INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Mineralocorticoid Receptor Antagonists***
-August 2025-

Background:

The Indian Health Service National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of mineralocorticoid receptor antagonists (MRAs) at its Summer 2025 quarterly meeting. Relevant to this clinical review is that spironolactone is currently listed on the National Core Formulary (NCF). Following clinical review and analysis, the NPTC made **no modifications** to the NCF.

Discussion:

Currently, there are three FDA-approved MRAs; spironolactone, eplerenone, and finerenone. The main difference among the steroidal MRAs, spironolactone and eplerenone and the nonsteroidal MRA, finerenone is the modulation of different transcriptional cofactors and expression/inhibition of a different gene profile. The first generation MRA, spironolactone, is a nonselective MRA that binds to mineralocorticoid receptors (MRs), as well as androgen and progesterone receptors.[6] Extensive studies on spironolactone have demonstrated significant benefits for heart failure with reduced ejection fraction (HFrEF), refractory hypertension, hyperaldosteronism, hypokalemia, ascites secondary to cirrhosis, alopecia, hypertrichosis, and acne. The use of spironolactone was further supported by the RALES trial where it exhibited a 30% reduction in all-cause death and a 35% reduction in frequency of hospitalization in patients with heart failure (HF) with left ventricular ejection fraction (LVEF) <35%.[7] However, spironolactone's anti-androgenic effects, due to its activity as both a progesterone and androgen receptor antagonist, can result in gynecomastia, breast tenderness, menstrual irregularities, impotence, and decreased libido, especially at higher doses. These side effects are at least partially ameliorated by the second-generation steroidal MRA, eplerenone.[8]

Eplerenone is more selective for the MR than spironolactone, with a 100- to 1,000-fold reduction in binding affinity for glucocorticoid, progesterone, and androgen receptors. The use of eplerenone was supported by the EPHESUS and EMPHASIS-HF trials, where it was responsible for a 15% reduction in all-cause death, a 13% reduction in CV death or hospitalization for CV event, and a 27% reduction in CV death or hospitalization for HF in patients with LVEF <35-40% already treated with ACE inhibitors.[8] Eplerenone demonstrated beneficial effects as early as 7 days after initiation, showing a comparative improvement in systolic and diastolic blood pressure changes compared with placebo, but it also showed a higher risk of hyperkalemia (5.5% in eplerenone group vs. 3.9% in placebo group, p=0.002).[7]

Spironolactone and eplerenone are well-established therapies for managing HFrEF, as recommended by European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology/Arrhythmia Heart Failure Academy (AHA/ACC/AHFA) for symptomatic patients with this condition.[9-11] Spironolactone is recommended by guidelines as an optimal fourth-line therapy in patients with resistant hypertension and eGFR >45 mL/min/1.73m^2 and serum potassium ≤ 4.5 mEq/L.[6] A meta-analysis of 10 studies compared the effectiveness and safety of eplerenone and spironolactone in patients with HFrEF. Eplerenone exhibited lower all-cause mortality rates (HR 0.74, 95% CI: 0.59-0.94), lower CV mortality rates (HR 0.54, 95% CI: 0.39-0.74), lower withdrawal rates (RR 0.63, 95% CI: 0.46-0.85), and a decreased risk of gynecomastia (RR 0.06, 95% CI: 0.01-0.34). Eplerenone and spironolactone had comparable mortality rates in HF patients with mid-range ejection fractions (HFmrEF) and similar rates of HF hospitalization, hyperkalemia, renal failure, and hypotension.[12] Due to the risk of both acute kidney injury (AKI) and hyperkalemia, they are still underused clinically, especially in patients with impaired kidney function.[13]

Finerenone, a novel third-generation MRA, has a unique binding mode that determines high potency and selectivity for the MR, inhibits binding of both aldosterone and cortisol, and reduces recruitment of transcriptional cofactors in the absence of aldosterone. Differently from steroidal MRAs, finerenone has tissue distribution (equal distribution between the heart and kidney), a short half-life (2-3 hours), no active metabolites, a greater MR selectivity than spironolactone, and a higher receptor binding affinity than eplerenone. Finerenone is 6- to 10-fold less lipophilic than steroidal MRAs and does not cross the blood-brain barrier. Also of note, there is less blood pressure lowering with finerenone and eplerenone than with spironolactone.[6]

