ECHO IDAHO

Managing Heart Failure in Primary Care

Mineralocorticoid Receptor Antagonists & SGLT2 Inhibitors

Foundational Therapies in Heart Failure: Evidence-to-Practice

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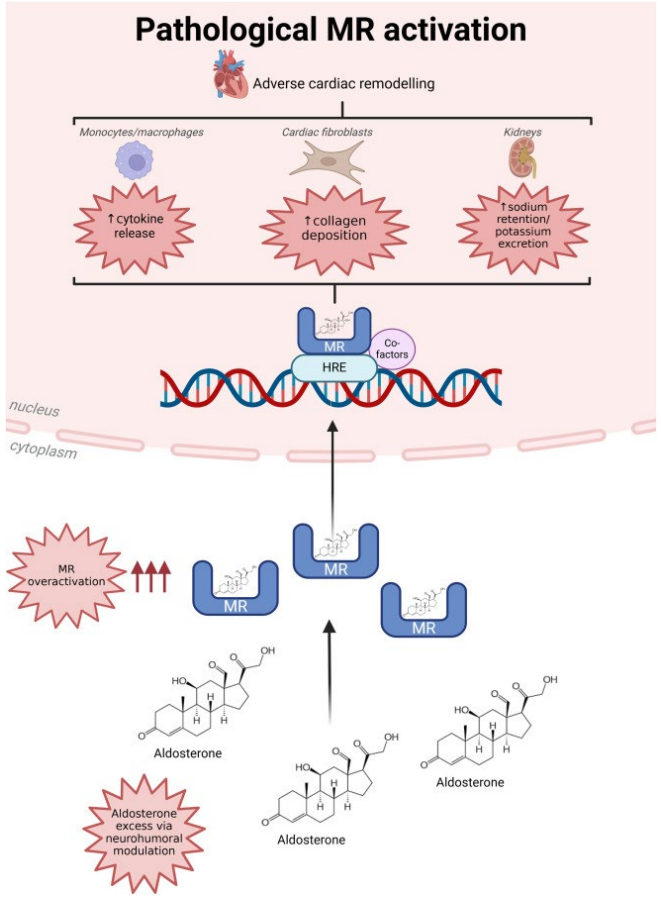
Learning Objectives

- **Identify** the distinct pathophysiological pathways targeted by Mineralocorticoid Receptor Antagonists (MRAs) and Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors in heart failure.
- **Describe** the current guideline-based recommendations for initiating MRA and SGLT2 inhibitor therapy across the spectrum of heart failure (HFrEF, HFmrEF, HFpEF).
- **Recognize** key practical considerations for implementing MRA and SGLT2 inhibitor therapy, including patient selection criteria (eGFR, K+ levels), essential safety monitoring protocols, and common adverse effects.

Two Key Pathophysiological Targets in Heart Failure

- **1. RAAS Overactivation (Classic Neurohormonal Pathway):**
  - Leads to excess **Aldosterone**, causing long-term damage like **scarring** (fibrosis) and **fluid retention**.
  - **Target:** Mineralocorticoid Receptor (MR)
- **2. Cardiorenal-Metabolic Dysregulation (Novel Pathway):**
  - Involves the body mismanaging Na^+ and sugar, leading to poor heart **energy** use and kidney strain.
  - **Target:** Sodium-Glucose Cotransporter 2 (SGLT2)



MRA Class: Steroidal vs. Non-Steroidal

- **Steroidal MRAs (Spironolactone, Eplerenone):**
  - Highly effective in HFrEF; established long-term mortality benefit.
  - Safety challenge: **Hyperkalemia** (high potassium) and **Kidney Disease (CKD)**
- **Non-Steroidal MRA (Finerenone):**
  - Acts on heart and vascular tissue with **less effect on the kidney's potassium balance**, leading to a lower risk of **Hyperkalemia**.
  - Shown benefit in HFmrEF/HFpEF and Diabetic Kidney Disease.

SGLT2i Class: Beyond Diuresis (The Cardiorenal Protective Effect)

- **Key Protective Mechanisms:**
- **Energy Boost:** Shifts the heart's fuel source to more efficient compounds, providing improved **cardiac energy**.
- **Better Heart Function:** Works directly on heart cells to regulate minerals, leading to improved pumping power and rhythm stability.
- **Hemodynamics:** Causes moderate fluid removal and relaxes blood vessels, **reducing the heart's workload**.
- **Renal Protection:** Reduces high pressures inside the kidney, helping to **preserve kidney function**.

