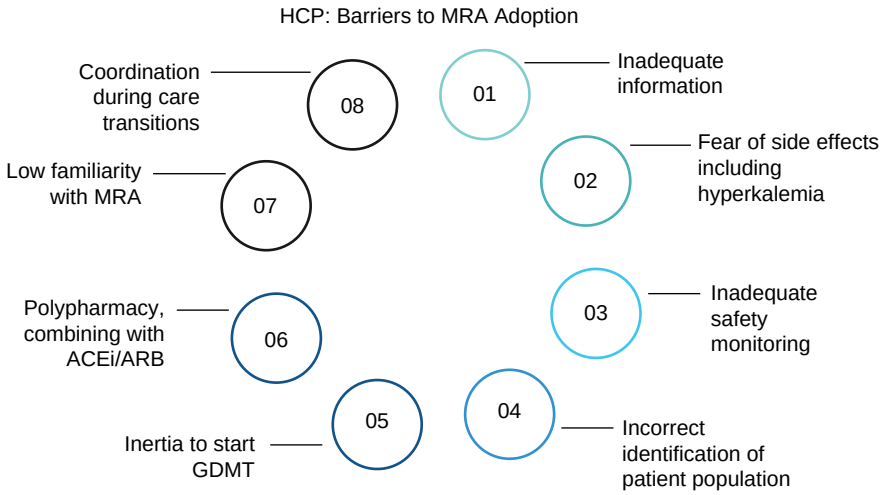

Fig. 1: HCP level barriers to MRA adoption in HF treatment paradigm

staffing and quality-of-care improvement initiatives.[12,19,35,37]

Barriers of Mineralocorticoid Receptor Antagonist Adoption and Mitigation Strategies

A focus-group analysis identified eight barriers to MRA adoption under three categories—system-related, HCP-related, and patient-related.[11] These barriers were also reported in India.[1,19] Identifying these barriers to MRA adoption in India can help develop mitigation strategies. The system-related barriers included patient overload and limited HCP resources, leading to time constraints and lack of systematic follow-up procedures.[11] Patient nonadherence was mainly due to concerns about polypharmacy and adverse effects. The HCP-level barriers are shown in Figure 1.[1,11,19,38–40]

The barriers to MRA adoption by HCPs and patients can form the basis for formulating factually correct messages to be disseminated to all primary, secondary, and tertiary healthcare professionals. These messages are covered in Table 1 and could be disseminated to better penetrate the messages.

With changing times, electronic health records, algorithmic initiation and titration of GDMTs, remote monitoring, patient

Table 1: Correct messaging to HCPS about MRAs to increase adoption

	Correct messaging
Addressing HCP-related barriers	
MOA	Explaining the mechanism of action of MRA in HF can help us better understand its importance. MRAs attenuate the effect of aldosterone and RAAS activation,[1] and prevent disease progression and provide symptom relief in HF[13,40–42] MRAs decrease preload and edema; symptom relief by reducing sodium and water retention MRAs improve hemodynamics by lowering blood pressure and afterload Improved cardiac function: MRAs prevent myocardial fibrosis and remodeling (left ventricular hypertrophy and diastolic dysfunction are reduced) MRAs decrease inflammation and oxidative stress; improve endothelial dysfunction, reduce arrhythmia, and prevent sudden cardiac deaths
Inertia to follow guideline recommendations	Reinforcing guideline recommendations during continued medical education programs, medical representative visits, and other opportunities through easy-to-read ready reckoners.[2–10] MRA carry class 1A recommendation from ESC and AHA/ACC/HFSA for HFrEF and AHA/ACC/HFSA[3] and ESC[9] class II recommendation for HFmrEF and HFpEF. MRA also carry class IA recommendation from ESC[43] for HF patients with type 2 diabetes and chronic kidney disease
Identifying the correct patient population	Guidelines recommend MRAs for NYHA class II to IV HF patients. MRA can be used in HF patients with diabetes, CKD etc. as long as eGFR >30 mL/min/1.73 m^2, creatinine <2.5 mg/dL, and potassium <5.0 mEq/L[2–10]
Role in HFrEF	Guidelines[2–7,9,10] recommend MRAs in HFrEF for lowering cardiovascular and all-cause mortality in HF and reducing the risk of hospitalizations across all spectrums of HFrEF
Role in HFmrEF and HFpEF	MRAs is guideline-recommended for reducing hospitalizations for HF and cardiovascular mortality in patients with LVEF ≥45 and <55% in HpmrEF and HFpEF[8,9,44]
Addressing fear for hyperkalemia	Various surveys show that HCPs fear hyperkalemia.[40,45,46] Correct communication to mitigate this fear: Clinical evidence shows no significant differences in serum potassium levels with MRA use or nonuse[40,45] Further, MRAs continue to confer benefits in HF even at higher potassium levels and can be continued with dose adjustment[40,45] The risk of hyperkalemia is higher in patients with lower eGFR (<25 mL/minute/1.73 m^2).[47] Hence, MRAs should be avoided in these patients The fear of hyperkalemia can be mitigated by careful monitoring of electrolytes and creatinine at the recommended frequency[40]: • 1 and 4 weeks after starting/increasing MRA dose • 8th and 12th week after starting/increasing MRA dose • At 6, 9, and 12 months • Every 4 months thereafter
Addressing fear for coprescription with RAASi	The 2024 KDIGO guidelines recommend that an MRA can be combined with the maximum tolerated dose of a RAASi in patients with normal serum potassium and renal dysfunction if the eGFR >25 mL/minute per 1.73 m^2 and albuminuria >30 mg/gm [>3 mg/mmol][47]
Addressing patient-related barriers	
Addressing adherence	Scheduling regular follow-up visits and addressing HF medication adherence at all follow-up visits. Educating HCPs to educate patients about not stopping HF treatment without consulting their treating doctors. HCPs can communicate the detrimental effects of worsening HF and the increasing cost of treatment due to hospitalizations if HF medications are stopped[39,48]

AHA/ACC/HFSA, American Heart Association/American College of Cardiology/Heart Failure Society of America; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HCP, healthcare professional; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KDIGO, Kidney Disease: Improving Global Outcomes; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; RAASi, renin–angiotensin–aldosterone system inhibitor

empowerment, and multidisciplinary virtual care can be used to implement GDMT in HF patients.[49] However, these novel strategies are difficult to implement across India and are still far from reality.

Conclusion

The GDMTs in HF are lifesaving and reduce the risk of readmission. However, their uptake in patient care and adherence is low in India. MRAs are the least prescribed among GDMTs. Correct communications with HCPs on the advantages of early initiation of GDMTs, including MRA, are essential to improve awareness and allay the fears. The barriers to MRA adoption in India can be mitigated by spreading awareness of the importance of MRAs as a pillar drug in HF management.

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REVIEW ARTICLE

Tackling Therapeutic Inertia on Mineralocorticoid Receptor Antagonist Adoption in Heart Failure

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Abstract

Clinical inertia is a major cause of mineralocorticoid receptor antagonist (MRA) underuse and failure to intensify MRA dose in heart failure (HF). Hyperkalemia and worsening of renal function are the main causes of clinical inertia seen with MRA. However, evidence shows that the risk of hyperkalemia is not very high with MRA use, and patients often die due to MRA withdrawal rather than hyperkalemia itself. Hence, addressing this fear of hyperkalemia is important to improve MRA prescription and patient outcomes. Other androgenic side effects of MRAs should also be managed for better adoption of this guideline-directed medical therapy in HF.

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Introduction

Clinical inertia is a major underlying cause of inadequate chronic disease care, leading to potentially preventable adverse events, excess healthcare costs, disability, and even death.[1–3] "Clinical inertia is defined as a lack of treatment intensification in a patient not at evidence-based goals for care."[1,3]

Physician inertia and fear of side effects are the biggest barriers to guideline-directed medical therapy (GDMT) initiation in heart failure.[4] This results in failure to correctly implement the four GDMT pillars in heart failure, angiotensin receptor blocker (ARB) and neprilysin inhibitor (ARNI)/angiotensin-converting enzyme inhibitors (ACEi), beta blockers (BB), mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter 2 inhibitor (SGLT2i).[4] The optimal and correct use of GDMT in heart failure can significantly reduce all-cause mortality, cardiovascular mortality, and hospitalization for heart failure.[5–10] Evidence shows that initiating the four GDMT pillars in heart failure with reduced ejection fraction (HFrEF) increases a 55-year-old's event-free survival by 8.3 years.[11] However, to get the maximum benefit of GDMTs in heart failure, the individual drugs have to be titrated to their optimal dose.[4,12] In India, <50% of heart failure patients are initiated on GDMTs, and up-titration to optimal dose is very low (seen in only 15–27% of patients at 1 year).[4] Clinical inertia is a major contributing factor for the non-intensification of heart failure GDMT to its optimum target dose.[3,13]

Understanding MRA-associated Clinical Inertia in Heart Failure

Evidence shows that clinical inertia contributes to the nonintensification of MRAs in 25.4% of cases.[13] The risk of adverse events was the main reason for non-intensification in 31.6% of cases.[13] Worsening kidney function and/or hyperkalemia are common barriers to initiating GDMT and titrating it to the target dose.[14]

Hyperkalemia: The Primary Barrier to MRA Use

Hyperkalemia is serum potassium >5.0 mmol/L.[15–17] The Asia-Pacific and Indian Expert Panel considers serum potassium levels of >5.0–5.4 mmol/L as mild, 5.5–5.9 mmol/L as moderate, and ≥6.0 mmol/L as severe hyperkalemia.[16,17] Similarly, the ESC guidelines consider serum potassium levels >5.0–<5.5 mEq/L as mild, 5.5–6.0 mEq/L as moderate and >6.0 mEq/L as severe hyperkalemia.[15]

