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REVIEW

Mineralocorticoid receptor antagonists in heart failure with preserved (and mildly reduced) ejection fraction: a comparative review of spironolactone and finerenone

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Abstract

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure presentations and remains associated with substantial mortality, ranging from 15% at 1 year to nearly 75% within 5-10 years following hospitalization. Mineralocorticoid receptor antagonists (MRAs), which blunt maladaptive activation of the renin-angiotensin-aldosterone system and thereby attenuate myocardial fibrosis, sodium retention, inflammation, and progressive ventricular remodeling, have been explored as a mechanistically grounded therapeutic strategy in HFpEF. Spironolactone, the most extensively studied steroidal MRA, was evaluated in the TOPCAT trial involving 3445 patients with symptomatic HFpEF or heart failure with mildly reduced ejection fraction; however, the trial did not demonstrate a significant overall benefit, while treatment was associated with increased rates of hyperkalemia and worsening renal function. Moreover, concerns regarding trial design, conduct, and marked regional heterogeneity in outcomes have further complicated interpretation, contributing to ongoing uncertainty regarding the role of spironolactone in routine HFpEF management. In contrast, finerenone, a non-steroidal MRA with greater receptor selectivity than spironolactone, demonstrated favorable outcomes in the FINEARTS-HF trial, which enrolled 6001 patients with symptomatic heart failure and left ventricular ejection fraction ≥40%, significantly reducing worsening heart failure events and cardiovascular death (rate ratio 0.84; 95% CI, 0.74-0.95), with consistent effects across the ejection fraction spectrum. Despite these findings, the substantially higher cost of finerenone compared with spironolactone may limit its accessibility and real-world use, particularly in resource-limited settings, and the absence of head-to-head randomized trials precludes definitive conclusions regarding comparative efficacy, safety, and cost-effectiveness; future studies should therefore directly compare these agents across clinical and economic outcomes in HFpEF.

Key words: HFpEF; spironolactone; finerenone; mineralocorticoid receptor antagonists.

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Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately 50% of all heart failure (HF) cases, with reported mortality ranging from about 15% at 1 year to nearly 75% within 5-10 years following hospitalization.[1,2] The prevalence of HFpEF continues to rise in tandem with the aging population and epidemics of obesity, diabetes, and hypertension.[3,4] Despite its considerable clinical burden and escalating healthcare expenditures, evidence-based pharmacological therapies capable of meaningfully improving outcomes in HFpEF remain limited.[5,6]

Maladaptive activation of the renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in the pathophysiology of HFpEF by promoting sodium retention, myocardial fibrosis, and progressive cardiac remodeling.[7,8] Mineralocorticoid receptor antagonists (MRAs) counteract these effects by blocking aldosterone signaling, thereby attenuating RAAS-mediated injury and reducing myocardial fibrosis and ventricular stiffening, providing a strong theoretical rationale for their use in HFpEF.[9] However, in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, the largest randomized study of spironolactone in HFpEF, no significant overall benefit was demonstrated, while treat-

ment was associated with increased rates of hyperkalemia and worsening renal function.[10] Moreover, concerns regarding trial design, conduct, and marked regional heterogeneity in outcomes have further complicated the interpretation of these findings, contributing to uncertainty regarding the role of spironolactone in routine HFpEF management.[11,12]

More recently, the non-steroidal MRA finerenone was evaluated in the FINEARTS-HF (Finerenone trial to investigate Efficacy and Safety superior to placebo in patients with Heart Failure) trial, where it demonstrated favourable cardiovascular outcomes with an acceptable safety profile in patients with HFmrEF or HFpEF.[13] These findings have reignited discussion about the broader role of MRAs in HFpEF and, more importantly, have renewed interest in finerenone as a potentially preferable option to spironolactone. Nevertheless, in the absence of direct comparative evidence between the two, important uncertainties remain regarding their relative clinical positioning. Therefore, in this review, we examine the contemporary evidence surrounding spironolactone and finerenone in HFpEF, highlighting their mechanistic distinctions, clinical trial data, and evolving roles in treatment.

