JACC: HEART FAILURE VOL. 13, NO. 10, 2025

STATE-OF-THE-ART REVIEW

Nonsteroidal and Steroidal Mineralocorticoid Antagonists

Rationale, Evidence, and Unanswered Questions

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HIGHLIGHTS

- sMRAs have established efficacy in patients with HFrEF; their role in patients with HFpEF is less clear.
- Limited evidence of benefit, potential harm in patients with kidney disease, and frequent adverse effects have restricted the broader use of sMRAs.
- There is evolving evidence for the efficacy of nsMRAs to improve clinical outcomes in patients with diabetes and CKD, and patients with HFpEF.
- MR modulators and aldosterone synthase inhibitors may offer alternatives to target the aldosterone-MR axis.
- Head-to-head comparison trials of sMRA vs nsMRA and other emerging therapies in this space are lacking.

ABSTRACT

Steroidal mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, have demonstrated substantial benefits in randomized controlled trials for patients with heart failure with reduced ejection fraction. However, their effectiveness in heart failure with mildly reduced ejection fraction and heart failure with preserved ejection fraction remains uncertain, and the implementation of this class has remained low, in part due to its side effects and tolerability profile. Emerging therapies that target the mineralocorticoid receptor and/or the production of aldosterone may offer alternative strategies to treat the aldosterone–mineralocorticoid receptor axis. For instance, the nonsteroidal MRA finerenone has shown efficacy in reducing cardiovascular and renal events in patients with type 2 diabetes mellitus and chronic kidney disease, as well as decreasing the combined endpoint of cardiovascular death and heart failure hospitalizations in heart failure with mildly reduced ejection fraction and heart failure with preserved ejection fraction populations. Large-scale, direct comparative outcome studies are currently lacking that compare steroidal MRAs vs emerging therapies. This review critically assesses the structural and mechanistic distinctions between nonsteroidal and nonsteroidal MRAs as well as mineralocorticoid receptor modulators and aldosterone synthase inhibitors; summarizes available evidence across heart failure, diabetes, and chronic kidney disease populations; and highlights ongoing and forthcoming research aimed at addressing key unanswered questions in this rapidly evolving therapeutic field. (JACC Heart Fail. 2025;13:102637) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2025.102637

ABBREVIATIONS AND ACRONYMS

ASi = aldosterone synthase inhibitor

CKD = chronic kidney disease

DM = diabetes mellitus

HFmrEF = heart failure with mildly reduced ejection

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HHF = hospitalization for heart failure

MRA = mineralocorticoid receptor antagonist

MRM = mineralocorticoid receptor modulator

nsMRA = nonsteroidal mineralocorticoid receptor antagonist

sMRA = steroidal mineralocorticoid receptor antagonist

Mineralocorticoid receptor antagonists (MRAs) play a pivotal role in the management of heart failure (HF) by mitigating the deleterious effects of aldosterone-induced inflammation, fibrosis, and volume retention.[1,2] Whereas steroidal mineralocorticoid receptor antagonists (sMRAs) such as spironolactone and eplerenone are well-established in clinical use, their safety concerns—particularly hyperkalemia and endocrine-related adverse effects—have limited widespread adoption, especially in patients with chronic kidney disease (CKD) or diabetes mellitus (DM).[3] However, multiple new classes of therapies targeting the aldosterone-mineralocorticoid receptor axis may offer alternative treatment options. Nonsteroidal mineralocorticoid receptor antagonists (nsMRAs) may provide enhanced receptor selectivity and potentially improve safety profiles due to differences in their structural composition, pharmacokinetics, pharmacodynamics, and tissue distribution.[4] Other emerging therapies, including mineralocorticoid receptor modulators (MRMs) and aldosterone synthase inhibitors (ASis), act through differential action on the mineralocorticoid receptor or by directly inhibiting aldosterone production, potentially offering additional alternative strategies.

We review the contemporary data supporting sMRA use in patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), the real-world use of this drug class in patients with HF, and the factors that often hamper sMRA use. We then review the mechanistic differences between sMRAs and the emerging classes of nsMRAs, MRMs, and ASIs, explore existing safety and efficacy data, and describe the ongoing trials that will further define their role in patients with HF and CKD (**Central Illustration**).

EVIDENCE FOR sMRAs IN HF

Robust data exist to support the use of sMRAs in patients with HFrEF, and as a result, guidelines on the management of HF consistently recommend a Class 1A recommendation for their use in HFrEF (**Table 1**, **Figure 1**).[1,2,5] In randomized clinical trials, both spironolactone and eplerenone have been shown to decrease all-cause (spironolactone) or cardiovascular (eplerenone) death and hospitalization for heart failure (HHF) in patients with HFrEF significantly, including in patients with recent myocardial infarction.[6-8] In trials of eplerenone,[7,8] but not spironolactone, the risk of hyperkalemia was consistently greater in patients randomized to sMRA.[6]

Data on the clinical benefits of sMRA in patients with heart failure with mildly reduced ejection fraction (HFmrEF) and HFpEF are based mainly on a single trial of spironolactone in patients with HF and ejection fraction (EF) ≥45%. TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) did not demonstrate a significant reduction in the occurrence of primary endpoint including a composite of death from cardiovascular (CV) causes, aborted cardiac arrest, or HHF (HR: 0.89 [95% CI: 0.77-1.04]) with spironolactone vs placebo.[9] Patients randomized to spironolactone were twice as likely to experience hyperkalemia (18.7% vs 9.1%). In a post hoc secondary analysis of this trial, it was observed that patients in Russia and Georgia had substantially lower event rates in the placebo group compared with those in the Americas, raising concerns that enrolled patients in some regions may not have had HF, and had minimal treatment effects of on blood pressure, potassium, and creatinine, as well as poor reported adherence, and lacked expected MRA metabolites in their blood stream, suggesting that the overall use of the investigational drug in the trial may have been low in the region.[10] When patients in the Americas were analyzed separately from those in Russia and

