

Higher medication doses in heart failure?

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Clinical question

Does getting patients to target or using higher doses of heart failure (HF) medications improve outcomes?

Bottom line

In HF, higher-dose angiotensin-converting enzyme inhibitors (ACEIs), β -blockers (BBs), and angiotensin receptor blockers (ARBs) result in non-significant improvements in mortality, inconsistent decreases in HF hospitalizations, and more dizziness or hypotension (4% to 15%), dose reductions (20%), and stopping medication (2% to 8%). Starting patients on low doses and focusing on tolerability is essential.

Evidence

The largest RCTs, usually in patients with class II HF, of high versus low doses found the following.

- For BBs:
 - The MOCHA¹ trial (N=345) compared 25 mg with 6.25 mg of carvedilol twice daily for 6 months.
 - There was no statistical difference in mortality (1% vs 6%), cardiovascular hospitalizations (both 11%), or dizziness (24% vs 38%), but increased bradycardia (12% vs 1%, NNH=10).
 - The J-CHF² trial (N=364) compared 10 mg with 1.25 mg of carvedilol twice daily for 3 years.
 - There was no difference in death, HF hospitalization, and cardiovascular disease (21% vs 23%), but an increase in dose reductions (23% vs 0.7%, NNH=5).
 - Meta-regression confirmed lack of dose benefit.³
- For ACEIs:
 - The ATLAS⁴ trial (N=3164, 77% class III HF) compared 32.5 to 35 mg with 2.5 to 5 mg of lisinopril for 4 years.
 - There was no difference in mortality (43% vs 45%) or any hospitalization (37% vs 39%), but there was decreased mortality plus hospitalization (80% vs 84%, NNT=25), and there was more dizziness (19% vs 12%) and hypotension (11% vs 7%).
 - The NETWORK⁵ trial (1532 ACEI-naïve patients) compared 10 with 2.5 mg of enalapril twice daily for 6 months.
 - There was no difference in death, HF hospitalization, or worsening symptoms (15% vs 13%), but more treatment withdrawals (27% vs 19%, NNH=13).
- For ARBs:
 - The HEAAL⁶ trial (N=3846) compared 150 mg with 50 mg of losartan for 4.7 years.
 - There was decreased death plus HF admission (43% vs 47%, NNT=30) and HF admission (23% vs 26%, NNT=35), similar mortality (33% vs 35%), and more hypotension and hyperkalemia (NNH about 30).

Context

- Target doses are often unattainable, even in clinical trials: about 50% of patients achieve 50% of target doses.⁷
- Despite inconsistent RCT evidence, guidelines recommend trying to achieve targets and using higher doses,⁸ based in part on non-dose-response HF studies.⁹⁻¹¹

Implementation

Aldosterone antagonists, ACEIs, ARBs, and BBs reduce morbidity and mortality in HF patients with reduced (<40%) left ventricular ejection fraction; benefits have not been shown with preserved ejection fraction.¹² Aldosterone antagonists have similar benefit but are prescribed less often.¹³ Ideally, patients should be taking ACEIs, ARBs, BBs, or aldosterone antagonists, but which to start first and how to optimize tolerability is unknown. After initiation or dose increases, monitor for adverse events (eg, hypotension, bradycardia, dizziness, and electrolyte or creatinine abnormalities).¹² 🌿

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Competing interests
None declared

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