

Mineralocorticoid Receptor Antagonist Use in Contemporary Heart Failure Care

Jolie Bruno ^{1,2,3,4} Alexandre Mebazaa ^{1,2,3} Lída Zytynski Moura ⁵ Jelena Čelutkienė ^{6,7}
Andrew Sindone ⁸ and Giuseppe Rosano ^{9,10}

1. INSERM UMR-S 942, Cardiovascular Markers in Stress Condition (MASCOT), Paris, France; 2. Université de Paris Cité, Paris, France; 3. Department of Anesthesiology, Critical Care and Burn Unit, University Hospitals Saint-Louis et Lariboisière, AP-HP, Paris, France; 4. Department of Cardiology, Inselspital, Bern University Hospital, Bern, Switzerland; 5. Department of Internal Medicine, Advanced Cardiovascular Disease and Heart Failure, Pontificia Universidade Católica do Paraná, Curitiba, Brazil; 6. Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Medical Faculty, Vilnius University, Vilnius, Lithuania; 7. Centre of Innovative Medicine, Vilnius, Lithuania; 8. Department of Cardiology and Cardiac Rehabilitation, Concord Hospital, University of Sydney, Sydney, Australia; 9. Department of Human Sciences and Promotion of Quality of Life, San Raffaele Open University of Rome, Rome, Italy; 10. Department of Cardiology, IRCCS San Raffaele Roma, Rome, Italy

Abstract

Heart failure (HF) continues to challenge clinicians worldwide, not only because of its high morbidity and mortality, but also due to the persistent difficulty in translating therapeutic advances into routine care. Despite the availability of effective treatments, data show striking gaps in the optimal use of guideline-directed medical therapy. Among the four pillars of guideline-directed medical therapy, mineralocorticoid receptor antagonists (MRAs) remain the least prescribed. This underuse is concerning considering the evidence demonstrating consistent benefits of MRAs across different HF phenotypes. In this review, we revisit the role of MRAs across the spectrum of HF. We summarise the supporting evidence, discuss their mechanisms of action and provide practical guidance on patient eligibility and initiation strategies. In addition, we address common barriers that often limit their use. By combining mechanistic insights, trial evidence and pragmatic recommendations, this review aims to facilitate broader and earlier use of MRAs, thereby helping to close a major gap in the implementation of evidence-based HF care.

Keywords

Mineralocorticoid receptor antagonist, heart failure, cardiac rehabilitation, therapy, prognosis, chronic heart failure, acute heart failure

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Correspondence: Giuseppe Rosano, Department of Cardiology, IRCCS San Raffaele, Via di Val Cannuta 249, 00161 Rome, Italy. E: giuseppe.rosano@gmail.com

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Heart failure (HF) remains a global health challenge, with a persistently high burden of morbidity and mortality. Despite major therapeutic advances over the past decades, real-world data continue to underscore a troubling gap between evidence and implementation, and the inadequacy of current strategies in reversing disease trajectory. Even in recent studies, less than 50% of eligible patients receive all four classes of guideline-recommended drugs and only about 1% are treated with fully optimised, target-dose therapy.^{1–4}

The recent REVOLUTION HF study sheds light on a crucial aspect: in patients with *de novo* HF, the first weeks following diagnosis are characterised by the highest rates of hospitalisation and mortality.⁵ These findings reinforce a critical issue: the failure to promptly recognise and initiate guideline-directed medical therapy (GDMT) at an early stage, when its impact on outcomes may be greatest.

Among the recommended therapies, mineralocorticoid receptor

antagonists (MRAs) remain the least prescribed. Real-world data confirm that this underuse represents a global issue: national and international registries have consistently reported low MRA prescription rates among eligible patients.^{4,6,7} This is partly due to the legacy of a traditional sequential approach to HF management and concerns related to potentially overestimated adverse effects.⁸ These prescribing patterns remain unchanged, both shortly after diagnosis and over time, despite the consistent evidence from landmark trials supporting the benefits of MRAs on clinical outcomes.^{1,3}

In this context, this narrative review aims to revisit the critical role of MRAs in HF and to provide practical guidance on when and how to deploy them effectively. This work was developed through a targeted, non-systematic search of the literature using PubMed, focusing on studies published up to November 2025. Priority was given to randomised controlled trials, meta-analyses and international guideline documents addressing the use of MRAs in HF. Relevant mechanistic studies and key observational data were also included to provide pathophysiological and clinical context.

Established Evidence Supporting Use of MRAs in Heart Failure

Landmark Trials with Hard Clinical Endpoints in Chronic Heart Failure

The foundation for the use of MRAs in HF was laid by the landmark RALES trial, which demonstrated a 30% relative reduction in all-cause mortality (both from progressive HF and sudden death) over a 2-year follow-up in patients with severe systolic dysfunction and advanced symptoms (New York Heart Association [NYHA] class III–IV).⁹ This study provided the proof of concept for aldosterone blockade as a life-prolonging intervention in HF with reduced ejection fraction (HFrEF).

Subsequent trials expanded the therapeutic scope of MRAs to broader populations. Eplerenone was evaluated in post-MI patients with reduced or mid-range ejection fraction in the EPHEUS trial.¹⁰ Over a median follow-up of just over 1 year, eplerenone reduced the dual primary endpoint of time to all-cause mortality by 15% and cardiovascular (CV) mortality or CV events, including hospitalisation for heart failure (HHF) by 13%.