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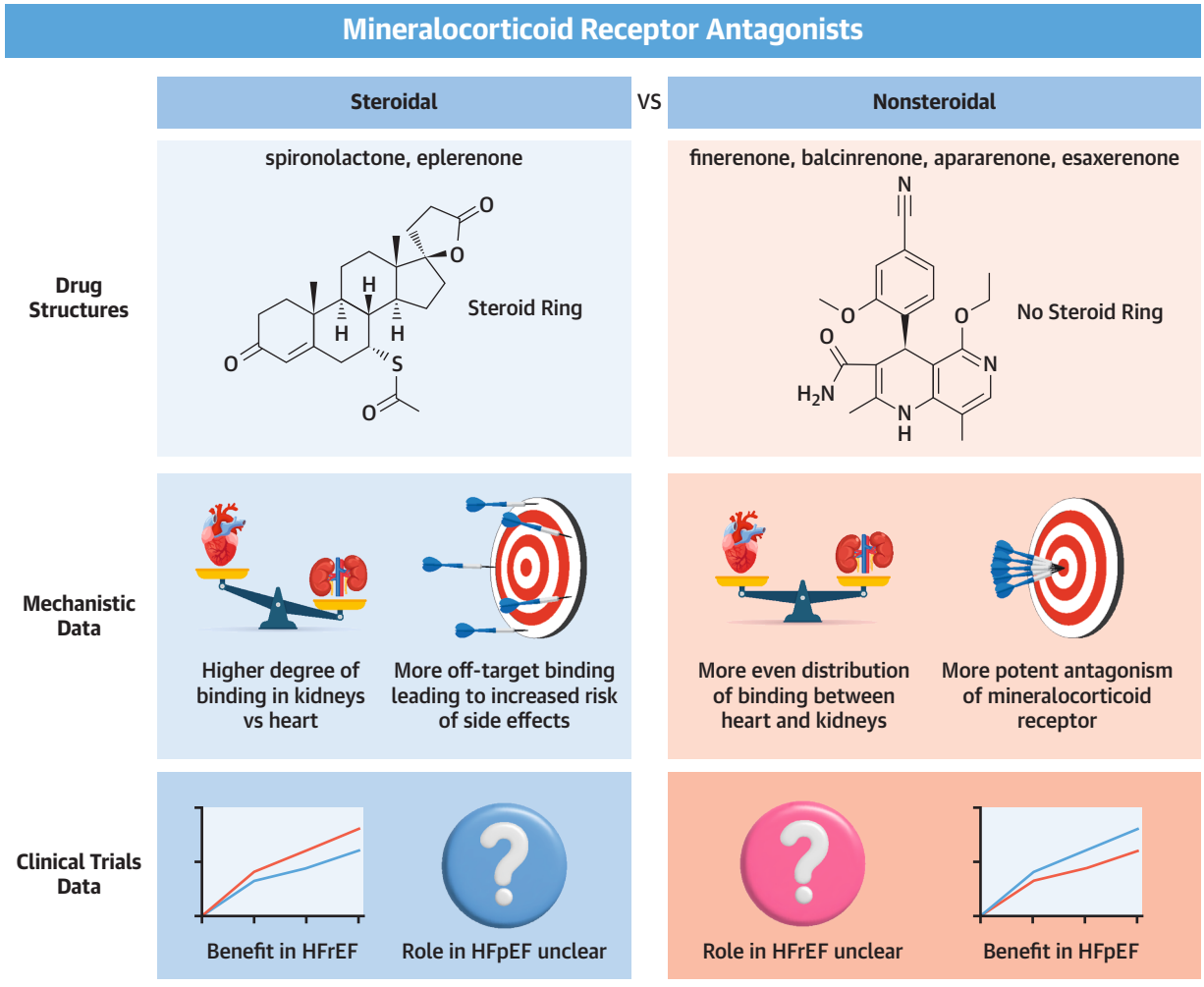
Biykem Bozkurt, MD, PhD, served as acting Editor-in-Chief and main adjudicator for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 5, 2025; revised manuscript received July 10, 2025, accepted July 16, 2025.

CENTRAL ILLUSTRATION **Comparative Overview of sMRA vs nsMRAs**



Harrington JL, et al. JACC Heart Fail. 2025;13(10):102637.

Structural class drives key pharmacological differences between traditional sMRAs (eg, spironolactone, eplerenone) and the emerging nsMRAs (eg, finerenone, balcinrenone, apararenone, esaxerenone). The absence of a steroid nucleus in nsMRAs yields a more balanced heart-to-kidney receptor affinity profile and tighter on-target antagonism, translating into a distinct efficacy-safety signature across the heart failure spectrum. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; nsMRA = nonsteroidal mineralocorticoid receptor antagonist; sMRA = steroidal mineralocorticoid receptor antagonist.

Georgia, a significant benefit was observed in patients from the Americas (HR: 0.82 [95% CI: 0.69-0.98]). In contrast, no difference was detected in those randomized in Russia and Georgia (HR: 1.10 [95% CI: 0.79-1.51]). Patients in the Americas region were significantly more likely to experience hyperkalemia with spironolactone (OR: 3.46 [95% CI: 2.62-4.56] in the Americas vs OR: 1.30 [95% CI: 0.95-1.77] in Russia and Georgia). As a result of the TOPCAT trial, sMRAs have a Class IIb recommendation for patients with HFmrEF in the ESC (European Society of Cardiology) guidelines, and for patients with either HFmrEF or HFpEF in the ACC (American College of Cardiology)/AHA (American Heart Association) and JCS (Japanese Circulation Society)/JHFS (Japanese Heart Failure Society) guidelines.[1,2,5]

There are no contemporary large-scale clinical data to support the use of sMRAs for CKD, with several older trials suggesting a lack of benefit and increased risk of worsening kidney function (with