The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) trials were phase II trials designed to test the safety and tolerability of finerenone in patients with HFrEF and mild-to-moderate chronic kidney disease (CKD). In the first ARTS trial, finerenone had smaller increases in serum potassium concentration for all doses vs. spironolactone 50 mg daily, and decline in eGFR was reduced with finerenone, leading to fewer patients with hyperkalemia, kidney failure, or kidney impairment. Noticeable findings were in the ARTS-HF trial where there was >30% decline in the cardiac

biomarker NT-proBNP, which was similar with both finerenone and eplerenone. Also, there was a reduction in the composite clinical CV endpoint despite not being powered for this endpoint. In the ARTS-DN trial where they investigated finerenone in CKD, there was a reduction in UACR but not much increase in hyperkalemia events (~2%).[14]

In the FIDELITY pooled analysis, the combined phase 3 trials of FIGARO-DKD and FIDELIO-DKD. FIDELIO-DKD enrolled patients with more advanced CKD stages and showed finerenone not only reduced the risk of CV events by 14% but also slowed kidney disease progression by 18%.[15] FIGARO-DKD focused more on CV protection and earlier CKD stages, revealing a 13% reduction in the primary composite outcome (death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or HHF) and a 29% reduction in HHF.[16] FIDELITY aimed to provide more robust estimates of finerenone's effects on CV and kidney outcomes compared to placebo in patients with more advanced CKD and type 2 diabetes, eGFR ≥25 mL/ min/1.73m^2, and on maximum-tolerated ACE inhibitors or ARBs. Finerenone revealed a 14% reduction in the CV endpoint (HR 0.86; 95% CI: 0.78-0.95), 22% reduction in HHF (HR 0.78; 95% CI: 0.66-0.92), 23% reduction in the kidney outcome (HR 0.77; 95% CI: 0.67-0.88), and 20% reduction in dialysis (HR 0.80; 95% CI: 0.64-0.99). This analysis confirmed that finerenone's benefits on CV and kidney outcomes were consistent, regardless of whether patients received SGLT2 inhibitors or not, which are strongly recommended in this population.[17] The 2024 Kidney Disease: Improving Global Outcomes guidelines recommend a nonsteroidal MRA with proven kidney and CV benefit for patients with type 2 diabetes, eGFR ≥25 ml/min/ 1.73 m^2, normal serum potassium, and albuminuria (UACR ≥30 mg/g) despite maximum-tolerated ACE inhibitors or ARBs.[18]

The CONFIDENCE trial investigated whether SGLT2 inhibitors and MRA dual therapy was superior to finerenone alone, empagliflozin alone, or both, in reducing UACR after 6 months. At day 180, the reduction in UACR with combination therapy was 32% greater than with empagliflozin alone (0.68; 95% CI: 0.59-0.79, p<0.001). The UACR was reduced by 52% with combination therapy. The incidence of AKI was uncommon (1.9%) in the combination-therapy group.[19]

The FINEARTS enrolled both patients with HFmrEF and preserved ejection fraction and demonstrated that, alongside standard medical care, patients who received finerenone achieved a 16% reduction in the risk of CV death and unplanned or urgent HHF (RR 0.84; 95% CI: 0.74 to 0.95; p=0.007). The benefit was driven by a reduction in worsening HF events and resulted in the FDA expanding the indication for finerenone to include patients with HF with a LVEF of at least 40%.[20]

Findings:

Finerenone has shown meaningful CV and renal benefits in patients with CKD and type 2 diabetes, making it a valuable option beyond traditional MRAs. Current ACC and ESC guidelines recommend spironolactone or eplerenone in HFrEF, but emerging evidence suggests finerenone may provide broader benefit, especially in patients with CKD and diabetes, or in those who cannot tolerate steroidal MRAs due to hyperkalemia or hormonal side effects. As HF care advances, guidelines may need to expand to reflect finerenone's role. Its favorable safety and efficacy profile make it particularly relevant for high-risk patients, and it fulfills an important gap in the management of HF patients with left ventricular ejection fraction >40%, where current MRA options have limited impact. Further randomized controlled trials, particularly head-to-head studies in patient populations, are needed to define finerenone's role and clarify its therapeutic potential.

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