The EMPHASIS-HF trial further extended the benefit of eplerenone to ambulatory patients with HFrEF and milder symptoms (NYHA class II), showing a 37% reduction in the composite outcome of CV death or HHF over a median follow-up of approximately 21 months.¹¹

The role of MRAs in HF with preserved (HFpEF) or mildly reduced ejection fraction (HFmrEF) has been more controversial. The TOPCAT trial, which investigated spironolactone in patients with HFpEF and HFmrEF, failed to demonstrate a significant reduction in the primary composite outcome of CV death, aborted cardiac arrest or HHF in the overall cohort.¹² However, a significant reduction in HHF was observed as a secondary endpoint over a median of 3.3 years. Notably, the interpretation of this trial has been challenged by substantial regional disparities in event rates and concerns regarding trial conduct and drug adherence in certain geographic areas, particularly in Russia and Georgia. Subsequent analyses suggested that a proportion of participants in these regions may not have had true HF and the measurement of drug levels in urine samples raised concerns about inadequate exposure in a substantial subset of patients, raising questions about the trial's validity. In contrast, in the prespecified Americas subgroup, where event rates were higher and adherence appeared more reliable, spironolactone was associated with a significant reduction in the

primary endpoint.¹³ However, these findings are derived from subgroup and post hoc analyses and should therefore be interpreted cautiously.

More recently, finerenone, a selective MRA, has expanded the evidence base in this population. The FINEARTS-HF trial reported a 16% reduction in the composite outcome of worsening HF or CV death over nearly 2 years in patients with HFpEF and HFmrEF, with this benefit driven by HHF with no effect on mortality.¹⁴

Figure 1A shows outcomes from the major MRA trials; Figures 1B and 1C provide focused analyses on CV mortality and HHF as individual endpoints. Among the trials evaluating MRAs in HFpEF and HFmrEF, TOPCAT and FINEARTS-HF failed to reach statistical significance for CV death as a single outcome. Accordingly, current guidelines assign a class 1, level a recommendation for patients with left ventricular ejection fraction (LVEF) <40% and a class 2b recommendation for HFmrEF. For patients with HFpEF, the American guidelines maintain a class 2b recommendation, whereas the European guidelines provide no formal indication.^{15,16}

Expanding the Therapeutic Spectrum: Mechanistic Studies and Emerging Clinical Settings

A growing body of evidence has explored the role of MRAs in broader CV and renal contexts or in earlier stages of disease. These studies, although often centred on surrogate or mechanistic endpoints, have expanded our understanding of the therapeutic versatility of this drug class.

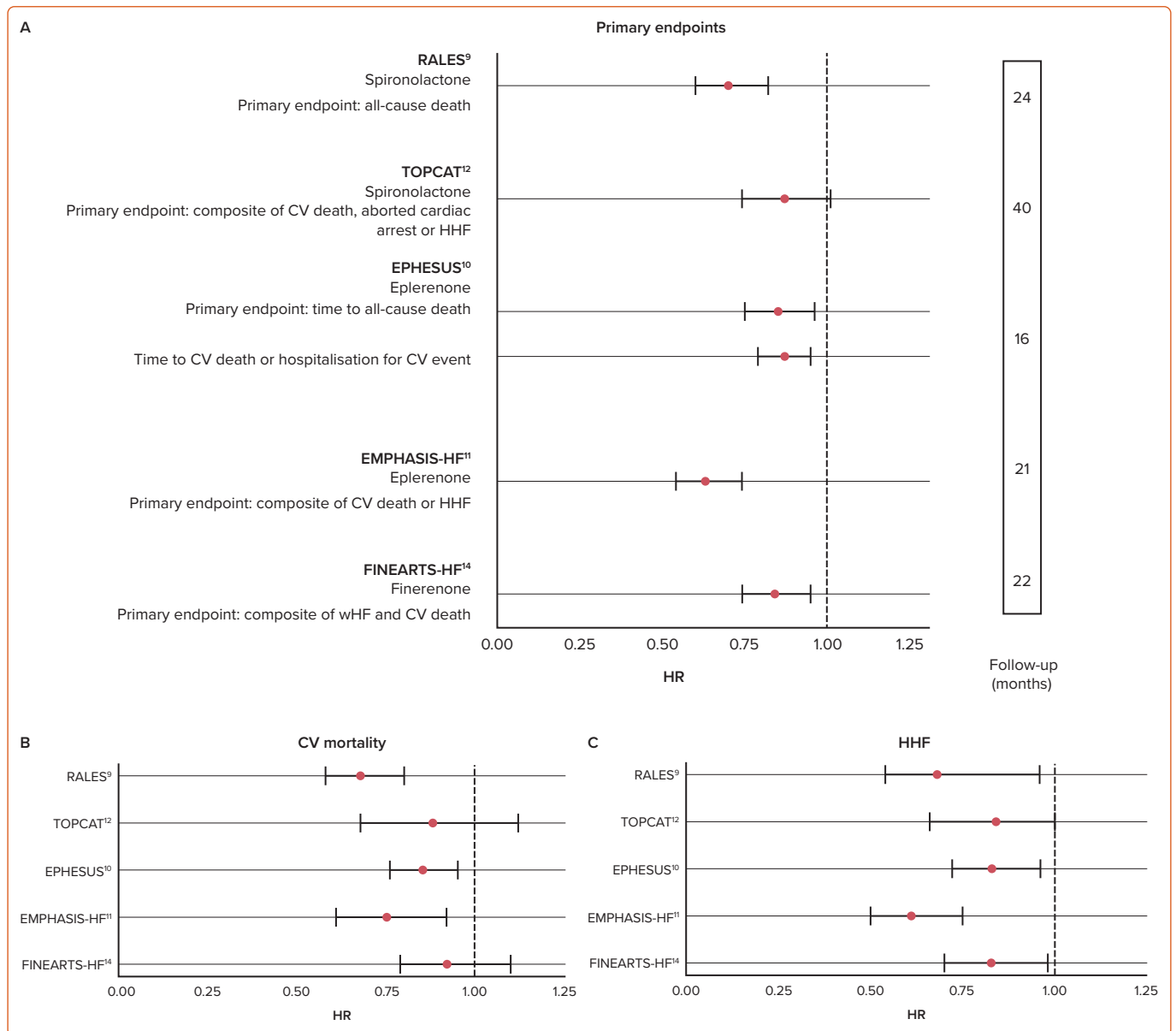
Concerning MRA-induced improvement in heart function, spironolactone improved diastolic function in patients with HFpEF in the Aldo-DHF trial, as measured by the E/e' ratio, suggesting a favourable impact on ventricular remodelling.^{17,18} Similarly, in the ARTS-HF trial, eplerenone and finerenone improved N-terminal pro-B-type natriuretic peptide in HFrEF with chronic kidney disease (CKD) and/or type 2 diabetes (T2D).¹⁹ However, in patients with end-stage kidney disease on chronic dialysis but without HF, the ALCHEMIST trial and a related meta-analysis showed that spironolactone failed to reduce major CV events, including HHF.²⁰ These findings may suggest that the clinical benefit of MRAs depends on the presence of ventricular dysfunction and neurohormonal activation, and that in the absence of these mechanisms their therapeutic effect may be limited.