HFrEF (EF ≤ 40%)
The Four Pillars

- Guideline-Directed Medical Therapy (GDMT) mandates initiation and up-titration of all four classes (Class I, Level of Evidence A):
- **ARNI / ACEi / ARB:** RAAS Inhibition
- **Evidence-Based Beta-Blocker:** Neurohormonal Modulation
- **MRA:** Aldosterone Blockade
- **SGLT2 Inhibitor:** Metabolic/Hemodynamic Modulation

Landmark MRA Trials in HFrEF

- **RALES (1999) - Spironolactone:** Cut the risk of **all-cause mortality by 30%** in severe HFrEF (NYHA III-IV).
- **EPHESUS (2003) - Eplerenone:** Showed clear **mortality benefit** post-MI with HFrEF.
- **EMPHASIS-HF (2011) - Eplerenone:** Significantly reduced CV death/HF hospitalization in mild HFrEF (NYHA II).

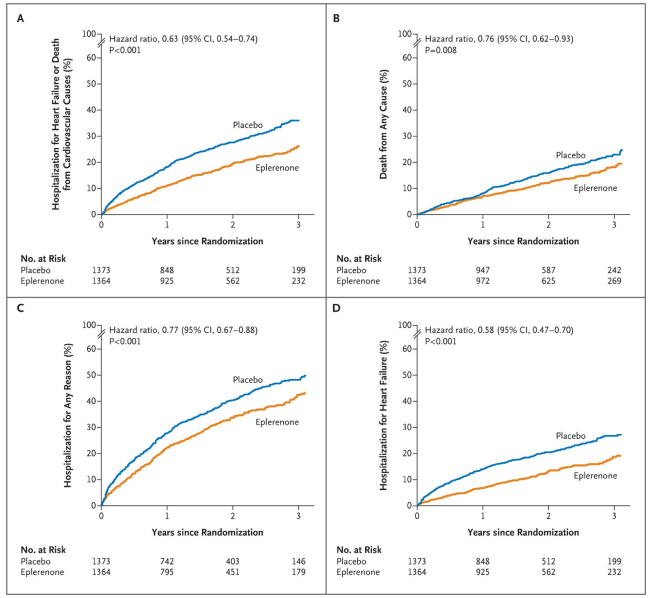
Clinical Takeaway

Sustained, long-term survival benefit for patients.

TABLE 3. RELATIVE RISKS OF THE COMBINED END POINTS OF DEATH OR HOSPITALIZATION IN THE SPIRONOLACTONE GROUP.*

END POINT	RELATIVE RISK (95% CI)	P VALUE
Death from cardiac causes or hospitalization for cardiac causes	0.68 (0.59–0.78)	<0.001
Death from any cause or hospitalization for any reason	0.77 (0.68–0.86)	<0.001
Death from any cause or hospitalization for cardiac causes	0.68 (0.60–0.77)	<0.001

*Each analysis represents the time to the first occurrence of an event. For patients with both events, the analysis includes only the first event. CI denotes confidence interval.



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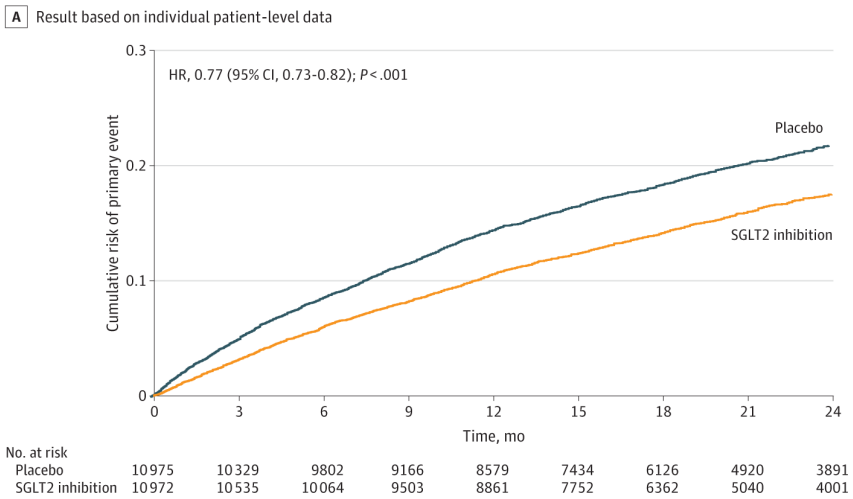
Landmark SGLT2i Trials in HFrEF

- **DAPA-HF (2019) & EMPEROR-Reduced (2020):**
  - Consistently reduced the risk of CV death or HF hospitalization by about **25%**.
  - Benefit seen **quickly**, with event curve separation observed within **30 days** of initiation.
- **Conclusion:** The **immediate clinical benefit** and favorable safety profile make SGLT2i an excellent choice for early initiation.



