Aldosterone antagonists in systolic heart failure

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Clinical question

What is the role of aldosterone antagonists in patients with chronic systolic heart failure (HF)?

Bottom line

Aldosterone antagonists reduce mortality and hospitalizations in patients with congestive HF (class II to IV). Benefits appear similar to β-blockers or angiotensin-converting enzyme inhibitors (ACEIs). Close monitoring is required for those at risk of hyperkalemia.

Evidence

- RALES[1]: an RCT of 1663 patients with class III or IV HF taking ACEIs and diuretics; patients received spironolactone or placebo. Results at 24 months:
  -A statistically significant ($P<.001$) reduction in mortality (35% for spironolactone vs 46% for placebo, number needed to treat [NNT] of 10) and cardiovascular hospitalization (32% for spironolactone vs 40% for placebo, NNT = 12).
  -Adverse events included gynecomastia or breast pain (10% for spironolactone vs 1% for placebo, number needed to harm of 11) and serious hyperkalemia (potassium ≥ 6 mmol/L); not statistically different.
- EMPHASIS-HF[2]: an RCT of 2737 patients with class II HF and most using ACEIs or β-blockers; patients received eplerenone or placebo. Results at 21 months:
  -A statistically significant reduction in mortality (13% for eplerenone vs 16% for placebo, NNT = 34; $P=.008$) and cardiovascular hospitalization (22% for eplerenone vs 29% for placebo, NNT = 15; $P<.001$).
  -Adverse events included hyperkalemia (>5.5 mmol/L) (increase of 12% with eplerenone and 7% with placebo, number needed to harm of 22) and no difference in gynecomastia or renal failure.
- Two meta-analyses found similar results.[3,4]

Context

- With a relative risk reduction in mortality of about 25%,[1,2] aldosterone antagonists compare favourably to other agents used in congestive HF: about 29% for β-blockers[5] and 23% for ACEIs.[6,7]
- Aldosterone antagonists are prescribed at less than half the rate of β-blockers and ACEIs and represent the greatest potential for increased systolic HF survival.[8]
- Titration to target doses of ACEIs and β-blockers before adding aldosterone antagonists has been advocated[9]; the rates and doses of these medications were quite different in the 2 RCTs,[1,2] but they had similar outcomes.
- There is no head-to-head trial of spironolactone versus eplerenone. Spironolactone ($12 per month) could be used first; if gynecomastia or breast pain develop, switch to eplerenone ($100 per month).

Implementation

Hyperkalemia might be more common in practice than in trials.[10] High-risk, complex patients were excluded, and electrolytes were monitored frequently (eg, every 4 weeks initially in RALES). Additionally, higher doses of ACEIs and β-blockers, as well as other medications that affect potassium or renal function (nonsteroidal anti-inflammatory drugs, potassium supplements, angiotensin receptor blockers), can also increase hyperkalemia.[10,11] Suggestions to minimize this risk include using studied doses, frequent monitoring of electrolytes and renal function (check within first 1 to 2 weeks of starting the medication), and considering the use of a preplanned monitoring schedule with laboratory requisitions for patients.[12]

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