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%)?

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%.1–5 Focusing on the most complete (results statistically significant unless otherwise stated):
  - MRAs [13 randomized controlled trials (RCTs), 4459 patients, follow-up ~3 years]:1
    - HF hospitalization: 11.2% versus 13.6% (placebo), number needed to treat (NNT)=41.
    - Hyperkalemia (≥5.5mmol/L): 17.5% versus 8.3% (placebo), number needed to harm (NNH)=11.
  - SGLT2i:
o Meta-analysis (5 RCTs, 9726 patients): 29% relative risk reduction in HF hospitalization with SGLT2i versus placebo, regardless of diabetes
  ▪ EMPEROR-Preserved: 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:
  o ACE inhibitors (8 RCTs, 2061 patients)
  o Angiotensin-receptor blockers (ARBs) (8 RCTs, 8755 patients)
  o Beta-blockers (10 RCTs, 3087 patients)
  o Sacubitril-valsartan (3 RCTs, 7702 patients)
    ▪ Original meta-analysis erroneously suggested reduced hospitalizations. When re-analyzed, no benefit found.  

• No RCTs of clinical outcomes for loop diuretics in HF.

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

REFERENCES

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Authors do not have any conflicts of interest to declare.