TABLE 1 Evidence for Steroidal Mineralocorticoid Receptor Antagonists in HF

Study Name	N	Treatment Arms	Follow-Up Duration, y	Primary Efficacy Outcome	Safety Outcomes
HFrEF					
RALES	1,663	Spironolactone vs placebo	2	All-cause death (RR: 0.70 [95% CI: 0.60-0.82])	Increase in median creatinine (0.05-0.10 mg/dL) and potassium (0.30 mmol/L) in spironolactone arm ($P < 0.001$)
EPHESUS (post MI)	6,642	Eplerenone vs placebo	1.3	All-cause death (RR: 0.85 [95% CI: 0.75-0.96]) CV death, CV hospitalization (RR: 0.87 [95% CI: 0.79-0.95])	Increase in mean creatinine (0.06 vs 0.02 mg/dL) ($P < 0.001$) and potassium (0.3 vs 0.2 mmol/L) ($P < 0.001$)
EMPHASIS-HF	2,737	Eplerenone vs placebo	1.75	All-cause death and HHF (HR: 0.63 [95% CI: 0.54-0.74])	Increase in mean creatinine (0.09 vs 0.04 mg/dL) and potassium (0.16 vs 0.05 mmol/L) ($P < 0.001$)
HFmrEF or HFpEF					
TOPCAT	3,445	Spironolactone vs placebo	3.3	CV death, HHF, and aborted cardiac arrest (HR: 0.89 [95% CI: 0.77-1.04])	Hyperkalemia rates (18.7% vs 9.1%) Doubling of creatinine (10.2% vs 7.0%)
TOPCAT Americas (secondary analysis)	1,767 Americas 1,678 Russia/ Georgia	Spironolactone vs placebo	3.3	Americas: CV death, HHF, and aborted cardiac arrest (HR: 0.82 [95% CI: 0.69-0.98]) Russia/Georgia: CV death, HHF, and aborted cardiac arrest (HR: 1.10 [95% CI: 0.79-1.51])	Americas: Hyperkalemia (OR: 3.46 [95% CI: 2.62-4.56]) Doubling of creatinine (HR: 1.60 [95% CI: 1.25-2.05]) Russia/Georgia: Hyperkalemia (OR: 1.30 [95% CI: 0.95-1.77]) Doubling of creatinine (HR: 0.95 [95% CI: 0.49-1.85])

CV = cardiovascular; HF = heart failure; HHF = hospitalization for heart failure; MI = myocardial infarction.

35% of patients stopping spironolactone in one trial due to deteriorating kidney function) and hyperkalemia (Table 2).[11,12]

LIMITATIONS AND REAL-WORLD USE OF sMRAs

Data suggest that, even for patients with HFrEF, for whom there is a Class Ia recommendation for sMRA use, only 20% to 30% of patients in the United States actually receive an sMRA.[13,14] Reasons for this finding are varied, but typically include perceived patient frailty and concern for inducing kidney injury, hypotension, and hyperkalemia.[15,16] Among patients with existing kidney dysfunction, there is also concern that sMRAs may contribute to or accelerate worsening renal function.[17] Although the impact on prescription rates is less clear, existing data also suggest that spironolactone use raises glycosylated hemoglobin (HbA_{1c}) levels and may contribute to metabolic disease.[18] Overall, sMRA use remains suboptimal, even in patient populations in whom its use is strongly associated with a benefit.

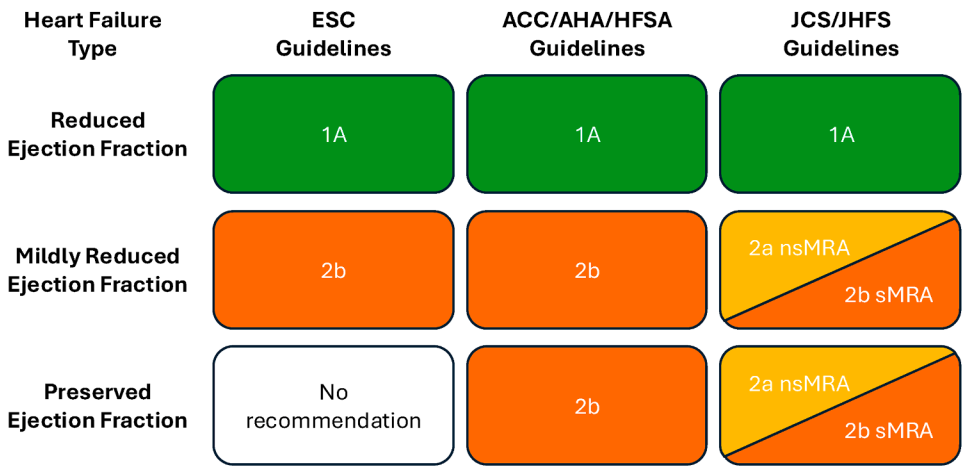
EMERGING THERAPIES TARGETING THE ALDOSTERONE–MINERALOCORTICOID RECEPTOR AXIS

Drugs from multiple classes of therapies are emerging to target the aldosterone-mineralocorticoid receptor axis in HF and CKD. Both nsMRAs and MRMs antagonize the mineralocorticoid receptor, with preclinical models suggesting that these drugs may act differently at the mineralocorticoid receptor than sMRA.[19-21] In contrast with many membrane-bound receptors, the mineralocorticoid receptor directly interacts with the genome to trigger multiple pathways as modified by the recruitment of distinct cofactor peptides. In preclinical models, MRM balcinrenone has been shown to alter the recruitment of nuclear cofactor peptides, selectively fully antagonizing the profibrotic and inflammatory genes while preserving the benefits of MRAs, and partially antagonizing the electrolyte-handling genes, thereby reducing the risk of hyperkalemia.[19,20] ASis act upstream of the mineralocorticoid receptor, directly reducing the production of aldosterone. Theoretically, this may result in fewer adverse effects from direct mineralocorticoid receptor antagonism, including hyperkalemia, although the impact of this inhibition on other adrenal hormones remains an area of investigation.[22]

STRUCTURAL AND RECEPTOR SELECTIVITY DIFFERENCES BETWEEN STEROIDAL AND nsMRAs

Structurally, sMRAs have a core steroidal backbone, which allows them to bind to the mineralocorticoid receptor but also leads to cross-reactivity with other steroid hormone receptors, such as androgen, progesterone, and glucocorticoid receptors, leading to

FIGURE 1 MRAs in Contemporary HF Guidelines Across the EF Spectrum



Note: JCS/JHFS guidelines were the first to incorporate emerging data of nsMRA in heart failure with mildly reduced or preserved ejection fraction. Data from sMRA in heart failure with reduced ejection fraction cannot be extrapolated to nsMRA at this time given a paucity of evidence.