Beyond chronic HF, MRAs have also been explored in acute HF (AHF). Although the ATHENA-HF trial failed to show a significant diuretic benefit of high-dose spironolactone in this setting, data from KCHF and RELAX-AHF-2 trials suggested benefit from MRA therapy in hospitalised AHF patients, regardless of ejection fraction.^{21–23} However, these trials did not consistently specify the MRA agent used (but predominantly spironolactone). The EARLIER trial, though underpowered for clinical events, showed a reduction in loop diuretic use with MRA treatment.²⁴

MRAs have also been evaluated in post-MI remodelling. While EPHEUS confirmed the benefit of eplerenone in patients with reduced ejection fraction following acute MI, subsequent trials (ALBATROSS, REMINDER and CLEAR), which enrolled patients with preserved ejection fraction and no overt HF, failed to demonstrate meaningful clinical benefit.^{10,25–27} The full spectrum of MRA use across HF phenotypes is summarised in Figure 2, reflecting the evolution from HFrEF to broader applications across the HF continuum.

On-going research efforts aim to address remaining evidence gaps and extend the role of MRAs into novel clinical domains. The SPIRIT-HF (NCT04727073) and SPIRRIT (NCT02901184) trials will evaluate

Figure 1: Effect of Mineralocorticoid Receptor Antagonists on Clinical Outcomes in Major Randomised Controlled Trials



HRs with 95% CIs from five landmark randomised controlled trials evaluating MRAs on major clinical endpoints. A: The primary composite outcome reported in each trial, with the corresponding follow-up duration (in months) indicated alongside each study name; B: CV mortality; C: HHF. CV = cardiovascular; HHF = hospitalisation for heart failure; MRA = mineralocorticoid receptor antagonist; wHF = worsening heart failure.

spironolactone in patients with HFmrEF and HFpEF. REDEFINE-HF (NCT06008197) will assess the efficacy of finerenone in these populations, with a focus on composite risk of HHF and CV death. Other studies are targeting specific subgroups where MRA use remains uncertain or underused. FINALITY-HF (NCT06033950) will investigate finerenone in HFpEF patients intolerant to steroidal MRAs.

Concerning MRA-induced improvement in renal function, two MRAs (spironolactone and finerenone) showed similar benefits in HFpEF patients with CKD in the ARTS trial.²⁸ These findings, together with data from ARTS-DN, which demonstrated reduced albuminuria with finerenone in patients with T2D, CKD, and albuminuria but without HF, supported the hypothesis that MRAs play a role in the prevention of kidney failure and slowing progression of kidney dysfunction, in addition to the metabolic positive effects.²⁹ This was further supported by the CONFIDENCE trial, which demonstrated the additive benefit of

combining finerenone with sodium–glucose cotransporter 2 inhibitors (SGLT2Is) in reducing albuminuria.³⁰

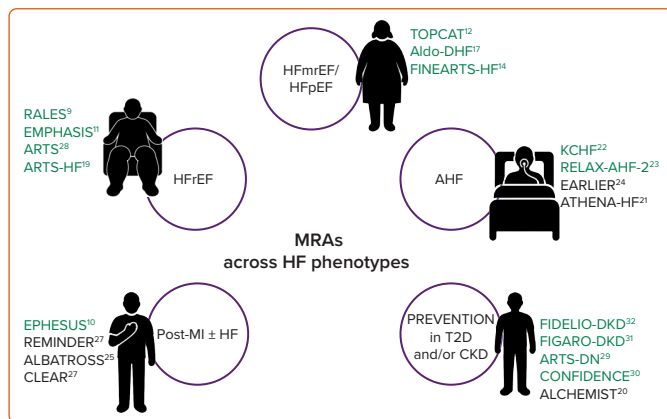
Combined benefits of MRA on CV and renal function have been seen in large-scale trials (FIDELIO-DKD and FIGARO-DKD) in which finerenone reduced both CV and renal events in patients with T2D and CKD.^{31–33}

Head-to-head Evaluation of MRAs

While the efficacy of MRAs across the HF spectrum has been well established, important differences remain between available agents in terms of pharmacological profile, tolerability and clinical impact. No event-driven head-to-head trials comparing different MRAs are currently available, and results are limited and often subject to methodological constraints; nevertheless, available data may offer some insights that could support therapeutic preferences in specific clinical contexts.