Mineralocorticoid receptor antagonist-related hyperkalemia occurs because MRAs block the action of aldosterone in the distal tubule and collecting duct of nephrons, where aldosterone maintains chemical and acid-base balance by promoting sodium reabsorption and potassium and hydrogen excretion from the kidneys (Fig. 1).[18,19]

Mineralocorticoid receptor antagonist-related hyperkalemia occurs in 54% of HF patients in clinical trials, and hyperkalemia occurs due to other causes in 46% of HF patients.[20] Irrespective of its origin, hyperkalemia is a cause for lower implementations of MRA in HF.[20,21] Hyperkalemia (serum potassium >5.0 mmol/L) was seen in only 7% of HF patients in the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry that included patients from 11 Asian countries/regions, including India.[22] Despite the low incidence of hyperkalemia, MRAs were prescribed in only 58% of patients with HF in the ASIAN-HF study.[23] Of the patients from India in the ASIAN-HF, only 10% had hyperkalemia.[22] However, MRAs were underdosed in 51–58% of the patients from India in the ASIAN-HF study.[23] The disproportionately high MRA underuse compared to the actual MRA-related hyperkalemia risk indicates that the fear of hyperkalemia could be a major barrier to MRA implementation.[24]

However, MRA-treated HF patients with hyperkalemia experience increased mortality, not due to hyperkalemia itself but due to withdrawal of MRA.[25] For similar potassium levels, patients treated with spironolactone experienced lower mortality rates than those treated with placebo.[25] Real-world data show that stopping an MRA after a hyperkalemia episode reduced the 2-year risk of recurrent hyperkalemia but increased the risk of death and CV events.[26]

Strategies to Mitigate Hyperkalemia-related Factors

Preventive Measures

Identifying patients at risk of hyperkalemia, such as those on MRA and renin-angiotensin-

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aldosterone system inhibitor (RAASi) or having high baseline serum potassium or low eGFR, can help in the early initiation of preventive measures.[27]

Several measures for preventing MRA-associated hyperkalemia have been recommended by various guidelines and are covered in Table 1.[14,16] Potassium binders such as patiromer and sodium zirconium cyclosilicate (SZC) have been approved and guideline-recommended[15,28] for lowering hyperkalemia based on robust clinical data[14,29–31] demonstrating a significant reduction in potassium levels. These potassium binders can be safely used in cardiorenal disease, as their most common side effects (edema and constipation) are easily manageable.[30,31]

Addressing Hyperkalemia in Patients on MRA

Guidelines recommend that physicians note if there is a medical history of hyperkalemia in all HF patients.[35] Physicians should monitor potassium levels and estimated glomerular filtration rate (eGFR), and if hyperkalemia is detected, they should determine its etiology and degree of reversibility to formulate an action plan.[35]

MRA Dose Modification Based on Hyperkalemia Severity

The RALES investigators suggested giving spironolactone at 25 mg/day on alternate days if potassium levels increased to >5.5 mmol/L and re-evaluating the response in 1 week.[27] The RALES investigators also recommended increasing the dose to 50 mg/day if serum potassium remained stable over 8 weeks, but the patient showed signs of HF progression. However, the investigators cautioned that the 50 mg/day dose should only be used for a short period to stabilize the patient under strict potassium monitoring.[27] The patients in the RALES study had normal serum potassium levels (<4.5 mmol/L) and creatinine values ≤ 180 mol/L at study entry, and hence their response to MRA may differ from patients seen in real-world scenarios.

In the real world, guidelines recommend MRA and RAASi dose modification based on the severity of hyperkalemia (Table 2).

Addressing Fear of Hyperkalemia Due to Worsening Renal Function

Impaired renal function increases the risk of hyperkalemia.[36] Worsening renal function is one of the most frequent causes of MRA underuse.[37,38] In the ESC-HF-LT registry, worsening renal function was the reason behind ~10% of patients not achieving the target MRA dose,[38] However, prescriptions for MRA are low, even at eGFR levels where MRA could be prescribed (Table 3).[37] MRAs were discontinued even at eGFRs 30–60 mL/min/1.73 $m^{2,}$ where clinical trial data demonstrated their efficacy and safety.[5,7,37,39,40]

Physicians need to be educated that an early decline in renal function after initiating MRA is self-limiting, and is not an indicator of renal damage.[37] Further, pseudohyperkalemia is seen in chronic kidney disease (CKD) stage ≥3 and can occur due to hemolysis caused by a delay in laboratory processing of blood samples.[16,17] Hence, MRAs should not be discontinued unless potassium levels rise >6.0 mmol/L and creatinine levels ≤30 mL/min/1.73 m^2.[17]

Adjusting MRA dose according to both serum potassium and eGFR level can address the fear of hyperkalemia to a great extent, as shown in Table 2 and Table 4 for spironolactone or eplerenone,[17] and Table 5 for finerenone.[41]

Monitoring Serum Potassium Levels

Optimizing laboratory monitoring of serum potassium and eGFR could facilitate filling the gap of poor MRA use observed in the real world. The RALES investigators recommended monitoring serum potassium at 1, 4, and 8 weeks.[27]

Indian HF guideline for resource-limited settings recommends checking serum potassium and renal function within 2–3 days of MRA/RAASi initiation. The values should be rechecked at day 7 postinitiation and at least once a month for the first 3 months and every 3 months thereafter.[2] The panelists emphasize the need for strict renal and potassium monitoring in patients with diabetes or renal impairment. Another Indian Expert panel recommends checking serum electrolytes and serum creatinine at one and four weeks after starting MRA /increasing MRA dose. This

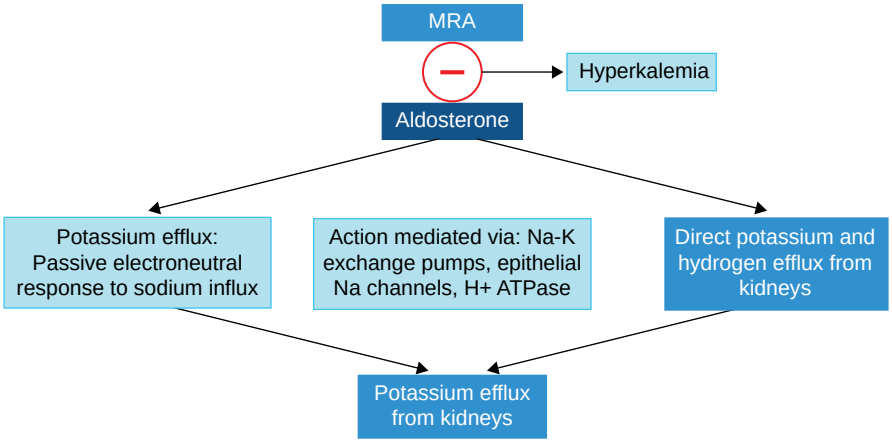

Fig. 1: Mechanism of MRA-related hyperkalemia

Table 1: Hyperkalemia preventive measures in HF patients on MRA[14,16,32–34]

Educate the patient to consume a low-potassium diet (e.g., red and green apples, pears, blueberries, cauliflowers, cabbage, beans, whole grains) and a Mediterranean diet
Avoiding potassium-containing salt and salt substitutes
Avoiding medications known to cause hyperkalemia: some commonly used medications: NSAIDs (e.g., ibuprofen, naproxen), verapamil, potassium-sparing diuretics (e.g., amiloride and triamterene), trimethoprim, pentamidine. Strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, nefazodone, ritonavir, telithromycin, and nelfinavir (only if eplerenone is used)
Use of guideline-recommended[15,28] and approved potassium binders, patiromer, and SZC can be used based on local access and availability
Using conventional potassium-binding resins, such as SPS and CPS
Concomitant medications in HF: • Co-administration of other HF GDMTs in patients at risk of hyperkalemia • SGLT2i may be prioritized over other GDMTs as their use may help mitigate hyperkalemia • Loop/thiazide diuretics may be given • BBs should be avoided • Avoid coadministration of ACEi/ARB

ACEi, Angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BBs, beta blockers, CPS, calcium polystyrene sulfonate; GDMT, guideline directed medical therapy; HF, heart failure; NSAIDs, nonsteroidal anti-inflammatory drugs; SGLT2i; sodium-glucose cotransporter 2 inhibitors; SPS, sodium polystyrene sulfonate; SZC, sodium zirconium cyclosilicate

Table 2: MRA dose modification based on severity of hyperkalemia

	Indian expert panel[17]		*An ESC working group*[15]	
Potassium levels	Dose at hyperkalemia detection	Adjustment	Potassium levels	Adjustment
4.0–5.4 mmol/L	Any	No adjustment	4.0 and 5.5 mmol/L	Prescribing or up-titrating RAASi
5.5–5.9 mmol/L	Spironolactone 50mg/day and eplerenone 100 mg/day	Decrease the dose by half	>5.0–≤6.5 mmol/L and not on guideline-recommended target dose	Initiate approved potassium lowering agent; up-titrate when potassium <5 mmol/L
	Spironolactone 25mg/day; eplerenone 50 mg/day	Spironolactone: give it every other day Eplerenone: reduce to half (25 mg/day)	5 > 5.0–≤6.5 mmol/L on guideline-recommended target dose of RAASi	Initiate approved potassium lowering agent; up-titrate when potassium <5 mmol/L
	Spironolactone 25mg/day every other day and eplerenone 25 mg/day	Interrupt treatment	–	–
>6 mmol/L	Any dose	Stop MRA treatment Reintroduce MRA along with a potassium binder when potassium levels are <6 mmol/L,	≥6.5 mmol/L	Withhold RAASi

ESC, European Society of Cardiology; MRA, mineralocorticoid receptor antagonists; RAASi, Renin-angiotensin-aldosterone system inhibitors

Table 3: Prescription rate of MRA according to eGFR[37]

eGFR	*Prescription rate*
≥60 mL/min/1.73 m^2	45%
45–59 mL/min/1.73 m^2	44%
30–44 mL/min/1.73 m^2	37%
<30 mL/min/1.73 m^2	24%

eGFR, estimated glomerular filtration rate

Table 4: Spironolactone or eplerenone dosing according to eGFR

eGFR mL/min/1.73 m^2	*Dosing*
≥50	Spironolactone 25 mg/day; eplerenone 50 mg/day
30–49	Spironolactone 25 mg/day every other day; eplerenone 25 mg/day
≤30	Withhold; restart after potassium stabilization and renal function improvement

eGFR, estimated glomerular filtration rate

Table 5: Finerenone dose after renal and potassium adjustment[41]

eGFR mL/min/1.73 m^2	*Dose at potassium ≤ 4.8 mmol/L*	*Dose at potassium 4.9–5.5 mmol/L*	*Dose at potassium > 5.5 mmol/L*
≥60	20 mg	20 mg	Withhold
≥25–<60	Start with 10; up titrate to 20 mg based on potassium level	10 mg	Withhold; restart at 10 mg when potassium <5.0 mmol/L

eGFR, estimated glomerular filtration rate

should be followed by regular monitoring at 8 and 12 weeks, followed by monitoring at 6, 9, and 12 months, and every 4 months thereafter.[17] The panel cautioned that any high potassium value should be double-checked to rule out pseudohyperkalemia due to hemolysis.