Current professional-society guidelines uniformly assign Class I, Level of Evidence: A recommendations for sMRAs in HFrEF, but diverge for HFmrEF and HFpEF. The JCS/JHFS guideline is the first to incorporate emerging outcomes data with nsMRAs, granting a Class IIa endorsement for finerenone in HFmrEF and HFpEF. In contrast, evidence for traditional sMRAs in these phenotypes remains weaker (Class IIb or no recommendation). ESC and ACC/AHA/HFSA statements continue to rate sMRAs as Class IIb in HFmrEF and provide no directive (pending additional trials) in HFpEF. Green cells indicate Class I, Level A recommendations (strong evidence/benefit >risk). Orange cells denote Class IIb guidance (benefit ≥risk but evidence limited or conflicting). Yellow/diagonal cells reflect JCS/JHFS split recommendations: upper half = Class IIa for nsMRA; lower half = Class IIb for sMRA. White cell indicates no recommendation issued. ACC = American College of Cardiology; AHA = American Heart Association; EF = ejection fraction; ESC = European Society of Cardiology; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFSA = Heart Failure Society of America; JCS = Japanese Circulation Society; JHFS = Japanese Heart Failure Society; MRA = mineralocorticoid receptor antagonist; nsMRA = nonsteroidal mineralocorticoid receptor antagonist; sMRA = steroidal mineralocorticoid receptor antagonist.

adverse side effects including gynecomastia, menstrual irregularities, sexual dysfunction, and impaired glycemic control (Table 3).[23]

In contrast, nsMRAs, including finerenone, apararenone, and esaxerenone, feature a dihydronaphthyridine-based structure that does not interact with steroid receptors.[21] Similar to balcinrenone, structural modeling shows that finerenone binds to distinct amino acids on the MR, leading to a more selective transcriptional profile with reduced activation of proinflammatory and profibrotic genes.[24]

PHARMACOKINETIC AND PHARMACODYNAMIC DISTINCTIONS OF sMRAs VS nsMRAs

The pharmacokinetic properties of MRAs significantly influence their efficacy, dosing regimens, and safety. Both spironolactone and eplerenone have longer half-lives (4-17 hours) compared with nsMRA finerenone (2-3 hours), in part due to the presence of active metabolites (seen in spironolactone, which has the most extended half-life), which may increase the risk of hyperkalemia. In contrast, finerenone has a shorter plasma half-life of 2 to 3 hours, does not produce active metabolites and reduces off-target effects.

ORGAN DISTRIBUTION AND SAFETY PROFILE OF sMRAs VS nsMRAs

A key distinction between sMRAs and nsMRAs is their tissue distribution, which influences their efficacy and safety profiles. The sMRAs spironolactone and eplerenone preferentially accumulate in the kidney. Finerenone exhibits a more balanced distribution between the heart and kidneys, decreasing excessive renal MR blockade while maintaining cardioprotective benefits.[25] It has been hypothesized

TABLE 2 Steroidal Mineralocorticoid Receptor Antagonists in Kidney Disease

Study Name	N	Treatment Arms	Follow-Up Duration	Primary Efficacy Outcome	Safety Outcomes
BARACK 3b CKD	1,372	Spironolactone vs placebo	3 y	Death, hospitalization for heart disease, stroke, HF, transient ischemic attack or peripheral arterial, or new onset of those conditions (HR: 1.05 [95% CI: 0.81-1.37])	Two-thirds of patients randomized to spironolactone stopped treatment within 6 mo, largely because of decreases in eGFR (35.4%), side effects of spironolactone (18.9%), or hyperkalemia (8.0%)
ALCHEMIST Hemodialysis	794	Spironolactone vs placebo	32.6 mo	HR: 0.996; 95% CI: 0.73-1.36	NR

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NR = not reported; other abbreviation as in Table 1.

that finerenone's distribution across organ systems, coupled with its short half-life, specific binding pattern, and subsequent transcriptional activation, may lead to lower levels of potassium accumulation and subsequent hyperkalemia, although this has not yet been proven conclusively.[25]

nsMRAs AND MRMs: EVIDENCE TO DATE

There are now large phase 3 outcomes trials available to support the use of nsMRA finerenone in patients with CKD and type 2 diabetes mellitus (T2DM) and in patients with HFmrEF/HFpEF (Table 4). Data from other smaller phase 2 and phase 3 trials overall suggest that other nsMRAs, including apararenone and esaxerenone, and the MRM balcinrenone also offer clinical benefit in patients with CKD and are well-tolerated.

nsMRAs AND MRMs IN PATIENTS WITH CKD AND T2DM. In phase 2 trials, the nsMRAs apararenone (a nsMRA) and balcinrenone (an MRM), have shown mixed evidence of kidney albenefit, though they were generally well-tolerated.[26,27] A trial with the combination of balcinrenone and dapagliflozin in 324 patients with CKD and fewer restrictions on entry

