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## Medications for Heart Failure with Preserved or Mildly-Reduced Ejection Fraction: Heart Failure or Heart Success?

### CLINICAL QUESTION

**Which medications reduce death or hospitalization in patients with heart failure (HF) with preserved or mildly-reduced ejection fraction (EF >40%)?**

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### BOTTOM LINE

**In patients with HF with EF >40%, only mineralocorticoid receptor antagonists (MRA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduce HF hospitalizations, and nothing has been shown to reduce death. Compared to placebo, one patient avoids HF hospitalization for every 41 receiving an MRA for ~3 years, or for every 32 receiving an SGLT2i for ~2 years.**

### EVIDENCE

- Five systematic reviews in last 5 years assessed medications in HF with EF >40%.<sup>1-5</sup> Focusing on the most complete (results statistically significant unless otherwise stated):
- MRAs [13 randomized controlled trials (RCTs), 4459 patients, follow-up ~3 years]:<sup>1</sup>
  - HF hospitalization: 11.2% versus 13.6% (placebo), number needed to treat (NNT)=41.
  - Hyperkalemia ( $\geq 5.5$ mmol/L): 17.5% versus 8.3% (placebo), number needed to harm (NNH)=11.
- SGLT2i:

- Meta-analysis (5 RCTs, 9726 patients):<sup>5</sup> 29% relative risk reduction in HF hospitalization with SGLT2i versus placebo, regardless of diabetes
  - EMPEROR-Preserved:<sup>6</sup> Largest blinded RCT (industry-funded): Empagliflozin 10mg/day versus placebo for 2.2 years (5988 patients, age 72, 55% male)
    - HF hospitalization: 8.6% versus 11.8% (placebo), NNT=32.
    - Adverse events: Hypotension (not defined) [6.6% versus 5.2% (placebo), NNH=56], urinary tract infections [9.9% versus 8.1% (placebo), NNH=56], and genital infections [2.2% versus 0.7% (placebo), NNH=67].
- Medications that do not reduce hospitalizations or deaths:<sup>1</sup>
  - ACE inhibitors (8 RCTs, 2061 patients)
  - Angiotensin-receptor blockers (ARBs) (8 RCTs, 8755 patients)
  - Beta-blockers (10 RCTs, 3087 patients)
  - Sacubitril-valsartan (3 RCTs, 7702 patients)
    - Original meta-analysis erroneously suggested reduced hospitalizations. When re-analyzed, no benefit found.<sup>7</sup>
- No RCTs of clinical outcomes for loop diuretics in HF.<sup>8,9</sup>
- No medication reduces mortality.<sup>1-6</sup>

## CONTEXT

- “HF with preserved EF”:
  - Means EF  $\geq$ 50%.<sup>10</sup>
  - Many trials include patients with EF 41-49% (now called mildly-reduced ejection fraction<sup>10</sup>).<sup>1-6</sup>
- ~50% of patients with HF have an EF >40%.<sup>11</sup>
- Guidelines (published before EMPEROR-Preserved) recommend treating hypertension and using loop diuretics for fluid overload,<sup>12-14</sup>  $\pm$  MRA and/or candesartan (based on limited evidence and options at the time of writing).<sup>12</sup>
- Costs: Spironolactone 25mg \$140/year, empagliflozin splitting 25mg in half=12.5mg (trial dose=10 mg) \$560/year.<sup>15</sup>

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