Androgenic Side Effects and Strategies to Mitigate Them

Steroidal MRAs, such as spironolactone, are not selective enough to bind only mineralocorticoid receptors. Rather, they also bind to androgen and progesterone receptors, resulting in androgenic side effects such as gynecomastia or breast pain in men, impotence and other sexual side effects, and menstrual irregularities.[42–44] Spironolactone causes gynecomastia through several mechanisms, including increasing testosterone clearance by displacing testosterone from sex hormone-binding globulin (SHBG), binding to androgen receptors, inhibiting enzymes involved in testosterone biosynthesis, such as 17α-hydroxylase and 17,20-desmolase, and increasing peripheral conversion of testosterone to estradiol.[45] The RALES study reported gynecomastia or breast pain in 10% of men on spironolactone versus 1% of men on placebo.[5] Eplerenone, another steroidal MRA, is a more selective MRA antagonist than spironolactone.[44,46] Thus, gynecomastia or other breast disorders were similar in the eplerenone versus placebo group of EMPHASIS-HF trial (0.7 versus 1.0%).[7] A systematic review and meta-analysis of heart failure trials comparing spironolactone with eplerenone reported that eplerenone significantly reduced the risk of gynecomastia versus spironolactone (risk ratio at 0.07, $p = 0.0001$).[47]

Spironolactone has 100–1000-fold higher binding affinities for androgen, glucocorticoid, and progesterone receptors than eplerenone.[44] Therefore, spironolactone results in a dose-dependent increase in sexual side effects, but eplerenone does not.[44]

Since finerenone is a nonsteroidal MRA with high affinity for the mineralocorticoid receptor, it is devoid of androgenic and sexual side effects.[48]

For patients on spironolactone, physicians can consider switching to eplerenone, as it is tolerated better than spironolactone.[42,44,49] For patients who wish to continue on spironolactone, physicians can consider lowering the dose or stopping the drug for a few months.[45]

Conclusion

Physicians should be educated to recognize and address causes of clinical inertia, prescribe MRA, and increase the intensity of the dose to the target dose. Fear of hyperkalemia and worsening of renal function are the main causes of clinical inertia toward MRA. However, the risk of hyperkalemia and worsening of renal function with MRA is not as high as feared. Rather, withdrawal, under prescription, or nonintensification of MRA due to this fear can increase mortality risk. Physician education, use of preventive methods, MRA

dose adjustments according to potassium and eGFR levels, and strict potassium and renal monitoring can help overcome this fear. For patients on long-term high-dose spironolactone, gynecomastia and sexual side effects can be concerning. These can be managed by reducing/stopping spironolactone or switching to eplerenone.

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REVIEW ARTICLE

Early Initiation and Dose Optimization of Mineralocorticoid Receptor Antagonists in Heart Failure

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Abstract

Guidelines recommend that the foundation four guideline-directed medical therapy (GDMT), which includes mineralocorticoid receptor antagonists (MRAs), should be initiated early in the treatment paradigm of heart failure due to mortality benefits and reduction in hospitalization for heart failure. However, the practical implementation of these guidelines in the real-world clinical scenario is lacking. Delay in initiating MRA is common, and patients often do not receive the optimum dose of MRA. The clinical considerations and guideline recommendations for early initiation and optimum dosing of MRA in HF can form the scientific basis for improving the correct usage of MRA in HF in real-world settings.

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Introduction

Recent HF guidelines recommend that the foundation four guideline-directed medical therapy (GDMT) should be started simultaneously or in parallel in HF, unless contraindicated, as this will produce the maximum benefit. The foundation four GDMT in HF include angiotensin receptor blocker (ARB) and neprilysin inhibitor (ARNI) or angiotensin-converting enzyme inhibitors (ACEi), beta blockers (BB), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 inhibitor (SGLT2i).[1–3]

The rationale for this recommendation is based on the fact that the efficacy of one GDMT does not seem to impact the efficacy of the other, as they have different mechanisms of action.[4–8]

Need for Early Initiation of Mineralocorticoid Receptor Antagonists

Evidence shows that early initiation of the foundation four GDMT in the recommended dose is feasible and can significantly reduce symptoms, all-cause mortality, cardiovascular mortality, and hospitalization for HF.[1,6,9] However, early initiation of GDMT, including MRA, faces many implementation gaps in the real world.[10,11]

Early initiation of MRAs in the treatment paradigm of HF is essential to achieve the maximum benefit in reducing symptoms and preventing adverse cardiac remodeling.[12] However, despite pivotal clinical trials establishing the efficacy and safety of MRA, especially spironolactone and eplerenone, in significantly reducing mortality and hospitalizations after heart failure (HF) for reduced ejection fraction (HFrEF),[13–15] and hospitalizations for HF in patients with HF for preserved ejection fraction (HFpEF),[16,17] early initiation of MRAs at their recommended dose in HF remains a challenge.[12] The EVOLUTION HF study conducted in Japan, Sweden, and the US showed that 42.2% of patients on MRA discontinued therapy and 5.1% did not achieve their target dose.[18]

Understanding the benefit of early initiation of MRA at their recommended doses in HF may help clinicians understand its importance and improve early prescription rates of MRAs.[19]

Impact of Early Initiation of Mineralocorticoid Receptor Antagonist in Heart Failure: Clinical Evidence

The initiation of chronic HF GDMT, including MRA, during admission for HF and before discharge is recommended due to its benefits in improving mortality and rehospitalizations.[2,20,21] This was demonstrated by the secondary analysis of data of 6,197 patients from the RELAX-AHF-2 study.[20] In-hospital MRA initiation was independently associated with significantly lower risks of the composite of cardiovascular death and/or rehospitalization for HF or renal failure [hazard ratio (HR) 0.71; $p < 0.0001$] at 180 days vs patients not initiated with MRA during hospitalization. Significant benefits of initiating MRA vs not initiating MRA during hospitalization were seen at 180 days for hospitalization for HF or renal failure (HR 0.72; $p = 0.0003$), all-cause mortality (HR 0.76; $p = 0.02$), and cardiovascular death (HR 0.77; $p = 0.06$).[20]

Further, the STRONG-HF trial showed that in patients hospitalized for HF and not receiving the optimal GDMT doses, including MRA doses, MRA could be initiated 2 days before anticipated discharge, uptitrated during admission, and then rapidly and safely uptitrated to the optimal target dose within 2 weeks of discharge.[21] This uptitration to the optimal dose combined with robust safety monitoring was associated with significant risk reduction in ≤180 days all-cause mortality and readmission for HF by 8.1% ($p = 0.0021$).[21]

A 30-day delay in initiating an MRA approximately doubles the mortality risk after 1 year.[22] This was demonstrated by a retrospective study in patients hospitalized for a first episode of decompensated

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congestive HF. A 30–90-day delay in MRA initiation after discharge from hospital resulted in a significant increase in 1-year mortality [7.1 vs 13.4%; hazard ratio (HR) 1.93; $p = 0.007$] compared with MRA initiation at discharge.[22]

A *post hoc* analysis of the EMPHASIS-HF trial of cardiovascular hospitalization (CVH; 64% were for HF) in patients with HF reported that eplerenone was initiated after a median time of 42 days postdischarge.[23] The absolute reduction in the composite of cardiovascular deaths and hospitalization for HF was greater in the <42 days group compared to the >42 days initiation group (−5.61 vs −3.58 events per 100 patient × years).[23] The absolute rate reduction was also higher in the <42 days group for HF hospitalization (−4.43 vs −3.05 events per 100 patient × years) and all-cause mortality (−1.95 vs −1.17 events per 100 patient × years).[23] The analysis showed that early initiation of MRA after discharge improved survival and is likely to prevent readmission for HF.

Insights from the EPHESUS trial showed that initiating eplerenone within 7 days of myocardial infarction (MI) significantly improved outcomes vs placebo (Fig. 1).[24]

Initiating eplerenone 7 days after MI had no significant impact on outcomes compared to placebo. Further, subgroup analysis of the EMPHASIS-HF trial showed a significant reduction in the composite of cardiovascular death or first hospitalization for HF 26 days after randomization (HR 0.58; $p = 0.049$). The benefits of early initiation of eplerenone in reducing the risk of the composite of cardiovascular death or first hospitalization for HF were seen across all patient profiles (Fig. 2).[25]

Another *post hoc* analysis of the MRA HFrEF trials pooled analysis of RALES[13] and EMPHASIS-HF[15], MRA HFpEF TOPCAT[16] trial, and the EPHESUS[14] trial in postacute MI demonstrated a statistically significant benefit of early initiation of MRA in HF within days of starting therapy (Table 1).[19]

Thus, robust clinical evidence shows that MRAs should be initiated early in HF to reduce the risk of all-cause and cardiovascular mortality and readmission for HF.