TABLE 3 Key Differences Between Key Differences Between sMRAs and nsMRAs

	sMRAs (Spironolactone, Eplerenone)	nsMRAs (Finerenone)
Structural differences		
Core structure	Steroid based	Dihydronaphthyridine based
Receptor selectivity	Binds to multiple hormone receptors (androgen, progesterone, glucocorticoid)	Highly selective for MR only Higher antagonism
Transcriptional activity		Reduced activation of proinflammatory and profibrotic genes
Size		Bulkier (finerenone)
Side effects	Gynecomastia, menstrual irregularities, sexual dysfunction, hyperglycemia	Minimal hormonal side effects
PK/PD		
Half-life	Long spironolactone: 13.8-16.5 h Eplerenone 4-6 h	Short (finerenone: 2-3 h)
Metabolism	Produces active metabolites (spironolactone)	No active metabolite
Risk of hyperkalemia	Higher (owing to accumulation in the kidneys)	Lower (more balanced tissue distribution)
Tissue distribution and safety		
Organ distribution	Primarily in kidneys	Balanced between heart and kidneys
Hyperkalemia risk	High (especially in CKD patients)	Lower risk
Antifibrotic and anti-inflammatory effects	Present but with side effects	Possibly stronger with fewer side effects
Clinical implications	Effective but with hormonal side effects and hyperkalemia risk	More selective, safer in CKD patients and better for heart kidney protection
Overview of MRAs		
Function: block aldosterone effects to reduce inflammation, fibrosis, and volume retention		
Used in HF and CKD management		

MRA = mineralocorticoid receptor antagonist; nsMRA = nonsteroidal mineralocorticoid receptor antagonist; PK/PD = pharmacokinetics and pharmacodynamics; sMRA = steroidal mineralocorticoid receptor antagonist: other abbreviation as in Tables 1 and 2.

TABLE 4 Available Evidence From Trials of nsMRAs and MRMs in HF and Kidney Disease

Study Name, Therapy Class, and Population	N	Treatment Arms	Follow-Up Duration	Primary Efficacy Outcome	Safety Outcomes
CKD–phase 2					
MIRACLE, MRM, HF, and CKD	133	Balcinrenone (multiple doses) + dapagliflozin vs placebo + dapagliflozin	12 wk	Change in UACR −54.9%, −52.5%, and −47.6% for balcinrenone 15 mg, 50 mg, and 150 mg plus 10 mg dapagliflozin vs −29.9% with placebo	Hyperkalemia 5.9% with 150 mg balcinrenone + dapagliflozin vs 9.1% with placebo = dapagliflozin
Trial of Apararenone, nsMRA, T2DM, and CKD	293	Apararenone (multiple doses) vs placebo	24 wk + 28 wk extension	Change in UACR 62.9%, 50.8%, and 46.5% for apararenone 2.5 mg, 5 mg, and 10 mg, respectively vs +113.7% with placebo, all $P < 0.001$	0.25 mmol/L increase in potassium noted with highest tested apararenone dose
ARTS-DN, nsMRA	823	Finerenone (multiple doses) vs placebo	90 d	Placebo-adjusted ratio of UACR between day 90 and baseline 0.67; 95% CI: 0.58-0.77 for 20-mg dose	Hyperkalemia leading to drug discontinuation in 0.0%-3.2% of those randomized to finerenone vs 0% placebo
ARTS, nsMRA, HF, and mild to moderate CKD	392	Finerenone vs spironolactone	22-29 d	Comparable decreases in BNP and albuminuria	Fewer hyperkalemic events with finerenone (5.3%) vs spironolactone (12.7%). $P = 0.048$
ARTS-HF, nsMRA, HFrEF, and CKD	1,066	Finerenone vs eplerenone	90 d	Comparable decreases in NT-proBNP	Similar increases in potassium
CKD–phase 3					
Trial of esaxerenone, nsMRA, T2DM, and CKD	455	Esaxerenone vs placebo	52 wk	Resolution of UACR, as defined by a UACR of <30 mg/g and a sustained ≥30 reduction from baseline in UACR, measured on at least 2 separate occasions; absolute difference 18%; 95% CI: 12-25%; $P < 0.001$	Hyperkalemia observed in 20 (9%) vs 5 (2%) in esaxerenone vs placebo arms, all asymptomatic
FIDELIO-DKD, nsMRA, T2DM, and CKD	5,734	Finerenone vs placebo	2.6 y	Kidney failure, a sustained decrease in eGFR of ≥40%, death from renal causes (HR: 0.82 [95% CI: 0.73-0.93])	Similar frequency of adverse events between arms Hyperkalemia-related drug discontinuation 2.3% vs 0.9%
FIGARO-DKD, nsMRA, T2DM, and CKD	7,437	Finerenone vs placebo	3.4 y	CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF (HR: 0.87 [95% CI: 0.76-0.98])	Hyperkalemia-related drug discontinuation 1.2% vs 0.4%
CONFIDENCE, nsMRA, T2DM, and CKD	807	Finerenone + empagliflozin vs finerenone alone or empagliflozin alone	180 d	Change from baseline in UACR 29% greater in those randomized to both finerenone and empagliflozin than to finerenone alone and 32% >with empagliflozin alone ($P < 0.001$ for both)	Lower rates of hyperkalemia with potassium >5.5 mmol/L with empagliflozin plus finerenone (15.3%) vs finerenone alone (18.6%)
HFmrEF					
FINEARTS-HF, nsMRA, HFpEF, and HFmrEF	6,001	Finerenone vs placebo	2.7 years	CV death and worsening HF (RR: 0.84 [95% CI: 0.74-0.95])	Hyperkalemia (>6 mmol/L) 3.0% vs 1.4%

BNP = B-type natriuretic peptide; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MRM = mineralocorticoid receptor modulator; NT-proBNP = N-terminal pro-B-type natriuretic peptide; T2DM = type 2 diabetes mellitus; UACR = urinary albumin-to-creatinine ratio; other abbreviations as in Tables 1 to 3.

potassium and kidney function has recently been completed (MIRO-CKD [A Phase IIb, Multicentre, Randomised, Double-Blind, Dose-finding Study to Evaluate the Efficacy, Safety and Tolerability of Balcinrenone in Combination with Dapagliflozin Compared with Dapagliflozin in Patients with Chronic Kidney Disease and Albuminuria]; NCT06350123). The nsMRA esaxerenone has phase 3 data to support its use in patients with CKD and T2DM, with significantly increased likelihood for improvement of the urinary albumin-to-creatinine ratio (UACR).[28]