A meta-analysis of 10 studies in patients with HFpEF, comprising four

Figure 2: Mineralocorticoid Receptor Antagonists across Heart Failure Phenotypes



Key clinical trials evaluating MRAs across the spectrum of HF phenotypes. The studies correspond to HFrEF, HFmrEF, HFpEF, post-MI (with or without HF), AHF and prevention of HF in high-risk patients, particularly those with T2D and CKD. The studies assessed different endpoints; those showing beneficial effects are highlighted in green, while the others had neutral outcomes. AHF = acute heart failure; CKD = chronic kidney disease; 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; MRA = mineralocorticoid receptor antagonist; T2D = type 2 diabetes.

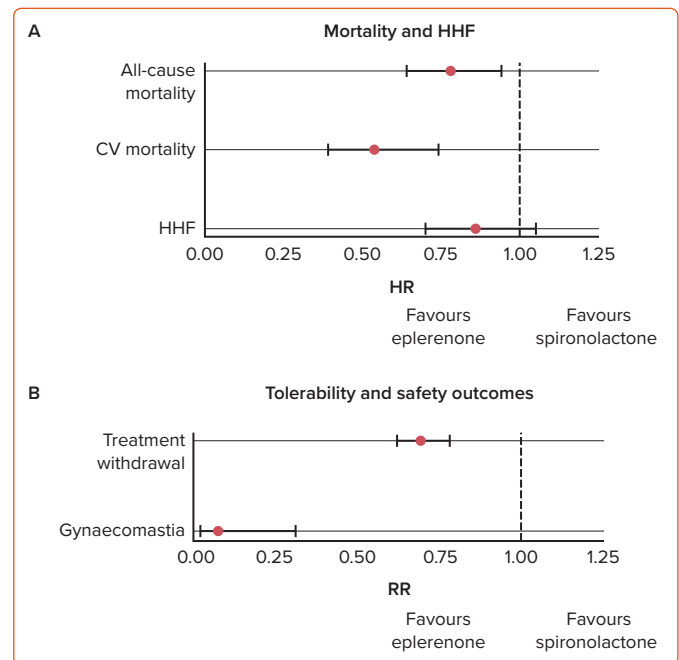
randomised controlled trials and six observational cohorts, suggested a signal toward greater reductions in all-cause and CV mortality with eplerenone compared with spironolactone.³⁴ However, these findings are derived from indirect comparisons data and are therefore subject to residual confounding, precluding definitive conclusions regarding superiority. Although no significant differences were observed in HHF, a numerical trend favoured eplerenone. Rates of hyperkalaemia, hypotension and renal dysfunction occurred at similar rates between the two agents, whereas eplerenone was associated with a significantly lower incidence of gynaecomastia and fewer treatment discontinuations (Figure 3).

The observed differences in clinical outcomes have not been consistently replicated across all HF phenotypes, and further comparative trials are warranted to better define the role of each agent across different patient populations. Nonetheless, the available data suggest that eplerenone may offer improved tolerability and treatment persistence, particularly in patients with HFrEF or those at increased risk of endocrine-related adverse effects (Figure 3). Eplerenone has also been associated with more pronounced effects on cardiac reverse remodelling compared with spironolactone in patients with HFrEF.³⁵

In contrast, direct comparisons involving finerenone are very limited. In the ARTS trial – a head-to-head comparison between finerenone and spironolactone in patients with HFrEF and moderate CKD – finerenone was associated with a similar reduction in natriuretic peptides and albuminuria, along with a smaller increase in serum potassium and a smaller reduction in estimated glomerular filtration rate (eGFR).²⁸ In the subsequent ARTS-HF trial, which enrolled patients with HFrEF and either T2D or CKD, finerenone demonstrated comparable efficacy to eplerenone in reducing natriuretic peptide levels.¹⁹

A recent meta-analysis of randomised trials indirectly compared steroidal and non-steroidal MRAs, showing greater efficacy of steroidal agents in HFrEF (RR 0.66) versus the milder effects of non-steroidal MRAs in HFmrEF/HFpEF (0.87). Rates of hyperkalaemia showed little heterogeneity

Figure 3: Comparative Effects of Eplerenone and Spironolactone in Heart Failure with Reduced Ejection Fraction



Findings from the most recent and inclusive evaluation of head-to-head studies assessing the comparative efficacy and safety of eplerenone versus spironolactone. A: Clinical outcomes, including all-cause mortality and HHF, reported as HRs with 95% CI; B: Safety and tolerability outcomes, including treatment withdrawal and gynaecomastia, reported as risk ratios with 95% CI. CV = cardiovascular; HHF = hospitalisation for heart failure.

across MRA types, although the lack of separation between on- and off-treatment events limits firm safety comparisons.³⁶ When focusing on specific subgroups, particularly patients with CKD and T2D, the efficacy of MRAs may diverge further, suggesting that disease-specific characteristics could influence comparative benefit and inform the design of future head-to-head trials.^{37,38}

Clinical Implementation: Practical Considerations for MRA Use

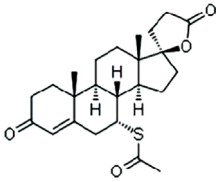
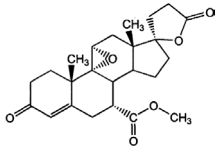
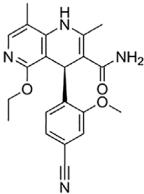
Transitioning from evidence to practice requires contextualising the pharmacological properties and trial-based outcomes of MRAs into real-world decision-making frameworks.