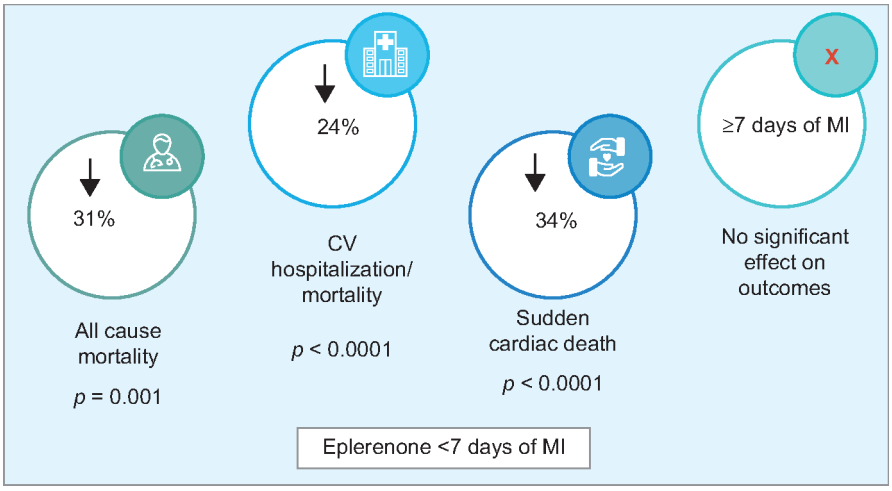

Fig. 1: Insights from the EPHESUS study: Impact of early initiation of MRAs after myocardial infarction (MI); CV, cardiovascular; MI, myocardial infarction

Early Initiation of Mineralocorticoid Receptor Antagonist: Practical Recommendations from Indian Expert Panel of Cardiologists

Indian experts suggest that initiating eplerenone in the predischarge hospital setting can be beneficial, especially in postacute MI patients, if not contraindicated[26]

The experts recommend that in chronic HF and hospitalized HF, initiating MRA early after ACEi/ARBs and BBs can be beneficial. The experts stress that eplerenone and

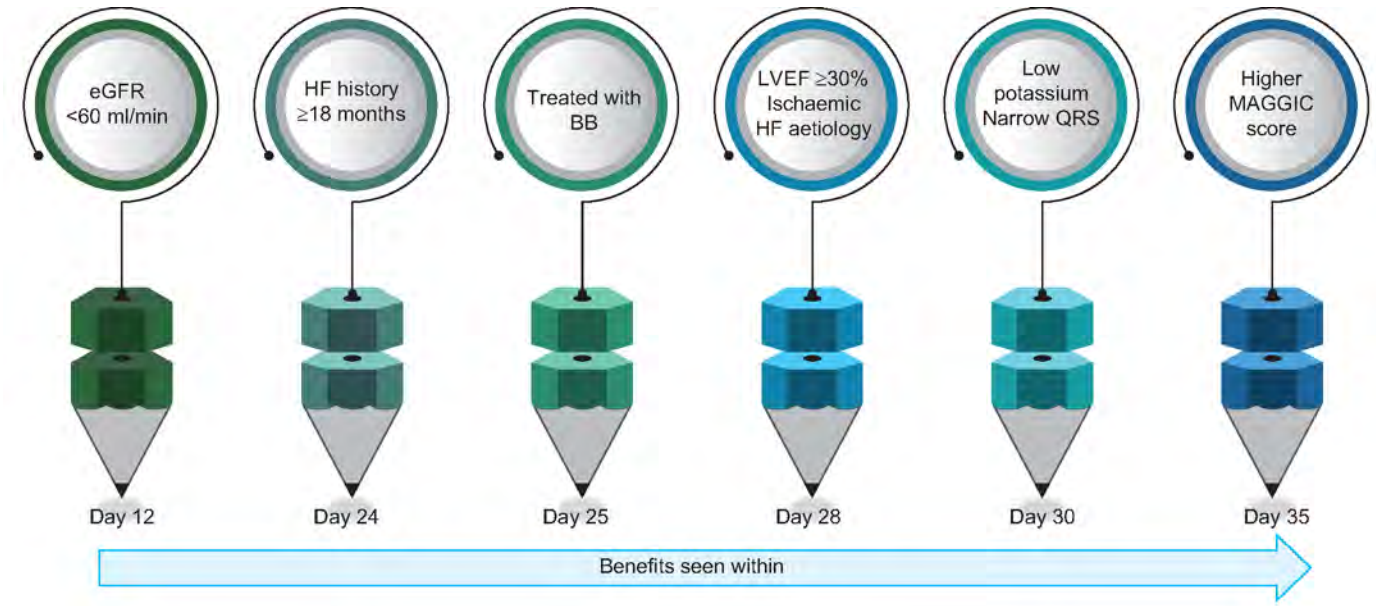

Fig. 2: Insights from the EMPHASIS-HF trial: Patient profiles benefitting from early initiation of MRAs and days within which benefits were seen; *Benefits: significant reduction in composite endpoint (cardiovascular death or first hospitalization for HF); BB, beta blockers; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure

spironolactone should be initiated only after starting ACEi/ARBs and BBs.[26]

Optimizing Mineralocorticoid Receptor Antagonist Doses in Heart Failure

Like any other drug, MRA dose optimization in HF is based on the principle of maximum efficacy with the least safety concern. The evidence for the optimal starting dose and the target dose of MRA in HF comes from clinical trials and guideline recommendations.

Clinical Evidence: Doses Used by Investigators of Landmark Clinical Trials

Higher MRA doses were associated with an increased risk of hyperkalemia, but there is no significant association between increasing MRA dose and clinical outcomes.[27]

The results of the RALES study established that 12.5–25 mg of spironolactone coadministered with ACEi, loop diuretics, and digitalis is effective in blocking the adverse effects of aldosterone in HF and the potential of hyperkalemia.[28] This dose range was also safe and did not increase the risk of hyperkalemia if serum potassium levels were monitored.[28] The incidence of hyperkalemia increased significantly with increasing spironolactone doses ($p = 0.001$) (Table 2).[28]

Similarly, the Aldo-DHF trial showed that a 25 mg/day spironolactone dose was sufficient for blocking the negative effects of aldosterone and improving left ventricular diastolic function in patients with HFpEF.[29]

The investigators of the EMPHASIS-HF15 started eplerenone at 25 mg once daily and increased it to 50 mg once daily after 4 weeks. In patients with estimated glomerular filtration rate (eGFR) of 30–49 mL/minute/1.73 m^2, they started eplerenone at 25 mg on alternate days and increased it to 25 mg daily. All dose increases were done only if the serum potassium level was ≤5.0 mmol/L.

Guideline Recommendations for Dosing and Uptitration

The European Society of Cardiology (ESC) Clinical Practice Guidelines[2] and the American College of Cardiology Expert Consensus Decision Pathway in HF[6] recommend starting the MRA at a lower dose and up-titrating it to the target dose in 4 to 8 weeks under regular potassium and renal monitoring (Table 3).[2]

The ESC guideline recommends reducing the dose to half the starting dose for potassium levels >5.5 mmol/L or creatinine >2.5 mg/dL (221 mmol/L) and stopping MRA for potassium levels >6.0 mmol/L or creatinine >3.5 mg/dL (310 mmol/L).[2]

Table 2: Hyperkalemia (≥5 mmol/L) with spironolactone vs placebo (5%)

Daily dose	*% of patients*
12 mg	5%
25 mg	13%
50 mg	20%
75 mg	24%

The Indian Expert Panel of Cardiologists also recommended starting MRA, eplerenone, or spironolactone at 25 mg once daily and uptitrating it after 4–8 weeks based on serum potassium and eGFR levels.[26] The Indian HF guideline for resource-limited settings recommends monitoring serum potassium and renal function at the following frequency: within 2–3 days of initiating MRA, day 7 postinitiation, at least once a month for the first 3 months, and every 3 months thereafter.[30,31] Based on this monitoring, the Indian Expert Panel of Cardiologists recommends decreasing MRA dose by half for potassium levels 5.5–5.9 mmol/L and stopping MRA for potassium >6 mmol/L and eGFR ≤30 mL/minute/1.73 m^2. The guidelines recommend reducing MRA dose to half for eGFR 30–49 mL/minute/1.73 m^2. MRA may be re-initiated or dose uptitrated based on potassium/eGFR levels.[26]

Conclusion

It is important to initiate MRAs early in the treatment paradigm of chronic HF and also in patients hospitalized with HF. Any delay in starting MRA significantly increases the risk of mortality and readmission for HF. The recommended MRA doses should be achieved as soon as feasible for maximum benefit. Strict potassium and eGFR monitoring should guide the MRA dosing.