Mechanistic and pharmacologic differences between spironolactone and finerenone

Despite targeting a common receptor, spironolactone and finerenone differ substantially in their pharmacokinetic and pharmacodynamic properties. Spironolactone, a steroidal MRA, acts as a competitive antagonist at the MR.[14] Although it binds the receptor with high affinity, its selectivity is limited due to structural similarity to endogenous steroid hormones, permitting off-target interactions that contribute to adverse effects such as gynecomastia.[14,15] In addition, spironolactone exhibits partial agonistic activity under certain conditions, which may modulate downstream receptor signaling.[14] Its tissue distribution demonstrates marked renal predominance, with substantially higher concentrations in the kidney than in the heart.[14] Furthermore, spironolactone undergoes hepatic metabolism to active metabolites, including canrenone and 7α-thiomethylspironolactone, resulting in prolonged pharmacologic activity, with half-lives exceeding 20 hours.[14,16]

Finerenone, in contrast, is a non-steroidal MRA with a bulky molecular structure that confers greater MR selectivity and minimal interaction with other steroid hormone receptors.[17] Unlike spironolactone, finerenone functions as an inverse agonist and suppresses transcription of pro-inflammatory and pro-fibrotic gene programs downstream of MR activation. These ligand-specific interactions result in differential regulation of MR-dependent transcriptional pathways and distinct anti-inflammatory and anti-fibrotic effects in preclinical models.[17] Finerenone also demonstrates a more balanced tissue distribution, achieving comparable concentrations in both the heart and kidneys, thereby enabling more uniform MR blockade across organ systems.[18,19] In addition, its shorter plasma half-life of approximately 2–3 hours may facilitate more efficient renal potassium handling (Figure 1).[18]

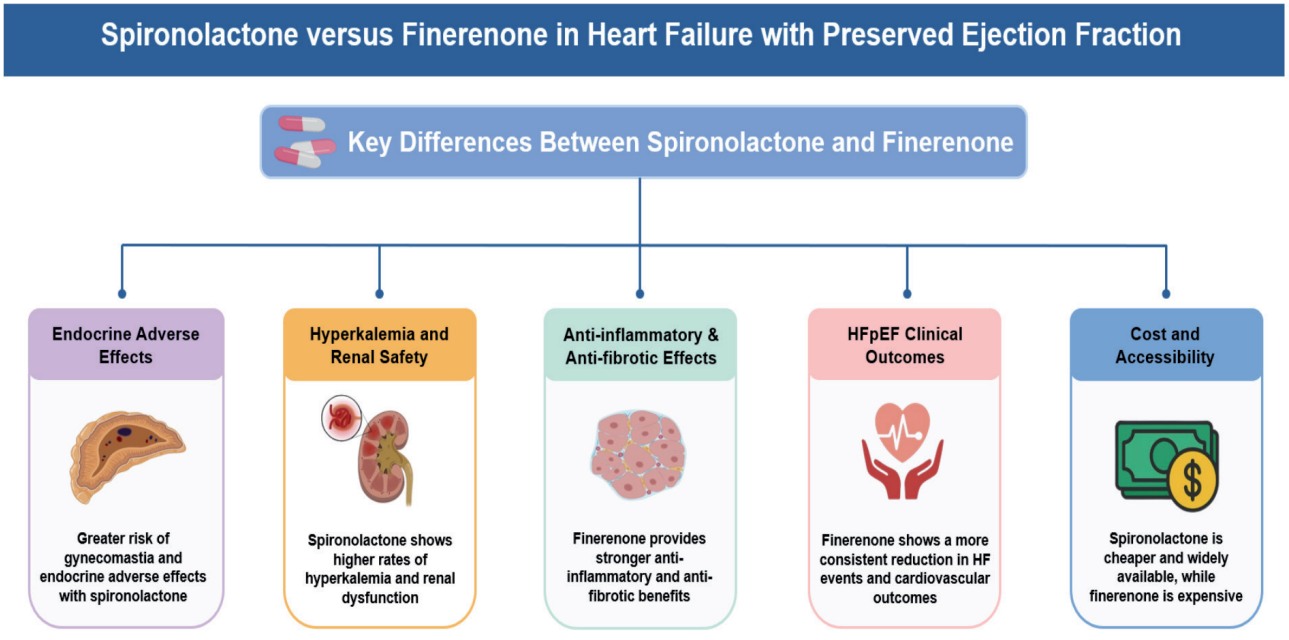

Figure 1. Major pharmacologic and clinical differences between spironolactone and finerenone in heart failure with preserved ejection fraction (HFpEF).

Current clinical evidence comparing spironolactone and finerenone in heart failure with preserved ejection fraction

Recently, a retrospective propensity-matched cohort study using the TriNetX database compared finerenone with spironolactone in patients with HFpEF.[20] Finerenone use was associated with significantly lower risks of HF exacerbation (P<0.001), all-cause mortality (P<0.001), and hypokalemia (P=0.001), with consistent findings for HF exacerbation across subgroups stratified by diabetes mellitus and chronic kidney disease (CKD) (Table 1). These findings suggest possible comparative advantages in this dataset. A second, smaller propensity-matched analysis found no statistically significant differences in most outcomes (Table 1). Given the inherent limitations of observational comparisons, including potential residual confounding related to baseline renal dysfunction severity and concomitant nephrotoxic drug exposure, these findings should be interpreted as associations and require confirmation in randomized controlled trials (RCTs).