Pharmacokinetics and Pharmacodynamics of MRAs

MRAs exert pleiotropic effects across epithelial and non-epithelial tissues, influencing sodium handling as well as fibrotic and inflammatory pathways. Fibrosis is a hallmark of cardiorenal pathology and may represent a particularly sensitive target of the more selective non-steroidal agents, which are thought to block mineralocorticoid receptor (MR) activity more effectively in non-epithelial tissues.^{39,40} This mechanistic specificity may partly explain the more pronounced clinical benefits observed with these compounds in patients with cardiorenal comorbidities.

While all MRAs share a common mechanism of MR blockade, clinically relevant differences exist in receptor selectivity, pharmacokinetics, and tolerability. These differences are summarised in Table 1. MRAs have historically been classified as steroidal or non-steroidal agents. However, this dichotomy is based on their chemical structure, not on their drug–receptor interaction, and has no relevance to pharmacokinetic or pharmacodynamics and, thereby, their clinical effect. In contemporary

Table 1: Pharmacokinetics and Pharmacodynamics of Mineralocorticoid Receptor Antagonists

	Non-selective	Selective	
	Spironolactone	Eplerenone	Finerenone
			
Selectivity	+	+++	+++
Cofactor interaction	Recruitment	Recruitment	No Recruitment
Tissue distribution	Kidney >> heart	Kidney > heart	Kidney = heart
Active metabolite	+++	-	-
Metabolism	-	CYP3A4	-
Half-life	>20 hours	4–6 hours	2–3 hours
Renal dose adjustment	Yes	Yes	Yes
Hormonal adverse effects	++	-	-

+ = low; ++ = medium; +++ = high; - = no; > = greater; >> = much greater.

CYP3A4 = cytochrome P450 3A4.

clinical practice, a more meaningful distinction lies in their degree of selectivity for the MR, as this feature critically influences both therapeutic efficacy and patient adherence. Selectivity not only encompasses the steroidal versus non-steroidal classification but also integrates structural and functional consequences of receptor binding.

Non-selective MRAs

Spironolactone, a first-generation non-selective steroidal MRA, is associated with active metabolites and off-target hormonal effects.⁴¹ Pharmacodynamically, it acts as a competitive MR antagonist, inhibiting aldosterone-mediated sodium reabsorption at the renal level and increasing the risk of hyperkalaemia through reduced potassium excretion. In addition, spironolactone induces receptor conformational changes that permit cofactor interaction, potentially resulting in partial agonist activity and distinct transcriptional effects compared with more selective MRAs.

Selective MRAs

Eplerenone is a second-generation steroidal MRA and therefore associated with a lower incidence of sex hormone-related adverse events.⁴² It undergoes rapid hepatic metabolism via the cytochrome P450 3A4 (CYP3A4) pathway, resulting in susceptibility to drug–drug interactions, and has a shorter plasma half-life due to inactive metabolites. Eplerenone displays pharmacodynamic properties broadly similar to those of spironolactone.⁴¹

Finerenone, a non-steroidal selective MRA, acts as a receptor modulator by inducing a conformational change in the MR that prevents the recruitment of transcriptional cofactors, thereby avoiding the partial and pleiotropic agonist effects. It is rapidly absorbed and eliminated, has a balanced cardiorenal tissue distribution, no active metabolites and requires dose adjustment based on eGFR.³⁹

Clinical Indications and Patient Eligibility

The widespread adoption of MRAs in clinical practice is reflected in current HF guidelines, which assign varying classes of recommendation depending on the clinical setting and patient profile, with indications

spanning the entire spectrum of HF phenotypes – both chronic and acute.^{15,16,43} In HFrEF and AHF, both spironolactone and eplerenone are viable options; however, eplerenone may be preferable when available, due to its favourable profile in terms of both efficacy and tolerability and should also be preferentially used in patients with ischaemic HF.

In HFmrEF and HFpEF, all three agents (spironolactone, eplerenone and finerenone) may be considered. In patients with T2D and CKD, finerenone has demonstrated clinical benefits.⁴⁴ In other situations, eplerenone remains a reasonable first-line option, balancing efficacy with a lower risk of hormonal adverse effects.

In some European countries, potassium canrenoate (canrenone) is available for clinical use. However, this has never been tested in patients with HF, has never demonstrated any effect on clinical hard endpoints and is not endorsed by any guideline; therefore, it should not be used as an alternative MRA for the treatment of HF.

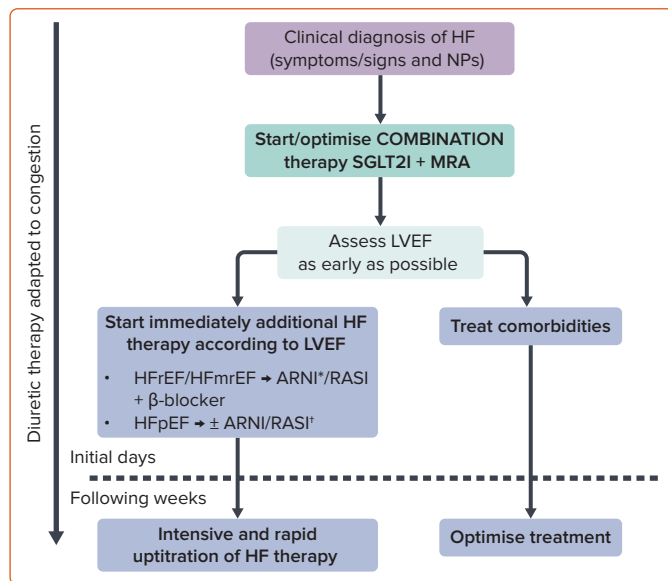
When more than one MRA is suitable, selection should be guided by patient comorbidities, tolerability and drug availability.