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Table 1: Days after initiation of MRA when benefits are seen

		Number of days after which significant statistical reduction occurred			
Trial	*HF type*	*CV death and HHF*	*HHF*	*CV death*	*All-cause death*
Pooled analysis of RALES[13] and EMPHASIS-HF[15]	HFrEF	19 days	11 days	122 days	332 days
TOPCAT[16]	HFpEF	208 days	224 days	–	–
EPHESUS[14]	Postacute MI HF	7 days	84 days	9 days	10 days

CV, cardiovascular; HHF, hospitalizations for heart failure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction

Table 3: MRA starting and target dose in HF

	Guideline	*Starting dose*	*Target dose*
Eplerenone	ESC[2]	25 mg once daily	50 mg once daily
	ACC Expert Consensus[6]	25 mg once daily	50 mg once daily
	Indian Panel of Experts[26]	25 mg once daily	Not mentioned. Titrate according to serum potassium and eGFR
Spironolactone	ESC[2]	25 mg once daily	50 mg once daily
	ACC Expert Consensus[6]	12.5–25 mg once daily	25–50 mg once daily
	Indian Panel of Experts[26]	25 mg once daily	Not mentioned. Titrate according to serum potassium and eGFR

ACC, American College of Cardiology; ESC, European Society of Cardiology

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REVIEW ARTICLE

Risk of Delaying or Omitting Mineralocorticoid Receptor Antagonists in Heart Failure

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Abstract

Despite strong class I, level A recommendations from major clinical guidelines, the early initiation and optimization of mineralocorticoid receptor antagonists (MRAs) in heart failure (HF) with reduced ejection fraction (HFrEF) remain suboptimal. MRAs, including spironolactone and eplerenone, provide significant morbidity and mortality benefits, particularly when introduced early in high-risk scenarios such as acute myocardial infarction (AMI) and acute decompensated heart failure (ADHF). Evidence from landmark trials and real-world registries underscores that early MRA therapy reduces cardiovascular events, prevents adverse ventricular remodeling, and lowers sudden cardiac death risk. Delaying or omitting MRAs, even by a few weeks, is associated with increased mortality, recurrent hospitalizations, and irreversible cardiac damage. Clinical evidence demonstrated that early aldosterone blockade exerts rapid and sustained benefits, often within days of initiation. Early initiation and aggressive optimization of MRAs must be prioritized in HFrEF management to fully realize their life-saving potential.

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Introduction

Mineralocorticoid receptor antagonists (MRAs) play a critical role in the treatment of heart failure (HF), particularly in patients with reduced ejection fraction (HFrEF). While therapies targeting the renin–angiotensin–aldosterone system (RAAS) are known to mitigate or even reverse left ventricular (LV) remodeling and improve outcomes, aldosterone levels often remain elevated due to the well-recognized "aldosterone escape" phenomenon. This persistent aldosterone activity continues to drive pathological processes such as LV hypertrophy, volume overload, myocardial fibrosis, endothelial dysfunction, and inflammatory responses.[1,2] The pathophysiological basis for aldosterone blockade is compelling, promoting the position of MRAs as a cornerstone of guideline-directed medical therapy in HFrEF.

Emerging evidence suggests that within mere hours of an acute myocardial infarction (AMI), plasma aldosterone levels begin to surge, setting off a cascade of harmful effects that drive adverse cardiac remodeling and worsen prognosis. This early rise, paired with increased transcardiac extraction of aldosterone, marks the heart's vulnerable window, a period when damage is not only unfolding but accelerating. Timely intervention during this critical phase can alter the trajectory. Studies now show that initiating aldosterone blockade within the first 24 hours after AMI may prevent the very remodeling that leads to progressive HF.[3–5] Thus, the timely initiation of MRAs is not just beneficial; it is potentially transformative, offering a vital opportunity to intercept disease progression before it becomes irreversible.

Benefits of Early Initiation of MRAs

Early initiation of MRAs has consistently demonstrated significant clinical benefits in HF, particularly in high-risk settings such as AMI and acute decompensated HF. In the landmark EPHESUS (Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial, patients with left ventricular dysfunction (LVEF <40%) were randomized to receive eplerenone within 3–14 days post-MI. Notably, early MRA therapy led to a significant reduction in cardiovascular events, affirming the life-saving potential of timely intervention. This benefit is likely due to the early rise in aldosterone levels following AMI, which contributes to adverse cardiac remodeling and fibrosis. By blocking aldosterone early, eplerenone may help prevent this pathological remodeling and improve long-term outcomes.[6–8]

Beyond post-MI care, emerging evidence supports early MRA use during acute HF hospitalizations. A prospective single-blinded trial showed that spironolactone initiated during hospitalization led to faster decongestion and notable reductions in natriuretic peptide levels by day 3, indicating improved hemodynamic status and reduced myocardial stress.[9] Additionally, a randomized controlled trial of 116 HF patients revealed a lower incidence of arrhythmias in those who began spironolactone compared to placebo, suggesting early MRA initiation may also mitigate sudden cardiac death, a leading cause of mortality in HF.[10]

A *post hoc* analysis of four major clinical trials, RALES, EMPHASIS-HF, TOPCAT-Americas, and EPHESUS, demonstrated that the protective effects of MRAs begin early and intensify over time. In patients with HFrEF, the combination of RALES and EMPHASIS-HF showed that a statistically significant reduction in cardiovascular death or hospitalization occurred as early as day 19,

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and even sooner for HF hospitalizations, by day 11. All-cause mortality benefit appeared by day 122, and cardiovascular death benefit by day 332. The urgency of early initiation was even more pronounced in post-MI patients from the EPHESUS trial, where a significant reduction in the composite outcome occurred by day 7, with benefits for all-cause death and CV death emerging within just 10 and 9 days, respectively.[11]

Analysis from the COACH (Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure) biomarker study highlights a significant advantage in starting or maintaining MRA therapy in patients with HF. Patients who were either initiated or continued on spironolactone had a markedly lower 30-day mortality compared to those who were not.[12]

Taken together, these findings emphasize that the timing of MRA initiation is pivotal. Initiating therapy early, whether post-MI or during acute HF exacerbation, not only maximizes survival benefit but may also reduce arrhythmic risk and accelerate clinical recovery. Delaying treatment may forfeit a critical therapeutic window during which MRAs exert their most profound effects.

Risks of Delaying or Omitting MRAs

Delaying the initiation of MRAs in HF management can substantially postpone life-saving benefits, exposing patients to a prolonged period of elevated risk (Fig. 1).

Data from the CHAMP-HF (Change the Management of Patients with Heart Failure) registry revealed that MRA prescription was omitted in two-thirds of eligible patients.[13] Historical GWTG-HF (Get With the Guidelines–Heart Failure) registry data confirm this gap, with fewer than one-third of eligible patients receiving MRA initiation, even after adjusting for renal function and electrolyte status.[14]

Insights from the EPHESUS trial observed that delaying eplerenone (≥7 days) significantly increases the risk of adverse outcomes. All-cause mortality was 26% higher with delayed MRA use (HR 0.74, 95% CI: 0.60–0.90, p = 0.003). The combined risk of death from cardiovascular causes or hospitalization for cardiovascular events rose by 18% when MRAs were started later (HR 0.82, 95% CI: 0.71–0.94, p = 0.006). The risk of sudden cardiac death increased by 29% with delayed therapy (HR 0.71, 95% CI: 0.51–0.99, p = 0.04).[8] These findings highlight that postponing MRA initiation in eligible patients may significantly elevate the risk of mortality and serious cardiovascular events.

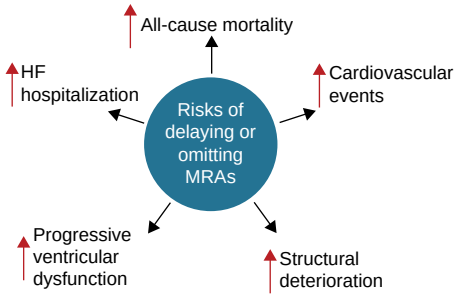

Fig. 1: Risk of delaying or omitting MRAs

Delaying MRAs after hospitalization for HF may significantly increase the risk of death. In a study by Rossi et al., involving 689 patients discharged after their first episode of decompensated HF, those who began MRA therapy late (30–90 days postdischarge) had nearly double the 1-year mortality compared to those who received early treatment (<30 days postdischarge). Specifically, mortality was 13.4% in the delayed group versus just 7.1% in the early group, with an adjusted hazard ratio of 1.93 (95% CI: 1.18–3.14). This striking difference emphasizes that even a 1-month delay in MRA initiation can substantially increase the risk of death, highlighting the urgent need for timely therapy in the postdischarge phase of HF care.[15]

Omitting MRAs in the early management of AMI may significantly increase the risk of adverse left ventricular (LV) remodeling and long-term cardiac dysfunction. In a randomized study of 134 patients with first anterior MI, those who did not receive MRAs despite revascularization and ACE inhibitor therapy experienced markedly worse structural outcomes. After 1 month, the MRA-omitted group showed a significantly greater increase in LV end-diastolic volume index (from 87.5 ± 1.3 to 106.8 ± 3.5 mL/m^2, $p_{interaction}$ = 0.002), reflecting detrimental ventricular dilation, compared to the MRA group [where the LV end-diastolic volume was significantly suppressed (86.5 ± 1.0 to 90.6 ± 2.4 mL/m^2, p = 0.002)]. Furthermore, LV ejection fraction improved more robustly in the MRA group (46.0 ± 0.6% to 53.2 ± 0.8%) than in the MRA-omitted group (46.5 ± 0.8% to 51.0 ± 0.8%, p = 0.012). Importantly, MRAs also significantly suppressed aldosterone activity and levels of procollagen type III aminoterminal peptide, a marker of myocardial fibrosis (p = 0.002), indicating reduced fibrotic remodeling. These findings underscore that excluding MRAs from early post-infarct treatment regimens may leave patients vulnerable to progressive ventricular dysfunction and structural deterioration, despite standard therapy with ACE inhibitors.[16]

Evidence from the Kyoto Congestive Heart Failure (KCHF) registry in Japan highlights the potential consequences of omitting MRAs at discharge. In this registry of 3,717 patients hospitalized with acute decompensated heart failure (ADHF), only 45.1% received an MRA at discharge. Propensity-matched analysis revealed that omission of MRAs was linked to a higher cumulative 1-year incidence of the composite primary outcome (all-cause death or HF hospitalization): 33.9% in the no-MRA group versus 28.4% in those who received MRA therapy (p = 0.003). Notably, HF hospitalizations alone were significantly higher in the MRA-omitted group, with a 30% relative increase (24.8% vs 18.7%, p < 0.01).[17]

These findings highlight a critical message: each day of delay in starting MRA therapy may prolong patient exposure to preventable cardiovascular events and death, especially in high-risk populations with HFrEF or recent myocardial infarction.