B Result based on study-level data

Trial	Events/total No. SGLT2 inhibition	Placebo	NNT	HR (95% CI)	Weight, %
EMPEROR-Preserved,[1] 2021	401/2997	489/2991	34	0.79 (0.69-0.90)	22.08
SOLOIST-WHF,[2] 2021	NR/608	NR/614	10	0.71 (0.56-0.90)	7.26
DAPA-HF,[3] 2019	384/2373	498/2371	21	0.74 (0.65-0.85)	21.66
EMPEROR-Reduced,[4] 2020	356/1863	459/1867	18	0.75 (0.65-0.86)	19.88
DELIVER,[5] 2022	508/3131	607/3132	31	0.82 (0.73-0.92)	29.12
Overall (I^2 = 0.0%, P = .70)	**1795/10972**	**2262/10975**	**23**	**0.77 (0.73-0.82)**	**100**

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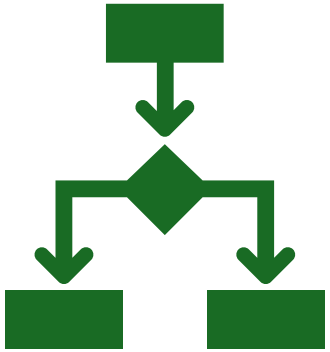
HFmrEF (EF 41-49%) & HFpEF (EF ≥ 50%)

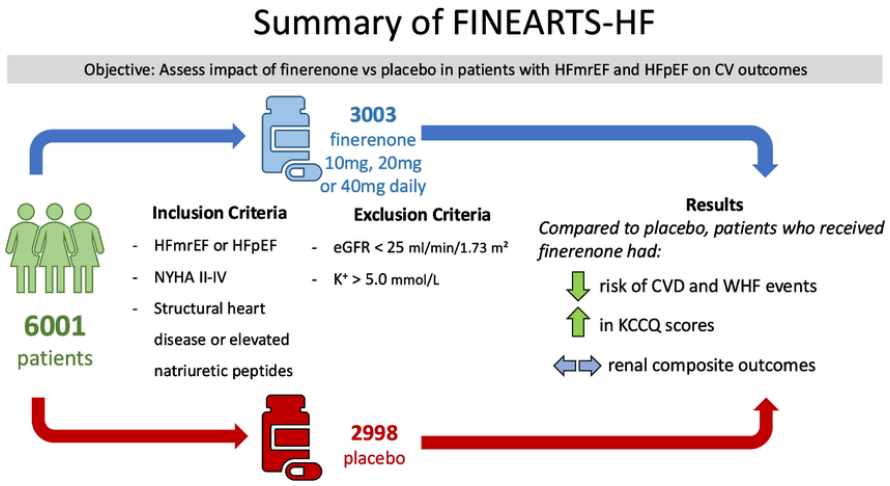
HFpEF: Highly complex, often driven by comorbidities (HTN, AFib, Obesity, CKD). Focus is on reducing high **HF hospitalization rates**.



HFmrEF: dynamic trajectory; patients benefit from multiple drug classes.

Key MRA Trials in HFpEF / HFmrEF: The Non-Steroidal Advance

- **TOPCAT (2014) - Spironolactone:** Overall *neutral* result for the primary composite outcome (**time to cardiovascular death, resuscitated cardiac arrest, or hospitalization for HF**). However, it did show a benefit in reducing hospitalizations in the North American subgroup.
- **FINEARTS-HF (2024) - Finerenone:** Showed a **16% reduction** in the primary composite endpoint (**total worsening HF events [hospitalizations or urgent HF visits] or death from cardiovascular causes**) across HFmrEF/HFpEF (EF ≥ 40%).