Additive Benefits of MRA–SGLT2I Combination Therapy

In the context of contemporary HF therapy, the recent introduction of SGLT2Is has triggered a wave of post hoc analyses and secondary evaluations of previously conducted trials, aiming to reassess the safety and efficacy of these agents when integrated. These investigations have yielded clinically meaningful insights, particularly regarding their interaction with MRAs, which warrant specific attention.

The combined use of MRAs and SGLT2Is seems to be associated with a greater relative reduction in CV mortality among patients with chronic HF treated with SGLT2Is who were also receiving MRAs compared with patients who were treated with SGLT2Is but not MRAs, regardless of ejection fraction.^{45,46} In addition, this combination appears to attenuate the risk of hyperkalaemia – probably because of the nephroprotective

Figure 4: Proposed Initial Therapeutic Approach Based on Expert Opinion Following a Heart Failure Diagnosis



Following the clinical diagnosis of HF – primarily based on signs, symptoms and elevated NPs – upfront combination therapy with an SGLT2I and an MRA should be initiated, given their additive prognostic benefit. Subsequently, LVEF should be assessed as early as possible to guide further HF therapy. In HFrEF/HFmrEF, a β-blocker and an ARNI/ACEi/ARB if ARNI should be initiated and uptitrated. Comorbidities should be systematically identified and managed accordingly. In all phenotypes, diuretic therapy should be adjusted in parallel based on signs and degree of congestion. *Should be preferred if available. †According to local guidelines. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-II receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; 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; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NPs = natriuretic peptides; RASi = renin–angiotensin system inhibitor; SGLT2I = sodium–glucose cotransporter 2 inhibitor.

effects of SGLT2Is and their beneficial effects on volume status – and it has been associated with lower rates of treatment discontinuation in clinical practice.^{47,48}

The recently published CONFIDENCE trial, which randomised patients with CKD and T2D to receive finerenone plus empagliflozin versus either agent alone, reported a 29% greater reduction in urinary albumin:creatinine ratio compared with finerenone monotherapy and 32% versus empagliflozin monotherapy at 180 days.³⁰ These findings support the emerging concept of an additive effect when the two drug classes are used in combination. Two on-going studies are further exploring this concept: CONFIRMATION-HF (NCT06024746) and MIRACLE (NCT04595370).

Practical Algorithm for Initiating MRA Therapy

The growing recognition that the benefits of MRAs extend across the full spectrum of LVEF, and that early therapeutic intervention can meaningfully influence outcomes, as highlighted by the REVOLUTION-HF study, has fostered a clinical approach favouring their prompt initiation, ideally at the time of HF diagnosis.⁵ Diagnosis is primarily based on clinical suspicion from signs and symptoms and is typically supported and confirmed by elevated natriuretic peptide concentrations. When feasible, initiating MRAs in parallel with SGLT2Is represents a rational strategy increasingly supported, given the complementary mechanisms of action, the potential for additive cardiorenal protection, attenuation of adverse events and broad therapeutic applicability.⁴⁹

This combination may be considered even before echocardiographic confirmation of LVEF – particularly when diagnostic delays are expected

– provided there is a high clinical likelihood of HF and alternative diagnoses have been excluded, with appropriate assessment of renal function and serum potassium. SGLT2Is, non-steroidal MRAs and glucagon-like peptide-1 receptor agonists are indicated for HF prevention in patients with diabetes and CKD.⁵⁰ However, there is no evidence for the use of finerenone in patients with HF and LVEF <45%.

Nevertheless, cardiac imaging with LVEF assessment remains essential, as it guides the introduction of additional disease-modifying agents. In patients with HFrEF or HFmrEF, β-blockers and renin–angiotensin system inhibitors (RASIs; including angiotensin receptor–neprilysin inhibitors [ARNIs]) should be promptly introduced, with rapid and intensive uptitration over the subsequent week.⁵¹ In HFpEF, RASI/ARNI may be considered based on guideline-directed indications and individual patient profile.

In parallel, comorbidities must be assessed and managed appropriately. These conditions may act as precipitating factors for AHF, contribute to the development of left ventricular dysfunction and significantly influence long-term disease progression and prognosis.^{52–54}

Congestive symptoms should be managed throughout the disease course with individualised diuretic therapy, typically loop diuretics administered intravenously or orally, based on clinical presentation. In patients at risk of diuretic resistance, such as those with reduced eGFR (<60 ml/min/1.73 m²) or chronic outpatient diuretic use, temporary combination therapy with acetazolamide (preferably) or thiazides may be warranted, depending on patient characteristics and local availability (Figure 4).^{55,56}

Clinical Hesitations and Practical Strategies for MRA Use

Once the indication for MRA therapy has been established, specific clinical features must be considered before and during treatment. Renal function, serum potassium levels, endocrine adverse effects and patient frailty not only influence the feasibility of initiating therapy, but also affect its safety, monitoring requirements, dosage and long-term persistence.