GDMT Initiation and Optimization

The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) unequivocally recommend initiation of MRAs in HFrEF patients to reduce the risk of HF hospitalizations and death (class I, level A recommendations). Specifically, MRAs such as spironolactone or eplerenone are recommended for patients with NYHA class II to IV symptoms to reduce morbidity and mortality, provided renal function and potassium levels are within safe limits (eGFR >30 mL/min/1.73 m^2 and serum potassium <5.0 mEq/L).[18,19] Both spironolactone and eplerenone are typically started at 25 mg daily for patients with GFR >60 mL/min/1.73 m^2. Dose should be optimized when GFR is between 30 and 60 mL/min/1.73 m^2, wherein the starting dose should be halved (12.5 mg daily), with a maximum of 25 mg. Eplerenone may be better tolerated than spironolactone in patients at risk of gynecomastia, and neither requires dose adjustment in hepatic dysfunction. After initiation or optimization, monitor renal function and potassium at 1 week, 1 month, and then every 6 months.[20]

Conclusion

Timely initiation of MRAs is a critical, evidence-based intervention that significantly improves outcomes in patients with HFrEF and postmyocardial infarction. The evidence unequivocal supports the early initiation of MRAs, particularly following AMI or hospitalization for decompensated HF, where it is associated with rapid and sustained reductions in mortality, hospitalizations, arrhythmic events, and adverse

remodeling. Conversely, postponing or omitting this therapy risks avoidable harm, with elevated mortality and structural deterioration that may not be reversible. In the face of compelling data and strong guideline support, timely and proactive MRA initiation must be prioritized. For patients with HFrEF or post-MI systolic dysfunction, each day matters, and with MRAs, that day could be the one that changes the course of the disease.

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REVIEW ARTICLE

Mineralocorticoid Receptor Antagonist and Its Combinations in Heart Failure

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Abstract

Mineralocorticoid receptor antagonists (MRAs) are strongly recommended by various guidelines for the management of patients with heart failure. Present and emerging clinical evidence also supports the beneficial role of MRAs in lowering the risk of heart failure-associated hospitalization and mortality. Loop diuretics play a crucial role in the management of edema associated with heart failure; however, their use has been associated with electrolyte abnormalities, activation of the renin–angiotensin–aldosterone and sympathetic systems, and diuretic resistance. Combined use of loop diuretics along with MRAs can help to overcome the diuretic resistance and improve the efficacy and safety of loop diuretics. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are another class of drugs that have shown significant benefits in patients with heart failure and are guideline-recommended for use in these patients. Combination therapy of SGLT2 inhibitors along with MRAs can improve various clinical outcomes in heart failure patients and reduce the risk of hyperkalemia, commonly associated with MRA therapy. Combination therapies can be potential opportunities to improve clinical outcomes and patient adherence in the management of patients with heart failure.

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Introduction

American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines define heart failure (HF) as a complex clinical syndrome with symptoms and signs arising due to any structural or functional impairment of ventricular filling or ejection of blood.[1]

Diuretics are the cornerstone therapy in the management of heart failure and are prescribed in patients with clinical evidence of fluid retention and congestion[1] as they play an important role in relieving edema in congestive heart failure.[2]

Mineralocorticoid receptor antagonists (MRAs) include steroidal MRAs, such as spironolactone and eplerenone, and nonsteroidal MRAs, such as Finerenone. They are one of the four pharmacological pillars in the guideline-directed management of HF.[3] MRAs are recommended for the management of HF with reduced ejection fraction (HFrEF).

American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines recommend MRAs (spironolactone or eplerenone) in patients with HFrEF and NYHA class II and IV symptoms if the estimated glomerular filtration rate (eGFR) is >30 mL/min/1.73 m^2 and serum potassium is < 5.0 mEq/L.[1]

As per the AHA/ACC/HFSA guidelines, MRAs may be considered to reduce the risk of cardiovascular mortality in patients with HFmrEF and lower the risk of hospitalization in patients with HFmrEF and HFpEF, especially with LVEF on the lower end.[1]

Spironolactone and eplerenone have been shown to reduce the mortality risk and hospitalization in patients with HFrEF in two pivotal clinical trials: RALES (Randomized Aldactone Evaluation Study)[4] and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure).[5]

Combination therapies of MRAs with other drugs, which are also recommended in the management of heart failure, can have potential benefits in terms of enhanced efficacy and safety, as very high doses of the individual drugs can be avoided, which can enhance the overall treatment outcomes. Use of combination therapies can also help in achieving better patient adherence to the therapy. This chapter aims to explore the benefits of combining MRAs with other classes of drugs that are guideline-recommended in the management of heart failure: loop diuretics and sodium–glucose cotransporter 2 (SGLT2) inhibitors.

Clinical Efficacy and Safety of Combining MRAs with Loop Diuretics

Loop diuretics are the preferred diuretic agents for patients with heart failure.[1] Loop diuretics inhibit sodium (Na^+) and chloride (Cl^-) reabsorption in the kidneys and increase urine production (diuresis).[6] Torsemide is a loop diuretic that is primarily indicated to manage hypertension and edema associated with heart failure, chronic renal disease, and hepatic cirrhosis.[6]

Combining two medications with well-defined roles in the management of HF (loop diuretics such as torsemide along with MRAs, which are also neurohormonal blockers) can be favorable for the management of heart failure patients.[7]

Loop diuretics have been associated with electrolyte abnormalities,[8] including hypokalemia, hyponatremia, and hypomagnesemia, which may further aggravate the risk of cardiac arrhythmias and sudden cardiac death.[9,10] MRAs inhibit epithelial sodium channel (ENaC) synthesis and the Na^+/K^+ exchange in the nephron,

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which helps in natriuresis.[11] MRAs have also been shown to block the aldosterone-related effects on cardiac cells, which results in antiarrhythmic activity.[12]

Use of potassium-sparing diuretics with loop diuretics can effectively lower the risk of electrolyte abnormalities, including hypokalemia and hypomagnesemia, and associated complications such as cardiac arrhythmias and sudden death in patients with hypertension.[13]

Loop diuretics, when used in heart failure, may cause activation of the sympathetic nervous system and renin–angiotensin–aldosterone (RAAS) system, and deterioration of renal function.[9,14] This can lead to inadequate diuretic response, which is often called diuretic resistance and can further cause worsened clinical outcomes.[15]

A clinical study was conducted involving 51 patients diagnosed with symptomatic congestive heart failure and reduced left ventricular ejection fraction. These patients were treated with a combination of standard heart failure medications, including loop diuretics, β blockers, and either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Additionally, some patients received spironolactone and digoxin, depending on their individual clinical needs.[16] Doubling the dose of loop diuretics helped in significant weight loss and improvement in symptoms and 6-minute walk distance. However, no effect on the left ventricular systolic and diastolic function was seen.[16]

In a study including 48 patients with acute decompensated heart failure and resistant to loop diuretics, adding high-dose spironolactone (100 mg/day) helped in significant decongestion without any hyperkalemia or any deteriorating effects on renal function.[17]

Combination therapy of spironolactone and loop diuretics such as torsemide can assist in increased flow of urine from the kidneys (diuresis) as spironolactone causes excess salt and water secretion while torsemide prevents fluid retention by excreting sodium, chloride, and water.[6]

These treatment modalities may be associated with adverse events specific to their drug class. Adverse events such as electrolyte imbalance, dryness of mouth, hypotension, tachycardia, muscle fatigue and cramps, drowsiness, nausea, vomiting, and other[18] have been reported with torsemide, while spironolactone can cause hyperkalemia, hyponatremia, hypomagnesemia, hypotension, gynecomastia, erectile dysfunction, menstrual irregularities, and others.[19] Some severe skin reactions, including toxic epidermal necrolysis[20] and Stevens–Johnson syndrome[21] have been reported in some patients using torsemide and spironolactone combination therapy.

RESTORE-HF is a multicenter, observational, real-world evidence study in India that evaluated the efficacy and safety of a fixed dose combination of torsemide and spironolactone in the management of HF.[22] The study primarily aims to assess the change in body weight in 3 weeks from baseline, with a secondary endpoint to evaluate any change in NYHA functional class over 3 weeks and the safety of this combination.[22] Other important parameters studied would be demographics, associated comorbidities, and concomitant medications to have a better understanding of the management of HF patients in India.[22]

Combined use of established therapies for HF, such as torsemide along with spironolactone, could potentially have a beneficial effect on each other's efficacy and can also help to improve clinical outcomes in patients with HF.[23]

Clinical Efficacy and Safety of Combining MRAs with SGLT2 Inhibitors

Increasing clinical evidence on the beneficial role of SGLT2 inhibitors and MRAs in the management of heart failure has established these therapies as the foundational pillars in the goal-directed management of heart failure.[1] There is a growing interest in their use in ways that can enhance their efficacy and safety potential for better clinical outcomes in HF patients.

American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines recommend SGLT2 inhibitors in patients with symptomatic chronic HFrEF to reduce hospitalization and cardiovascular mortality irrespective of underlying type 2 diabetes mellitus.[1] SGLT2i can be beneficial in decreasing HF hospitalization and cardiovascular mortality in patients with HFmrEF and HFpEF.[1]

Renal dysfunction is a common comorbidity associated with HF, and it can negatively affect the outcomes, complicate HF treatment, and increase the risk of morbidity and mortality.[24] Pivotal trials of SGLT2 inhibitors: DAPA-CKD[25] and EMPA-KIDNEY[26] demonstrated the beneficial effect of SGLT2 inhibitors, seen as reduced risk of kidney disease progression, or mortality from renal or cardiovascular causes.

