Long-Term Care Updates

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Mineralocorticoid receptor agonists in heart failure with preserved or mildly reduced ejection fraction

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Introduction:

While clinical practice guidelines strongly recommend mineralocorticoid receptor antagonists (MRA) to reduce morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF), the guidelines offer only a weak recommendation on the use of these agents in patients with heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF).[1] This newsletter will review recent evidence on the use of MRAs in patients with HFmrEF and HFpEF.

Evidence Review:

The weak recommendation on the use of MRAs in patients with HFmrEF or HFpEF was primarily based on data from the TOPCAT trial, a double-blinded, randomized, placebo-controlled trial which evaluated the safety and efficacy of spironolactone versus placebo in nearly 3500 patients with symptomatic HFpEF. This study showed that spironolactone did not significantly reduce the composite risk of cardiovascular (CV) mortality, hospitalization due to heart failure (HF), or aborted cardiac arrest. However, spironolactone did reduce the risk of hospitalization due to HF by 17% when compared with placebo (p=0.04).[2] A secondary analysis of this study also suggested that spironolactone may be more effective in patients on the lower end of the left ventricular ejection fraction (LVEF) classification for HFpEF (LVEF of 45% to <50%).[3]

Novel Drug Approvals (September 2024)

Brand	Generic	Indication	Mechanism of Action	Dosage Form
Cobenfy	Trospium chloride; xanomeline tartrate	Schizophrenia	Muscarinic antagonist (trospium); muscarinic agonist (xanomeline)	Oral capsules
Ebglyss	Lebrikizumab-lbkz	Atopic dermatitis	Interleukin-13 antagonist	Subcutaneous injection
Ocrevus Zunovo	Ocrelizumab; hyaluronidase-ocsq	Relapsing MS; primary progressive MS	CD20-directed cytolytic antibody	Subcutaneous injection
Tecentriq Hybreza	Atezolizumab; hyaluronidase-tqjs	Alveolar soft part sarcoma; hepatocellular carcinoma; melanoma; NSCLC, SCLC	PD-L1 blocking antibody (atezolizumab); endoglycosidase (hyaluronidase)	Subcutaneous injection

In September 2024, results from the FINEARTS-HF trial were published. This double-blinded, randomized, placebo-controlled trial evaluated the safety and efficacy of long-term finerenone treatment in over 6000 patients with HFmrEF or HFpEF (LVEF ≥40%).[4] Finerenone is a nonsteroidal MRA that is FDA-approved to reduce the risk of sustained renal function decline, end stage kidney disease, CV death, non-fatal myocardial infarction (MI), and HF-related hospitalization in patients with chronic kidney disease associated with type 2 diabetes.[5]

Results from the FINEARTS-HF trial show that, over a median follow-up of 32 months, finerenone reduced the composite risk of CV death and worsening heart failure events (i.e., HF hospitalization or urgent HF visit) by 16% when compared with placebo (p=0.007). This was driven primarily by a 18% lower risk of worsening HF events (p=0.006), as the difference between finerenone and placebo for CV death was not statistically significant. When compared with placebo, finerenone also significantly improved symptoms and quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ). The benefits of finerenone were slightly more apparent in females, individuals aged 73 years or less, and patients with a baseline eGFR ≥60 mL/min/1.73m^2. While finerenone was generally well tolerated, hyperkalemia was more common. While no deaths due to hyperkalemia were reported in either group, investigator-reported hyperkalemia occurred in 9.7% and 4.2% of patients receiving finerenone and placebo, respectively. Hyperkalemia leading to hospitalization was reported in 0.5% and 0.2% of patients receiving finerenone and placebo, respectively.[4]

Shortly after publication of the FINEARTS-HF trial, Jhund and colleagues published a meta-analysis of patient-level data on the use of MRAs in HF. As part of this analysis, the researchers specifically looked at studies evaluating MRAs in patients with HFmrEF and HFpEF. Pooling of the two trials described previously (TOPCAT and FINEARTS-HF) showed that the use of spironoloactone or finerenone reduced the risk of the following:[6]

- CV death or first hospitalization for HF: 13% reduced risk vs. placebo
- CV death and total HF hospitalizations: 16% reduced risk vs. placebo
- First hospitalization for HF: 18% reduced risk vs. placebo
- Total HF hospitalizations: 18% reduced risk vs. placebo

Upon subgroup analysis, the researchers found that individuals with a baseline eGFR ≥60 mL/min/1.73m^2 and those with potassium levels below the median baseline value had significantly better outcomes than those with lower eGFR or higher potassium levels. However, while the use of MRAs in patients with HFmrEF and HFpEF improved HF-specific outcomes, pooling of data from the two trials did not result in a significantly lower risk of CV death or all-cause death when compared with placebo. Additionally, pooled results for studies evaluating MRAs in patients with HFrEF were significantly superior to the pooled results in patients with HFmrEF/HFpEF for all study outcomes.[6]

Conclusion:

While results from the FINEARTS-HF trial and pooled analysis of the TOPCAT and FINEARTS-HF trials provide confirmation that MRAs confer some benefit in patients with HFmrEF/HFpEF, specifically as it relates to HF hospitalization and urgent HF visits, the evidence is less convincing when compared with studies on the use of MRAs in patients with HFrEF. The decision to use an MRA in a patient with HFmrEF or HFpEF should be based on patient-specific factors, noting that those without evidence of renal impairment and/or those with lower serum potassium levels may benefit the most.

It is likely that Bayer, the manufacturer of finerenone, is seeking approval from the FDA for an indication in patients with HFmrEF/HFpEF. However, until then, any use of finerenone in this patient population should be considered off-label.

References:

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2. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370(15):1383-1392.
3. Myhre PL, Vaduganathan M, Claggett BL, et al. Association of Natriuretic Peptides With Cardiovascular Prognosis in Heart Failure With Preserved Ejection Fraction: Secondary Analysis of the TOPCAT Randomized Clinical Trial. *JAMA Cardiol*. 2018;3(10):1000-1005.
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