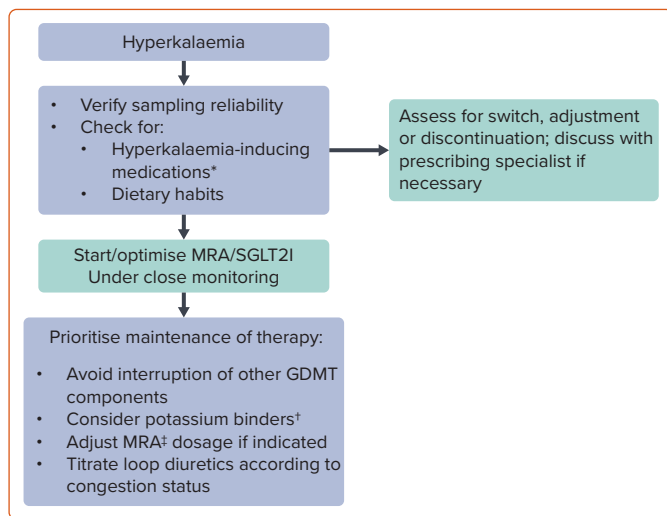
Effective strategies to overcome clinical hesitation may include the development of standardised protocols that clearly define eligibility criteria and safety thresholds for therapy initiation, such as acceptable serum potassium ranges, renal function limits and contraindications. Integration of these protocols into digital clinical systems may further facilitate implementation through automated alerts and clinical decision-support tools, helping to identify when therapy should be initiated, withheld, or closely monitored. Importantly, such pathways should also specify structured monitoring strategies, including the frequency and type of laboratory assessments and follow-up scheduling. Multidisciplinary care models, including collaboration with specialised HF teams, structured follow-up programmes and the involvement of trained non-physician healthcare professionals, particularly in resource-limited clinical settings, represent additional key components.⁵⁷

Renal Function

MRAs can generally be used down to an eGFR of 25 ml/min.^{43,58} In end-stage CKD, data suggest potential CV benefit, but the recent randomised ALCHEMIST trial in patients without HF failed to show improvements in CV outcomes.^{59,60} Importantly, spironolactone was not associated with an increased incidence of hyperkalaemia in this trial.²⁰ For finerenone, renal function is a critical determinant of dosing, as initial dose selection is directly based on eGFR.⁵⁸

During treatment, a rise in serum creatinine may occur that can be either

Figure 5: Management of Hyperkalaemia in Patients with a Diagnosis of Heart Failure



*Potassium-sparing diuretics, potassium supplements, NSAIDs, certain antibiotics, immunosuppressants and CYP3A4 inhibitors may increase serum potassium. †For example, patiromer or sodium zirconium cyclosilicate.^{68,69} ‡As outlined by Ferreira et al. 2020.⁶¹ CYP3A4 = cytochrome P450 3A4; GDMT = guideline-directed medical therapy; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; SGLT2I = sodium–glucose cotransporter 2 inhibitor.

transient or persistent. A decline in glomerular filtration can be expected within the first week to months of therapy and is generally functional in nature, reflecting haemodynamic changes rather than structural kidney damage. Importantly, an increase in creatinine of <40% from baseline, combined with clinical improvement, should not lead to drug discontinuation.⁶¹ The key to safe and effective use lies in appropriate monitoring, rather than indiscriminate avoidance.

Electrolyte Management

Managing electrolyte disturbances during MRA therapy requires an understanding of their clinical implications. Serum potassium exhibits a U-shaped relationship with outcomes, with both low and high levels associated with an increased risk of mortality.⁶² While hyperkalaemia often attracts clinical concern, it is important to recognise that hypokalaemia may carry an even greater hazard, with a two- to threefold increase in mortality at serum potassium levels below 3.5 mmol/l compared with normokalaemic patients.⁶²

Regarding hyperkalaemia, reported in just under 20% of HF patients starting MRA therapy, it should not preclude initiation of MRA therapy when serum potassium levels are <5.7 mmol/l.⁶³ In cases approaching or exceeding critical thresholds (Figure 5), it is essential to first exclude pseudo-hyperkalaemia (caused by potassium leakage from cells in the blood sample) and identify any concomitant medications that may increase potassium levels, such as potassium-sparing diuretics, supplements, non-steroidal anti-inflammatory drugs, trimethoprim, calcineurin inhibitors (e.g. tacrolimus, cyclosporine) and CYP3A4 inhibitors. Where feasible, these agents should be dose-adjusted or discontinued in consultation with the prescribing physician.

Dietary factors may also contribute to potassium elevation, although their overall impact is modest. A diet rich in fibre may help regulate potassium homeostasis by stimulating insulin release and reducing gut absorption, whereas consumption of processed meats should be minimised. However, strict potassium restriction is not routinely recommended, as the

bioavailability of potassium varies and no fixed dietary potassium-to-protein ratio has proven clinical benefit.⁶⁴

In cases where serum potassium exceeds 5.7 mmol/l, levels should be rechecked within a short interval, typically within 1 week. If values normalise, therapy may be initiated with close monitoring. The concomitant use of SGLT2Is is encouraged, not only for their additive CV benefits in HF and for their disease-modifying effects in patients with diabetes and CKD, where they are independently indicated, but also for their potential to mitigate the risk of hyperkalaemia. Indeed, suboptimal control of these comorbidities often represents the true driver of hyperkalaemia, rather than only a direct adverse effect of MRA therapy itself.⁶⁵ It is important to note that in cases of hyperkalaemia where MRA therapy is discontinued, patients face a more than sixfold increased risk of death (HR 6.44; 95% CI [4.45–9.33]); however, this excess risk is not attributable to hyperkalaemia itself, but rather to the discontinuation of the therapy.^{36,66–68} Therefore, it is essential to identify patients at elevated risk of developing hyperkalaemia and make every effort to prevent treatment discontinuation or allow treatment initiation, thereby ensuring that patients are not deprived of the clinical benefits associated with MRA therapy. There is currently no direct evidence from head-to-head studies indicating that one MRA carries a lower risk of hyperkalaemia than another.