Meta-analysis of important trials including DELIVER, EMPEROR-preserved, DAPA-HF, EMPEROR-Reduced, and SOLOIST-WHF demonstrated the strong beneficial role of SGLT2 inhibitors in reducing the risk of hospitalizations for HF and cardiovascular mortality in patients with heart failure, irrespective of ejection fraction.[27]

Potential synergism of combination therapy of SGLT2 inhibitors and MRAs in patients with HF may improve clinical outcomes, including enhanced efficacy and better safety profiles.[28]

A meta-analysis including five studies that evaluated the cardiovascular effects of SGLT2 inhibitors with or without the use of MRAs inHF patients (n = 21,947) demonstrated that SGLT2 inhibitors reduced all-cause mortality and adverse renal endpoints regardless of MRA use.[29] The findings suggested a higher reduction in cardiovascular diseases in chronic HF patients randomized to SGLT2 inhibitors and who received an MRA compared to the patients who received SGLT2 inhibitors but not MRAs.[29] As per the meta-analysis, SGLT2 inhibitors also reduced the risk of MRA-associated mild ($p < 0.001$) and severe ($p = 0.05$) hyperkalemia,[29] suggesting improved efficacy with the use of this combination therapy.[30]

Many ongoing studies are also exploring the benefits of SGLT2 inhibitors with MRAs and other novel mineralocorticoid receptor modulators in various other disease conditions. In a phase 2 trial, BI 690517, an aldosterone synthase inhibitor, along with empagliflozin and renin–angiotensin system blockade, reduced albuminuria, suggesting the potential of these combination therapies in chronic kidney disease without unexpected safety issues.[31]

Sodium–glucose cotransporter 2 inhibitors are generally well-tolerated. Adverse events commonly seen with SGLT2 inhibitors include genital mycotic infections, urinary tract infections, hypovolemia, or hypoglycemia when used along with insulins or insulin secretagogues.[32,33] These adverse events can be managed well or minimized with early symptom recognition or when prescribing as per individual patient profile.[32] There have also been conflicting reports of diabetic ketoacidosis with SGLT2 inhibitors and increased risk of bone fracture and lower limb amputation with canagliflozin.[32,33]

Conclusion

Various studies and data suggest that combination therapies of MRAs with other established and guideline-recommended treatment modalities, such as loop diuretics and SGLT2 inhibitors, can have potential

benefit in terms of enhanced efficacy and better safety outcomes in patients with HF and can also enhance adherence. However, the data is still very limited, and there is a need for more clinical studies in a broader patient population for stronger recommendations to establish the role of these combination therapies.

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REVIEW ARTICLE

Future Directions and Innovations in Mineralocorticoid Receptor Antagonist Therapy

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Abstract

Mineralocorticoid receptor antagonists (MRAs) are important pillars in the treatment of heart failure (HF), chronic kidney disease (CKD), and diabetic kidney disease (DKD). MRAs share complementary pathways with sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with cardiovascular–kidney–metabolic (CKM) syndrome. Combination therapies of MRA with SGLT2i and GLP-1RA are showing promising results in CKM than individual therapies. Further, the unique action of MRAs in antagonizing MR receptors and aldosterone, implicated in the pathophysiology of several conditions, is paving the way for clinical trials and promising results in these therapeutic areas. Disease-specific biomarkers such as UACR and eGFR are increasingly being used to individualize treatment with MRA. Utilizing MRA-specific biomarkers may open the path for precision medicine and further treatment individualization.

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Introduction

Mineralocorticoid receptor antagonists (MRAs) are of two types, steroidal and nonsteroidal. Steroidal[CE1] MRAs (such as spironolactone and eplerenone) have been historically used for heart failure (HF). Steroidal MRAs are guideline-recommended across the entire spectrum of HF, viz. heart failure with reduced ejection fraction (HFrEF)[1–8] and for heart failure with mildly reduced ejection fraction (HpmrEF) and heart failure with preserved ejection fraction (HFpEF).[7,9,10] Steroidal MRAs have a limited role in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). Nonsteroidal MRAs, on the other hand, have proven to be more beneficial than steroidal MRAs in T2D patients at high risk of CKD progression and cardiovascular events.[11] Finerenone is guideline-recommended for the prevention of HF hospitalization in patients with CKD and T2D.[11,12]

However, though MRAs are expected to help in various subsets of patients with HF, CKD, and diabetes, they are underused even in their guideline-recommended settings.[13–19] Hence, clinical trials are continuously exploring their benefits in HF, especially in hospitalized patients and in HFpEF. Further, MRAs are multifaceted drugs that are not yet fully explored for their true potential. In many conditions, mineralocorticoid receptor (MR) activation plays a major role in disease pathophysiology and progression. MRAs can be a useful strategy in these conditions due to their ability to antagonize MR activation.

Ongoing Clinical Trials and Pipeline

Though steroidal MRAs (such as spironolactone and eplerenone) have been in use for decades, they are continuously being explored in newer subsets of HF patients and for their potential role in CKD/diabetic kidney disease (DKD). However, of late, the focus has shifted from steroidal to nonsteroidal MRAs. Finerenone and other nonsteroidal MRAs are being investigated for their potential role in CKD with or without T2D and in HF. Many clinical trials are in progress, and the results of these trials may open new approvals and guideline recommendations for MRAs in different CKD, diabetes, and HF populations. Though finerenone is the most investigated nonsteroidal MRA, several trials of Balcinrenone have also been identified.

The basic details of the ongoing MRA randomized controlled trials (RCTs) and observational real-world studies in CKD, diabetes (mainly T2D and sometimes type 1 diabetes), and/or HF are captured in Table 1.

Role of MRAs in Newer Indications

Mineralocorticoid receptor antagonists are emerging as therapeutic agents beyond their established roles in cardiorenal diseases. They show promise in the management of diseases where MR overactivation or high aldosterone levels are one of the contributing pathophysiological pathways, such as atrial fibrillation (AF), pulmonary arterial hypertension (PAH), arrhythmia, sudden cardiac death (SCD), etc.[21] MRAs are also being investigated in kidney transplant recipients (KTRs)[22,23] and for their cognitive effects on various patient populations.[24] Though MRAs demonstrate promising results in these indications (Box 1), they are not yet licensed for these indications.

Atrial Fibrillation

Mineralocorticoid receptor activation is thought to increase the risk of AF by increasing left atrial fibrosis and through changes in various electrical pathways.[21] High-quality evidence from various meta-analyses shows that MRA therapy is cardioprotective and helps in reducing the risk of new-onset and recurrent AF, irrespective of baseline HF or prior AF status.[25–27]

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Table 1: Ongoing MRA trials in patients with CKD, diabetes, and/or HF

Trial ID	*Phase (estimated enrolment)*	*Population*	*Treatment arms*	*Primary endpoint*	*Estimated completion*
CKD, T2D, T1D trials					
IN-REALITY (NCT06763146)	Observational (*N* ~1,200)	Indian patients with T2D and CKD	Finerenone	Real world use parameters, such as date of initiation, dose, frequency, date of discontinuation, reason for discontinuation, actions taken after stopping finerenone	December 1, 2025
NCT05705271	IV (*N* ~200)	Indian patients with T2D and CKD	Finerenone	TEAEs (≤30 days from last dose), no of hyperkalemia events (≤ 19 months)	July 3, 2025
CAPTIVATE (NCT06058585)	III (*N* ~1,000)	CKD	Finerenone vs placebo	eGFR slope slope from randomization to day 108	December 31, 2026
FINE-ONE (NCT05901831)	III (*N* ~220)	T1D and CKD	Finerenone vs placebo	ΔUACR at 6 months	September 26, 2025
FIND-CKD (NCT05047263)	III (*N* ~1,584)	non-diabetic CKD	Finerenone vs placebo	eGFR slope from baseline to month 32	February 9, 2026
KSD-01 (NCT06838416)	Observational (patient registry) (*N* ~300)	T2D and CKD on stable ARB/ ACEI treatment for ≥4 weeks prior to enrollment	Finerenone	ΔUACR at week 48	December 31, 2026
NCT06608212	Observational (*N* ~1,50,000)	T2D and CKD	Finerenone vs other treatments	First occurrence of composite cardiovascular outcome (fatal or nonfatal acute myocardial infarction or an inpatient hospitalization with a primary diagnosis of heart failure)	June 30, 2025
FINE-REAL (NCT05348733)	Observational (*N* ~4,500)	T2D and CKD	Finerenone	Real-world use parameters such as date of initiation, dose, frequency, date of discontinuation, reason for discontinuation, and secondary therapies	January 14, 2028
FIVE-STAR (NCT05887817)	IV (*N* ~100)	T2D and CKD	Finerenone vs placebo	Vascular stiffness and cardiorenal biomarkers: ΔCAVI at 24 weeks	July 31, 2026
FIONA OLE (NCT05457283)	III (*N* ~100)	CKD with proteinuria in 1–18 years old	Finerenone	Δ serum potassium and SBP Day 540 ± 7; TEAE	February 27, 2029
FIONA (NCT05196035)	III (*N* ~219)	CKD with proteinuria pts on ACEi/ARB	Finerenone vs placebo	UPCR reduction of at least 30% from baseline to day 180 ± 7	August 31, 2027
FLAMINGO (NCT05640180)	Observational (*N* = 17,847)	T2D and CKD treated with an ACEi/ARB (max dose without unacceptable side effects) SGLT2i use at BL Patients from FIDELIO-DKD and FIGARO-DKD phase 3 trials	Finerenone + ACEi/ARB+SGLT2i vs. Placebo + ACEi/ARB+SGLT2i	Time to kidney failure, a sustained decrease of ≥40% in eGFR from BL over a period of ≥4 weeks, or death from renal causes Time to death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure	Study completed (December 20, 2023), results not available
FIND-CKD (NCT05047263)	III (*N* ~1,580)	Nondiabetic CKD treated with an ACEi/ARB (max dose without unacceptable side effects)	Finerenone + ACEi/ARB vs. Placebo + ACEi/ARB	Mean rate of change as measured by the total slope of eGFR from BL to month 32	February 09, 2026
CONFIDENCE (NCT05254002)	II (*N* = 1,664)	T2D and CKD treated with the maximum dose of ACEi/ ARB	Finerenone + ACEi/ ARB+empagliflozin vs. Finerenone + ACEi/ARB vs. Empagliflozin + ACEi/ ARB	ΔUACR at 180 days for combination vs finerenone or empagliflozin alone	Study completed March 14, 2025 results not available