The nsMRA finerenone has been studied in phase 2 and 3 studies across a wide range of patients with CKD in the ARTS (minerAlocorticoid Receptor Antagonist Tolerability Study) program of phase 2 trials and the FIDELITY (Combined FIDELIO-DKD

TABLE 5 Ongoing Trials of nsMRAs and sMRAs, MRMs, and Aldosterone Synthase Inhibitors in HF and Kidney Disease

Study Name	Key Inclusion Criteria	Anticipated Size	Treatment Arms	Primary Efficacy Outcome
nsMRAs—HF				
REDEFINE-HF nsMRA (NCT06008197)	HF with EF ≥40% and recent HHF	5,200	Finerenone vs placebo	CV death and total HF events
CONFIRMATION-HF nsMRA (NCT06024746)	HF (any EF) and recent HHF	1,500	Early initiation of finerenone and placebo vs usual care (open label)	Win ratio consisting of death, HF events, and change in KCCQ-TSS >5 points at 7 mo
FINALITY-HF nsMRA (NCT06033950)	HF with EF <40% and ineligible or intolerant of sMRA	2,600	Finerenone vs placebo	Time to CV death or HF event
BalanceD-HF MRM (NCT06307652)	HF (any EF), recent HHF and CKD	4,800	Balcinrenone and dapagliflozin vs dapagliflozin and placebo	Time to CV death and HF event
nsMRAs—CKD				
MIRO-CKD MRM (NCT06350123)	CKD	324	Balcinrenone and dapagliflozin vs dapagliflozin and placebo	Relative change in UACR from baseline to week 12
Aldosterone synthase inhibitors—CKD				
BaxDuo-PACIFIC ASi (NCT06742723)	CKD + HTN	5,000	Dapagliflozin + either baxdrostat or placebo	Sustained decrease of ≥50% in eGFR
BaxDuo-ARCTIC ASi (NCT06268873)	CKD + HTN	2,500	Dapagliflozin + either baxdrostat or placebo	Change in eGFR
ASi (NCT06150924)	CKD + HTN		Lorundrostat or placebo in addition to SGLT2 inhibitor and ACEI or ARB	Change in blood pressure
sMRAs—HF				
SPIRIT-HF sMRA (NCT04727073)	HF with EF ≥40%	1,300	Spironolactone vs placebo	CV death and total HHFs
SPIRRIT sMRA (NCT02901184)	HF with EF ≥40%	2,000	Spironolactone or eplerenone vs usual care	CV death and total HHFs
sMRAs—HF				
ACHIEVE sMRA (NCT03020303)	CKD on chronic dialysis	2,538	Spironolactone vs placebo	CV death and JJFs

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; EF = ejection fraction; HTN = hypertension; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; MRM = mineralocorticoid receptor modulator; SGLT2 = sodium glucose cotransporter 2; other abbreviations as in Tables 1 to 4.

[FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease] and FIGARO-DKD [Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease] Trial programme analYsis) program of phase 3 trials.[29-33] In ARTS and ARTS-HF, the only existing head-to-head trials of nsMRA vs sMRA, finerenone led to comparable decreases in natriuretic peptides and albuminuria vs with less (vs spironolactone) or similar (vs eplerenone) hyperkalemia. It is noteworthy that the doses of finerenone tested in the ARTS and ARTS-HF trials were lower than those subsequently tested in FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure) (5-20 mg/day vs 20-40 mg once daily). In the phase 2 CONFIDENCE (Combination Effect of Finerenone and Empagliflozin in Participants with Chronic Kidney Disease and Type 2 Diabetes Using a Urinary Albumin-to-Creatinine Ratio Endpoint) trial, the use of the nsMRA finerenone with empagliflozin led to significantly greater improvements in the UACR than with either finerenone or empagliflozin alone.[34]

Across 13,036 patients enrolled in FIDELITY, patients randomized to finerenone had significantly less risk of composite kidney outcomes (HR: 0.77 [95% CI: 0.67-0.88]) as well as a larger reduction in UACR (ratio of means: 0.68 [95% CI: 0.66-0.70]). Patients randomized to finerenone experienced higher rates of hyperkalemia. Still, there were no associated fatalities, and the incidence of hyperkalemia was lower than what has been reported in prior trials of sMRAs.[32] Use of finerenone in patients with CKD and T2DM also resulted in significantly fewer CV events. In FIGARO-DKD, which was a dedicated CV outcomes trial including 7,437 patients, finerenone significantly decreased a composite primary outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, and HHF (HR: 0.87 [95% CI: 0.76-0.98]) over 3.4 years, with the benefit driven primarily by a lower incidence of HHF (HR: 0.71 [95% CI: 0.56-0.90]).[33]

Prespecified secondary analyses from the FIDELITY program also suggest that finerenone may offer metabolic and antiarrhythmic benefits, including decreased HbA_{1c}, a lower risk of diabetes progression,

and lower rates of atrial fibrillation or flutter in patients with CKD and T2DM. Across the FIDELITY program, patients randomized to finerenone were significantly less likely to initiate new insulin or oral antidiabetic medications.[35] A secondary analysis from FIDELIO-DKD found that randomization to finerenone significantly decreased the occurrence of atrial fibrillation or flutter (HR: 0.71 [95% CI: 0.53-0.94]).[36] Notably, sMRAs have been linked to worsening of HbA_{1c} levels[18,37] and have not been associated with any change in atrial fibrillation incidence or recurrence.[38] In totality, these results suggest that finerenone use is nephroprotective and improves CV outcomes in high-risk patients with CKD and T2DM. Importantly, despite the high baseline risk for hyperkalemia associated with CKD, finerenone was well-tolerated in these cohorts, with relatively low rates of hyperkalemia.