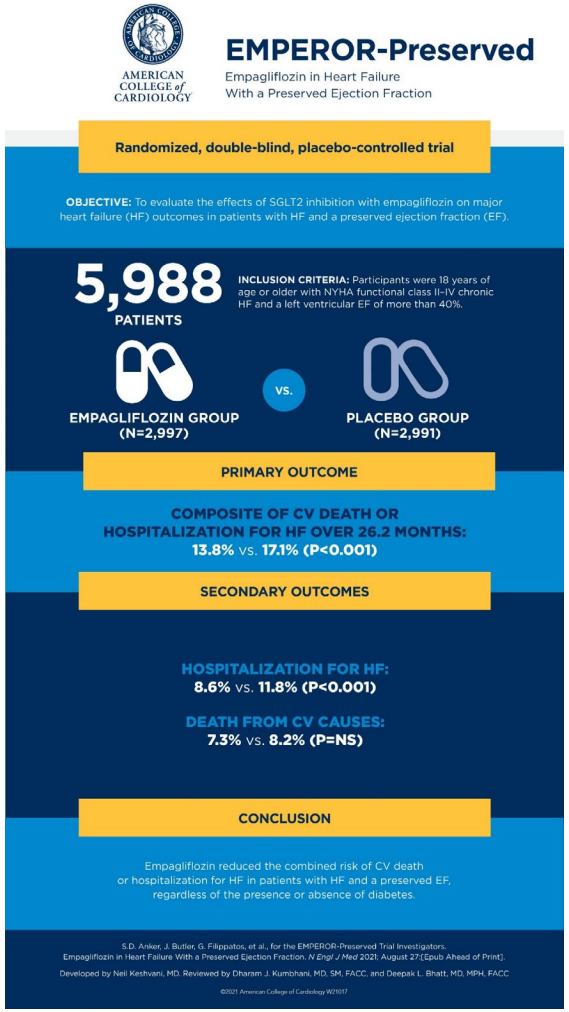


Clinical Significance:

- The newer non-steroidal MRA (finerenone) provides the strongest, most consistent evidence for an MRA in the broader non-HFrEF population (EF ≥ 40%).

Key SGLT2i Trials in HFpEF / HFmrEF: Broad Benefit

- **EMPEROR-Preserved (2021) & DELIVER (2022):**
  - Consistently reduced the risk of CV death or HF hospitalization by about **18-21%**.
  - **Pooled Analysis:** Confirms benefit across all HF categories (HFrEF, HFmrEF, HFpEF).
- **Guideline Impact:** SGLT2i are now a **Class 2a** recommendation (Reasonable to use) in all patients with EF > 40% to reduce HF hospitalizations and CV mortality.



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Special Populations

Population	SGLT2i Guidance	MRA Guidance
Diabetes	Class I for T2D + CVD/high risk. Synergistic cardiorenal benefit.	Effective regardless of T2D status.
CKD	Generally safe down to eGFR ~20 mL/min for HF benefit. Slows progression of CKD.	Contraindicated if eGFR < 30 mL/min. Use extreme caution if eGFR 30-50 mL/min
Potassium	Associated with small Potassium reductions, potentially **mitigating MRA-induced hyperkalemia**.	Initiate only if Potassium< 5.0. Hold if potassium> 5.5.
Post-MI	Role emerging in reduced EF post-MI.	Proven benefit in HFrEF post-MI (**EPHESUS** - Class 1B).

Practical Considerations & Safety Monitoring

MRA (Spironolactone/Eplerenone) Monitoring:

- **Hyperkalemia is the Main Risk:**
  - Check **Potassium and SCr** before initiation, at 3 days, at 7 days, and then monthly for the first 3 months.
  - **Action:** Hold MRA if potassium > 5.5 or if eGFR falls below 30 mL/min

Adverse Effects:

- **Spironolactone:** Can cause painful **gynecomastia** (switch to eplerenone or finerenone).
- **All MRAs:** Use caution with concurrent NSAIDs, which increase the risk of hyperkalemia.

SGLT2i (Dapagliflozin/Empagliflozin) Monitoring:

- **Volume Status:**
  - The SGLT2i diuretic effect may cause hypotension. Consider **reducing loop diuretic dose (e.g., Furosemide)** *before* or upon initiation to prevent dizziness and falls.
- **Rare, Serious Risk:**
  - **Euglycemic DKA:** Very rare, but serious. Instruct all patients (diabetic and non-diabetic) to **hold the drug 3-4 days before elective surgery** or if seriously ill (fever, vomiting).
- **Common Effects:**
  - **GU Infections:** More common, especially mycotic infections. Counsel patients on hygiene; easily managed with standard antifungals.

MRAs & SGLT2i Across the HF Spectrum

Heart Failure Type	HFrEF (≤ 40%)	HFmrEF (41-49%)	HFpEF (≥ 50%)
MRA Recommendation	**Class I-A (Mortality)**	**Class IIb-C (May consider)**	**Class IIb-C (May consider)**
SGLT2i Recommendation	**Class I-A (Mortality)**	**Class IIa-B (Reasonable)**	**Class IIa-B (Reasonable)**
Primary Goal	**REDUCE MORTALITY** & Hospitalizations	Reduce Hospitalizations & Worsening HF	Reduce Hospitalizations & Worsening HF

Key Points

Immediate Action: Start and optimize all **Four Pillars** therapies as soon as possible in HFrEF

Broaden Application: SGLT2i may be initiated (Level 2a) in patients with EF > 40% to reduce high hospitalization rates.

Harness New Tools: Consider finerenone, particularly in patients with EF ≥ 40% and/or **high risk of hyperkalemia/CKD** to achieve MRA benefit.

Monitor Closely, Don't Delay: While potassium and kidney function checks are required, manageable side effects should **not prevent** patients from getting this life-saving therapy.

Optimal management requires early initiation of these foundational therapies to improve outcomes across the heart failure spectrum.

Thank You!

Questions???

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