At present, no head-to-head RCT has directly compared finerenone and spironolactone in HFpEF, and the available evidence is therefore derived primarily from separate placebo-controlled trials. Evidence supporting spironolactone is largely based on the TOPCAT trial, which enrolled 3,445 patients with symptomatic HFpEF or HFmrEF [left ventricular ejection fraction (LVEF) ≥45%].[10] In the overall study population, spironolactone did not demonstrate a significant reduction in the primary composite endpoint of cardiovascular death, aborted cardiac arrest, or HF hospitalization. Among the individual components of the primary outcome, only hospitalization for HF was significantly reduced in the spironolactone group compared with placebo [hazard ratio (HR) 0.83; 95% CI, 0.69-0.99; P=0.04].

Interpretation of these findings has remained highly contentious because of substantial regional heterogeneity in baseline risk and treatment response.[11] Stratified analyses by geographic region demonstrated that participants from the Americas (Canada, United States, Argentina, and Brazil) derived a clear reduction in the primary outcome with spironolactone (HR 0.82; 95% CI, 0.69-0.98), whereas those enrolled from Eastern Europe (Russia and Georgia) did not experience significant benefit (HR 1.10; 95% CI, 0.79-1.51).[21] Direct comparison of regional cohorts further revealed that patients recruited from Eastern Europe, who comprised nearly half of the trial population, exhibited placebo event rates approximately one-fifth of those observed in the Americas, findings that were inconsistent with prior epidemiological and randomized trial data in HFpEF.[21] Indeed, mortality rates in Eastern Europe approximated those of the general population, raising substantial concerns regarding patient selection, adherence, and trial conduct in these regions.[11] These findings have led to greater emphasis on the Americas cohort; however, this regional analysis was post hoc and should be interpreted accordingly.[21]

The use of finerenone was evaluated in the FINEARTS-HF trial, which enrolled 6001 patients with symptomatic HF and (LVEF) ≥40%.[13] Compared with placebo, finerenone significantly reduced the rate of the primary composite endpoint of worsening HF events, including unplanned HF hospitalizations or urgent HF visits, and cardiovascular death [rate ratio (RR) 0.84; 95% CI, 0.74-0.95]. Importantly, the therapeutic benefit of finerenone remained consistent across the spectrum of LVEF ≥40%, including among patients with higher LVEF values.[22] In contrast, post hoc analyses of TOPCAT stratified by LVEF suggested that spironolactone conferred greater clinical benefit among patients at the lower end of the ejection fraction spectrum, particularly those with mildly reduced LVEF, with less apparent benefit observed in patients with LVEF in the normal range (>55-60%).[22]

Further, the risks of hyperkalemia and worsening renal function remain major barriers to the clinical implementation of MRAs, particularly given the high prevalence of chronic kidney disease (CKD) among patients with HFpEF, which has been estimated to range from 40% to 60%.[23] In FINEARTS-HF, investigator-reported hyperkalemia occurred in 9.7% of patients receiving finerenone and 4.2% receiving placebo.[13] In the Americas cohort of TOPCAT, hyperkalemia was reported in 25.2% of patients receiving spironolactone and 8.9% receiving placebo.[24] However, these rates should not be compared directly because the trials differed in population, follow-up, monitoring, and outcome definitions and therefore cannot establish a lower hyperkalemia risk with finerenone than with spironolactone.

Clinical implications and future directions

The currently available evidence suggests that finerenone confers clinically meaningful benefit in patients with HF and LVEF ≥40%, with reductions in worsening HF events and an acceptable safety profile in FINEARTS-HF, although hyperkalemia was more frequent than with placebo.[13] These findings may be relevant in patients with concomitant CKD, but comparative tolerability versus spironolactone remains uncertain. However, there are several important caveats to consider. The evidence base supporting spironolactone remains heavily influenced by the methodological limitations and regional inconsistencies of the TOPCAT trial, making it difficult to accurately determine the clinical benefit associated with spironolactone.[21] Importantly, participants enrolled from the Americas cohort experienced meaningful reductions in adverse cardiovascular outcomes,[11] raising the possibility that the neutral overall findings of TOPCAT may not adequately reflect the therapeutic potential of spironolactone in genuine HFpEF populations.

At present, comparisons between finerenone and spironolactone rely primarily on indirect evidence derived from separate placebo-controlled trials and observational analyses.[20] Important differences in trial design, eligibility criteria, endpoint definitions, baseline renal function, and background medical therapy substantially limit definitive conclusions regarding comparative efficacy and safety. Direct head-to-head randomized controlled trials, therefore, remain pertinent to determine whether the pharmacologic advantages of finerenone translate into clinically meaningful superiority in patients with HFpEF.

Table 1. Summary of key clinical studies evaluating cardiovascular outcomes of finerenone and spironolactone in heart failure with preserved ejection fraction.