nsMRAs IN PATIENTS WITH HFmrEF AND HFpEF. FINEARTS-HF is the first trial of either steroidal or nsMRAs to have shown a conclusive benefit with use in patients with HFmrEF/HFpEF (**Table 4**).[33] In this trial of 6,001 patients, randomization to finerenone vs placebo led to a significant decreased in a composite outcome of CV death and total HF events (RR: 0.84 [95% CI: 0.74-0.95]; $P = 0.007$). This result was mainly driven by a decrease in HF events (RR: 0.82 [95% CI: 0.71-0.94]; $P = 0.006$). The risk of hyperkalemia increased in patients randomized to finerenone. However, rates of hospitalization were low (0.5% and 0.2% in the finerenone and placebo arms, respectively), and there were no deaths attributed to hyperkalemia. The benefits of finerenone vs placebo were sustained across high-risk subgroups, including patients with advanced age and high kidney risk.[39,40] As a result of FINEARTS-HF, the nsMRA finerenone now holds a 2a recommendation for use in HFmrEF and HFpEF in Japan, as compared with a 2b recommendation for sMRA (**Figure 1**).[5]

A participant-level pooled analysis of FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF showed that patients randomized to finerenone had a significant decrease in incident atrial fibrillation or flutter (HR: 0.83 [95% CI: 0.71-0.97]).[41] Finerenone also appeared to offer particular benefit to patients with HFpEF and higher degrees of obesity, such that patients with higher body mass indexes derived a greater relative benefit ($P = 0.005$) from finerenone, with increasing body mass index.[42] Mechanistically, this result is plausible because adipose tissue both secretes aldosterone independently and may also drive greater adrenal release of aldosterone through paracrine and autocrine signaling.[43,44] Prior analyses of the sMRA eplerenone in patients with HFrEF also suggested a greater benefit in patients with obesity.[45] A similar trend toward benefit was observed in a TOPCAT analysis.[46]

Another group that appeared to derive particular benefit from finerenone in FINEARTS-HF were those with a recent HHF (within the last 3 months). Although this group only made up 54.8% of the overall FINEARTS-HF population, a secondary analysis from the trial suggested that the benefit seen with finerenone was driven by patients with a worsening HF event in the last 3 months, suggesting that early initiation of these therapies after HHF may provide the most marked relative benefit (RR: 0.74 [95% CI: 0.57-0.95] in those with a HF event during or within 7 days of randomization; RR: 0.79 [95% CI: 0.64-0.97] in those with an HF event in the last 7 days to 3 months; and RR: 0.99 [95% CI: 0.81-1.21] for those with either no HF events or >3 months since last HF event; $P_{interaction} = 0.07$).[47] Although only hypothesis generating, this observation contrasts with prior work from TOPCAT Americas that suggested that the benefits observed with spironolactone in HFpEF were greatest in those without a prior HHF.[48]

UPCOMING AND ONGOING TRIALS OF nsMRAs, MRAs, AND ASis

Key unanswered questions remain surrounding the role of nsMRAs in clinical practice, including which populations derive benefit and what the role of an nsMRA, MRM, or ASi vs an sMRA might be for these populations. The evidence generated in these upcoming trials will help to establish the overall role of these novel therapies, as well as their impact on high-risk patients who are intolerant of or ineligible for sMRAs due to side effects, kidney dysfunction, or other factors. Several of these trials incorporate the use of an sodium-glucose cotransporter 2 inhibitor into their protocols, building on findings that suggest sodium-glucose cotransporter 2 inhibitor use decrease the rates of hyperkalemia and enables tolerance of both selective mineralocorticoid receptor antagonists (sMRA) and nonselective mineralocorticoid receptor antagonists (nsMRA).[34,49] Multiple ongoing trials will help to clarify the role of sMRAs further, although additional questions are likely to remain unanswered and may be further explained in future research (**Table 5**).

The results of FINEARTS-HF and the use of finerenone in HF across the entire EF spectrum will be explored further in 3 significant phase 3 trials. Two of these ongoing trials will enroll patients with recent

HHF and HFmrEF/HFpEF (NCT06008197) or those with any EF (NCT06024746). The role of finerenone in patients with HFrEF will be explored further in FINALITY-HF (Study to Evaluate Finerenone on Clinical Efficacy and Safety in Patients with Heart Failure Who are Intolerant or Not Eligible for Treatment with Steroidal Mineralocorticoid Receptor Antagonists; NCT06033950). FINALITY-HF is based on the rationale that nsMRAs are better tolerated than sMRAs and that patients who would not usually be able to derive benefit from an MRA may be able to tolerate this newer MRA class. Additional data surrounding the effectiveness of an MRM in patients with HF across the spectrum of EF (with recent worsening HF and impaired kidney function) will be available based on the 4,800-patient, phase 3 trial of balcinrenone vs placebo in addition to dapagliflozin (BalanceD-HF [Study to Evaluate the Effect of Balcinrenone/Dapagliflozin in Patients With Heart Failure and Impaired Kidney Function; NCT06307652]).

Additional emerging data will also be available on the role of sMRAs in patients with HFpEF, including ongoing trials comparing spironolactone with placebo and spironolactone/eplerenone with usual care (eg, NCT04727073).[50] Multiple additional trials will explore the role of both sMRAs and nsMRAs as well as ASis in patients with kidney disease (**Table 5**).[51,52]

An important remaining question is likely to be about the absolute effective difference between nsMRA and sMRA use, or between an sMRA and an MRM or ASi. To date, only phase 2 data exist that directly compare an sMRA and nsMRA, and so differences in safety and efficacy remain areas for further investigation. A recent meta-analysis demonstrated strong evidence of benefit with sMRAs in HFrEF and with nsMRAs in HFmrEF and HFpEF, consistent with prior data. However, there was no interaction of trials (and, by extension, MRA class) on the effect of MRA on a composite of CV death or HHF. Furthermore, it should be noted that the baseline medications and population differences between older trials and more contemporary trials are substantial, including changes in standard-of-care medications for HF, making it difficult to compare data across these trials confidently. There are no currently planned head-to-head phase 3 trials of nsMRAs vs sMRAs, and additional studies will be needed to determine whether nsMRAs or other emerging therapies are: 1) better tolerated; 2) more effective; and/or 3) safer in patients with HFrEF than sMRAs. The use of sMRAs remains low in HF care, and it is not yet clear whether nonsteroidal agents will see better uptake or whether specific implementation strategies are needed to increase the overall adoption of MRAs. Finally, the cost-effectiveness of nsMRAs in HF is not yet established.