Contd…

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Trial ID	*Phase (estimated enrolment)*	*Population*	*Treatment arms*	*Primary endpoint*	*Estimated completion*
DapaBalci-Leap (NCT05884866)	II (*N* ~150)	Stage 3 CKD	Dapagliflozin + Balcinrenone vs Dapagliflozin + Balcinrenone placebo vs Balcinrenone + Dapagliflozin vs placebo both drugs	Δ 24h urine glucose excretion at day 28	January 31, 2025 no results available
MIRO-CKD (NCT06350123)	II (*N* ~324)	CKD and albuminuria	Balcinrenone/dapagliflozin vs dapagliflozin	ΔUACR at week 12	May 12, 2025
Heart failure studies					
REDEFINE-HF (NCT06008197)	III (*N* ~ 5,200)	Hospitalized with acute decompensated HF, HFmrEF, HFpEF (LVEF≥40%)	Finerenone vs placebo	Composite total of HF events and cardiovascular death; AEs leading to discontinuation; SAE	April 2026
FINALITY-HF (NCT06033950)	III (*N* ~ 2,600)	HFrEF patients intolerant or ineligible for steroidal MRA	Finerenone vs placebo	Time to first occurrence of cardiovascular death or HF event; AEs leading to discontinuation; SAE	April 2026
SPIRRIT (NCT02901184)	III (*N* ~ 2,000)	HFpEF	Spironolactone vs SOC without spironolactone	Total HF hospitalization and CV death	December 2026
CONFIRMATION-HF (NCT0602474)	III (*N* ~1,500)	Hospitalized with HF	finerenone plus empagliflozin vs usual care	Hierarchical composite of the following: Time to all-cause mortality; Number of total HF events; Time to first HF event; Difference of ≥5 points on KCCQ-TSS assessed by the win-ratio method; AEs leading to discontinuation; SAE	August 2026
BalanceD-HF (NCT06307652)	III (*N* ~4,800)	chronic HF and impaired kidney function	Balcinrenone + dapagliflozin vs. Dapagliflozin	Time to first occurrence of any of the components of the composite of: CV death; HF hospitalization; HF event without hospitalization	June 11. 2027
SOGALDI-PEF (NCT05676684)	II/III (*N* = 108)	HFpEF	Dapagliflozin [week 1–12]—Dapagliflozin + spironolactone [week 13–25] vs dapagliflozin + spironolactone [week 1–12]—dapagliflozin [week 13–25]	Between group comparison of of NT-pro BNP levels	November 29, 2024 No results are available, and records last updated in November 2024
NCT06655480	II (*N* ~50)	Advanced HFpEF	Triple combination therapy (ARNI, SGLT2i, MRA) vs SGLTi + previously taken RAAS blocker	At 52 weeks ΔMRI, 6MWD, NT-proBNP, LAVi, average E/e' ratio and tricuspid regurgitation velocity	December 31, 2026
MIRACLE (NCT04595370)	IIb (*N* = 153)	HF with LVEF <60% and CKD; stable background treatment for heart failure, hypertension, T2D or renal disease	Balcinrenone (3 different doses) + dapagliflozin vs dapagliflozin	% ΔUACR at 12 weeks combination vs dapagliflozin alone	Study completed (September 26, 2023) Enrollment stopped early due to poor recruitment; no significant between arm differences[20]
NCT04633005	I (*N* ~175)	HFrEF in low-income, racially diverse population	Polypill formulation consisting of metoprolol succinate, empagliflozin, and spironolactone vs GDMT	LVEF at 6 months	December 1, 2025

6MWD, 6-minute walking distance; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; AE, adverse event; HF, heart failure; KCCQ-TSS, Kansas City cardiomyopathy questionnaire—total symptom score; LAVi, left atrial volume index; MRI, myocardial extracellular volume; NT-proBNP, N-terminal pro b-type natriuretic peptide; SAE, serious adverse event; UPCR, Urinary protein-to-creatinine ratio

Ventricular Arrhythmias and SCD

Ventricular arrhythmias and SCD were seen in murine models with cardiac MR overactivation.[28] A meta-analysis of seven trials showed that MR antagonists (spironolactone and eplerenone) reduced the risk of SCD by 21% and ventricular tachycardia (VT) by 72% in HF patients with left ventricular systolic dysfunction (LVSD).[29] The spironolactone to reduce ICD therapy (SPIRIT) trial showed that spironolactone did not increase the incidence of VT or ventricular fibrillation (VF) compared to placebo in patients with implantable cardioverter-defibrillators (ICD) who are at moderately high risk for recurrent VT/VF.[30] Further, results of landmark trials, RALES,[31] EPHESUS,[32] and EMPHASIS-HF[33] showed that MR blockade (spironolactone and eplerenone) given with standard HF therapy reduced the incidence of SCD.

Pulmonary Artery Hypertension

Elevated plasma aldosterone levels and activated renin–angiotensin–aldosterone system (RAAS) have been implicated in PAH progression.[34,35] Data of patients receiving both ambrisentan (an endothelin receptor antagonist) and spironolactone in the ARIES trial showed that the World Health Organization (WHO) functional class improved by 1 ($p = 0.08$), the 6-minute walking distance improved by 94% ($p = 0.11$), and there was a decrease in brain natriuretic peptide levels ($p = 0.08$).[36]

A phase II trial (NCT01712620) is investigating the effect of spironolactone on inflammation and blood vessel function in patients with PAH.[37]

Box 1: MRAs—newer indications

Atrial fibrillation (AF)
Arrhythmia
Cancer
Cognition
Hyperandrogenism
Kidney transplant recipients
Metabolic syndrome
Other renal conditions: Alport Syndrome, primary membranous nephropathy (PMN), non-diabetic glomerulonephritis, IgA nephropathy
Other conditions: stroke, arrhythmogenic right ventricular dysplasia (ARVD), alcohol use disorder, anthracycline-induced cardiotoxicity, rheumatoid arthritis
Primary aldosteronism
Pulmonary arterial hypertension (PAH)
Sudden cardiac death (SCD)

Kidney Transplant

A narrative review reported that MRAs are safe in kidney transplant recipients (KTRs), and they have a favorable or neutral impact on blood pressure, glomerular filtration rate, urinary protein/albumin excretion, and oxidative stress. No data was found regarding major cardiovascular adverse events.[23] Another narrative review covered both preclinical and clinical studies in KTRs and reported that MRA use is associated with a reduction in proteinuria, ischemia-reperfusion injury, or calcineurin inhibitor-mediated nephrotoxicity. These benefits of MRAs in KTRs were seen without worsening renal function or clinically important adverse events such as hyperkalemia or hypotension.[22]

Other Renal Conditions

Pooled analysis of 16 RCTs in CKD patients requiring hemodialysis (HD) or peritoneal dialysis (PD) and treated with a steroidal MRA (spironolactone and eplerenone) identified some evidence that these MRAs could reduce cardiovascular and cerebrovascular disease, and the risk of all-cause mortality and cardiovascular death.[38] However, the authors identified the need for larger RCTs for conclusive evidence.

Primary Aldosteronism

Primary aldosteronism (PA) is usually bilateral and treated with conventional steroidal MRAs (spironolactone and eplerenone).[39] Several studies are investigating the efficacy and safety of steroidal MRA in new subsets of patients with PA and of nonsteroidal MRA in PA (Table 2).

Table 2: MRAs in primary aldosteronism

Trial details	*MRA*	*Research question*
The UPA-MEST (NCT05797558)	Eplerenone	Spirololactone versus surgery in unilateral PA
Phase IV, NCT05030545	Eplerenone	To evaluate the MFR change pre- vs post-6 months of eplerenone therapy in PA
Phase IV, NCT06381323	Finerenone	Efficacy and safety of finerenone in PA
Phase IV trials: NCT06457074; NCT05814770; FAVOR, NCT06164379	Finerenone vs spironolactone	Finerenone vs spironolactone in PA FAVOR: Hypertensive pts with PA

MFR, myocardial flow reserve; MRA, mineralocorticoid receptor antagonist; PA, Primary aldosteronism

Metabolic Syndrome

Mineralocorticoid receptor antagonists have the potential in metabolic syndrome because aldosterone activation is a common pathway connecting the components of metabolic syndrome, such as obesity, dyslipidemia, insulin resistance, hyperglycemia, hypertension, and renal dysfunction.[40,41]

Conclusion

Mineralocorticoid receptor antagonists are emerging as important pillars in the treatment of HF, CKD, and DKD. MRAs share complementary pathways with SGLT2i and GLP-1RA, and the combination of MRA with SGLT2i and GLP-1RA is emerging to be more beneficial in patients with HF, CKD and DKD than either of the drugs alone. Further, the unique action of MRAs in antagonizing MR receptors and aldosterone, implicated in the pathophysiology of several conditions, is paving the way for clinical trials and promising results in these therapeutic areas. Disease-specific biomarkers such as UACR and eGFR are increasingly being used to individualize treatment with MRA. Utilizing MRA-specific biomarkers may open the path for precision medicine and further treatment individualization.

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