Populations at elevated risk include elderly patients, those with CKD and individuals with T2D; they should undergo more frequent serum potassium and creatinine checks, within 1–2 weeks of therapy initiation and at wider intervals thereafter if values remain consistently within the target range. Their increased vulnerability reflects reduced renal potassium excretion, impaired aldosterone response and tubular dysfunction. Rather than contraindicating therapy, this risk profile warrants structured follow-up.

If potassium remains elevated despite these measures, options to adopt include avoiding premature discontinuation of other GDMT agents (e.g. RASIs) in order to prevent worsening of HF, introducing potassium binders, titrating MRA dose appropriately and adjusting loop diuretic intensity according to clinical signs of congestion.^{69,70} Recent expert reviews have outlined effective strategies for managing this clinical scenario.⁶²

Endocrine Adverse Effects

Steroidal MRAs such as spironolactone are well known for their hormonal adverse effects, including gynecomastia, menstrual irregularities and decreased libido, largely attributable to their non-selective affinity for androgen and progesterone receptors. Gynecomastia and/or accompanied by breast tenderness – the most frequently reported endocrine adverse effects – affect approximately 10–15% of male patients treated with spironolactone. In contrast, eplerenone and finerenone, due to their higher receptor selectivity, are not associated with these endocrine disturbances, making them particularly suitable for younger individuals, women of childbearing potential and patients concerned about sexual adverse effects.^{34,71} This pharmacological selectivity represents a clinically relevant advantage, likely to enhance adherence and overall treatment satisfaction.

Blood Pressure Effects

The available data on the blood pressure effects of MRAs are heterogeneous and must be interpreted based on the clinical indication. In HF populations, the net haemodynamic impact of MRAs is generally modest and substantially less pronounced than that of RASIs, ARNIs or diuretics. In studies conducted separately for each agent, spironolactone

has been associated with an average systolic blood pressure reduction of approximately 10 mmHg.^{28,72} Overall, spironolactone appears to exert the greatest blood pressure-lowering effect, followed by eplerenone and finerenone.^{28,72} However, meta-analytic data indicate that in HF patients these differences are not statistically significant, and the overall incidence of hypotension events does not differ meaningfully.^{34,71} Of interest, in patients with HF and systolic blood pressure <105 mmHg, MRAs increase blood pressure values at 1 month, while blood pressure reduction is seen only in patients with systolic blood pressure values >135 mmHg.⁷³

This favourable haemodynamic profile supports the use of MRAs even in very early phases of acute clinical conditions – such as immediately after stabilisation with diuretics in AHF, avoiding misattributing residual hypotension to the MRA itself, or during recovery from cardiogenic shock, in patients requiring only minimal inotropic support or temporary mechanical circulatory assistance – providing accurate monitoring.⁷⁴

Elderly Patients

MRAs retain their efficacy across the age spectrum, including in elderly patients.^{75,76} However, this population is more vulnerable to adverse events such as hyperkalaemia, renal dysfunction and hormonal adverse effects. In clinical trials, the primary safety endpoint often included treatment discontinuation due to one of these complications.⁶⁸ Given its more favourable tolerability profile, particularly the lower incidence of endocrine-related adverse events and comparable renal safety, eplerenone may be preferred in older adults when available.

Cost-effectiveness and Economic Considerations

MRAs not only offer substantial clinical benefits across the spectrum of HF, but also represent a highly efficient use of healthcare resources. In Brazil, a cost-effectiveness analysis in patients with HF_{rEF} demonstrated that both spironolactone and eplerenone yielded significant health gains at acceptable costs, with eplerenone showing the most favourable economic profile.⁷⁷ In the US, MRA therapy in patients with HF_{mEF} and HF_{pEF} was associated with an average gain of approximately one quality-adjusted life year (QALY) per patient, at a notably low incremental

cost of around \$10,000 per QALY.⁷⁸ In patients with ischaemic HF, the use of eplerenone in the UK was also found to be cost-effective compared with standard care, with incremental costs ranging from approximately \$5,700 to \$10,100 per QALY gained, depending on treatment duration.⁷⁹ In the setting of CKD and T2D, finerenone has demonstrated favourable economic value as well. A lifetime model in the US estimated that adding finerenone to standard therapy provided nearly half a QALY of additional benefit, at an incremental cost of approximately \$135,000 (below the willingness-to-pay threshold of \$150,000/QALY).⁸⁰

Beyond individual estimates, multiple systematic reviews involving tens of thousands of patients confirm the economic value of eplerenone across diverse healthcare settings.⁸¹ Although the acquisition cost of eplerenone is higher than that of generic spironolactone, this is counterbalanced by its superior safety profile, lower incidence of adverse effects and reduced need for treatment discontinuation or hospital admission. Canadian health-economic models, for instance, indicate that when downstream savings from reduced healthcare usage (such as fewer hospitalisations and less treatment modification) are accounted for, eplerenone not only becomes cost-effective but may even generate net cost savings over a 5-year time frame.⁸²

Conclusion

MRAs remain a foundational component of GDMT in HF, with robust evidence supporting their use in HF patients with reduced ejection fraction and emerging data in those with preserved ejection fraction. Their concomitant use with other components of GDMT, particularly SGLT2Is, confers additive and complementary effects, improving outcomes while mitigating potential adverse events. Importantly, these adverse effects should not be mistaken for the natural expression or worsening of the underlying disease. Therefore, every effort must be made to ensure that eligible patients receive and maintain MRA therapy, as only through comprehensive implementation of evidence-based treatment can we overcome the persistent undertreatment and improve the still-unfavourable prognosis of HF. □

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