Study [Ref].	Patient population	Age, mean	LVEF, %	Sample size (n)	Treatment arms	Outcome	Findings
			Observational studies				
Almas *et al.* 2026 [20]	Adults with HFpEF identified from the TriNetX database who were prescribed finerenone or spironolactone within 1 year of diagnosis	70	NA	982*	Finerenone *vs.* Spironolactone	HF exacerbation	HR: 0.63 (0.54–0.74) P<0.001
						Acute myocardial infarction	HR: 1.01 (0.67–1.53) P=0.741
						All-cause mortality	HR: 0.38 (0.23–0.64) P<0.001
						Acute kidney injury	HR: 0.81 (0.65–1.02) P=0.009
						Renal replacement therapy	HR: 0.86 (0.39–1.88) P=0.543
						Hypokalaemia	HR: 0.58 (0.40–0.85) P=0.001
						Hyperkalaemia	HR: 0.96 (0.69–1.33) P=0.325
Habib *et al.* 2025 [27]	Adults ≥18 years with new-onset HFpEF identified from the TriNetX database between January 2021 and August 2025	73	NA	502*	Finerenone *vs.* Spironolactone	Acute HF events	HR: 1.26 (0.58–2.74) P>0.05
						All-cause mortality	HR: 0.48 (0.23–1.00) P>0.05
						All-cause hospitalization	HR: 1.01 (0.70–1.45) P>0.05
						Acute myocardial infarction	HR: 1.51 (0.55–4.15) P>0.05
						MACE	HR: 0.98 (0.58–1.65) P>0.05
						Acute kidney injury	HR: 1.16 (0.65–2.07) P>0.05
						Hyperkalaemia	HR: 0.89 (0.42–1.89) P>0.05
			Randomized controlled trials				
Solomon *et al.* 2024 [13]	Adults ≥40 years with symptomatic HF and LVEF ≥40%, with evidence of structural heart disease and elevated natriuretic peptides	72	52.6	6001	Finerenone *vs.* Placebo	Composite of total worsening HF events and cardiovascular death	RR: 0.84 (0.74–0.95) P=0.007
						Total worsening HF events	RR: 0.82 (0.71–0.94) P=0.006
						Change in KCCQ total symptom score	MD: 1.6 (0.8–2.3) P<0.001
						Investigator-reported hyperkalemia (%)	9.7 *vs.* 4.2
						Hyperkalemia that led to hospitalization (%)	0.5 *vs.* 0.2
Pitt *et al.* 2014 [10]	Adults ≥50 years with symptomatic HFpEF (LVEF ≥45%) and prior HF hospitalization or elevated natriuretic peptide levels	69	56	3445	Spironolactone *vs.* placebo	Composite of cardiovascular death, aborted cardiac arrest, or HF hospitalization	HR: 0.89 (0.77–1.04) P=0.14
						Cardiovascular death	HR: 0.90 (0.73–1.12) P=0.35
						Hospitalization for HF	HR: 0.83 (0.69–0.99) P=0.04
						Aborted cardiac arrest	HR: 0.60 (0.14–2.50) P=0.48
						All-cause mortality	HR: 0.91 (0.77–1.08) P=0.29
						All-cause hospitalization	HR: 0.94 (0.85–1.04) P=0.25
						Myocardial infarction	HR: 1.00 (0.71–1.42) P=0.98

*After propensity score matching.

HFpEF, heart failure with preserved ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction; HR, hazard ratio; RR, rate ratio; CI, confidence interval; MACE, major adverse cardiovascular events; AKI, acute kidney injury; KCCQ, Kansas City Cardiomyopathy Questionnaire; MD, mean difference; AMI, acute myocardial infarction; NA, not available; RCT, randomized controlled trial.

Further, although finerenone may offer advantages over spironolactone, in the United States, its cited annual acquisition cost exceeds approximately $7000, whereas generic spironolactone is available for less than $100 per year.[25] This disparity carries major implications for affordability and equitable access, particularly within healthcare systems with constrained resources and among patients with limited insurance coverage.[26] Moreover, the high cost associated with finerenone may discourage treatment initiation entirely, especially in patients already burdened by the cumulative expense of multidrug HF regimens.[27] Future investigations should therefore extend beyond conventional efficacy and safety endpoints to incorporate formal pharmacoeconomic and cost-effectiveness analyses comparing finerenone and spironolactone across diverse healthcare systems and patient risk profiles.

Conclusions

While there is increasing evidence supporting finerenone in HFpEF, robust comparative data against spironolactone remain scarce. Prospective head-to-head RCTs comparing finerenone and spironolactone are necessary to resolve this uncertainty and define their respective roles in the management of HFpEF.

Authors' contributions

All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

Not required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

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