CONCLUSIONS

Although current evidence strongly supports sMRAs in treating patients with HFrEF, their clinical use is frequently limited by poor tolerability, notably due to risks of hyperkalemia, androgenic side effects, and kidney dysfunction. nsMRAs have improved receptor selectivity, balanced tissue distribution, and fewer off-target effects. Emerging clinical evidence increasingly supports the use of nsMRAs, particularly for patients with HFmrEF/HFpEF and comorbidities, including CKD and T2DM. Additional emerging therapies, such as MRMs and ASis, modulate the mineralocorticoid receptor or reduce aldosterone production and may provide additional potential alternative treatment strategies in this space. Nevertheless, significant unanswered questions remain, including the comparative effectiveness and safety of nsMRAs vs sMRAs, optimal patient selection for nsMRAs, and their potential as first-line therapies across various HF subtypes, considering clinical outcomes and cost effectiveness. Ongoing clinical trials will be critical in addressing these gaps and clarifying the future role of nsMRAs, as well as MRMs and ASis in HF management.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Harrington has received consulting fees from Novo Nordisk. Dr Solomon has received research grants from Alexion, Alnylam, Applied Therapeutics, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cytokinetics, Edgewise, Eidos, Gossamer, GlaxoSmithKline, Ionis, Lilly, MyoKardia, National Institutes of Health/NHLBI, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI; and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Cardurion, Cardiac Dimensions, Corvia, Cytokinetics, Daiichi-Sankyo, Dinaqor, GlaxoSmithKline, Janssen, Lilly, Lexicon, Merck, Moderna, MyoKardia, Novartis, Quantum Genomics, Roche, Sarepta, Sanofi Pasteur, Tremeau, Theracos, Tenaya, CellProThera, American Regent, Anacardio, Akros, and Val. Dr Teerlink has received research grants or consulting fees from 3ive Labs, Amgen, Angitia, AOP Medical, AskBio, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers-Squibb, Cardiac Dimensions, Cardurion, Cytokinetics, EBR Systems, Edgewise Therapeutics, Edwards, Endotronix, Impulse Dynamics, Kaiser Permanente, LivaNova, Lilly, Medtronic, Myovant, Novartis, PCORI, Pfizer, RECARDIO, ReCor Medical, Regeneron, Tectonic, V-Wave, ViCardia, and Windtree Therapeutics. Dr Vaduganathan has received research grants, advisory board fees, or speaker engagements from American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Bristol Myers Squibb, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; and has participated on clinical trial committees for studies sponsored by

Amgen, AstraZeneca, Boehringer Ingelheim, Galmed, Novartis, Bayer AG, Occlutech, Pharmacosmos, and Impulse Dynamics. Dr Zieroth has received research grant support, advisory board fees, or speaker engagements from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Eli Lilly, GlaxoSmithKline, Janssen, Medtronic, Merck, Novartis, Novo Nordisk, Otsuka, Pfizer, Roche, Salubrisbio, Servier, and Vifor Pharma; has served on clinical trial committees or as national lead for studies sponsored by AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, and Pfizer; and has nonindustry affiliations with Canadian Medical and Surgical KT Group, CCS, CHFS, Charité, EOCI, Liv, Medscape, Ology, PACE-CME, Radcliffe, Reach MD, and Translational Medicine Academy. Dr Bonaca serves as the Executive Director of CPC, a nonprofit academic research organization affiliated with the University of Colorado, which has received research grants or consulting funding from Abbott Laboratories, Agios Pharmaceuticals Inc, Alexion Pharma, Alnylam Pharmaceuticals Inc, Amgen Inc, Angionetics Inc, Anthos Therapeutics, Array BioPharma Inc, AstraZeneca and affiliates, Atentiv LLC, Audentes Therapeutics Inc, Bayer and affiliates, Bristol Myers Squibb Company, Cambrian Biopharma Inc, Cardiol Therapeutics Inc, CellResearch Corp, Cleerly Inc, Cook Regentec LLC, CSL Behring LLC, Eidos Therapeutics Inc, EP Trading Co Ltd, Epizon Pharma Inc, Esperion Therapeutics Inc, Everly Well Inc, Exicon Consulting Pvt Ltd, Faraday Pharmaceuticals Inc, Foresee Pharmaceuticals Co Ltd, Fortress Biotech Inc, HDL Therapeutics Inc, HeartFlow Inc, Hummingbird Bioscience, Insmed Inc, Ionis Pharmaceuticals, Janssen and affiliates, Kowa Research Institute Inc, Lexicon Pharmaceuticals Inc, Medimmune Ltd, Merck and affiliates, Nectero Medical Inc, Novartis Pharmaceuticals Corp, Novo Nordisk Inc, Osiris Therapeutics Inc, Pfizer Inc, PhaseBio Pharmaceuticals Inc, Prairie Education and Research Cooperative, Prothena Biosciences Limited, Regeneron Pharmaceuticals Inc, Regio Biosciences Inc, Sanofi-Aventis Groupe, Silence Therapeutics PLC, Smith & Nephew plc, Stealth BioTherapeutics Inc, VarmX, and Virta Health Corporation. Dr Sauer has received research funding from Pfizer, Boehringer Ingelheim, AstraZeneca, CSL Vifor, 35Pharma, Amgen, Abbott, Boston Scientific, Edwards Lifesciences, and Story Health; consulting fees from Abbott, Bayer, Boston Scientific, Edwards Lifesciences, Impulse Dynamics, Acorai, General Prognostics, Story Health, and Amgen; and also holds stock in ISHI and Pulsli (both privately held digital health companies). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS hyperkalemia, heart failure, mineralocorticoid receptor antagonist, steroidal, nonsteroidal