Higher medication doses in heart failure?

James McCormack PharmD Finlay A. McAlister MD MSc FRCPC Michael R. Kolber MD CCFP MSc

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 MOCHA[1] 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-CHF[2] trial (N = 364) compared 10 mg with 1.25 mg of carvedilol twice daily for 3 years.
    - —The 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 ATLAS[4] 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 NETWORK[5] 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 HEAAL[6] 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]

Dr McCormack is Professor in the Faculty of Pharmaceutical Sciences at the University of British Columbia in Vancouver. **Dr McAlister** is Professor and **Dr Kolber** is Associate Professor in the Faculty of Medicine and Dentistry at the University of Alberta in Edmonton.

Competing interests
None declared

References

1. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberg RE, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996;94:2807-16.
2. Okamoto H, Hori M, Matsuzaki M, Tsutsui H, Yamazaki T, Nagai R, et al. Minimal dose for effective clinical outcome and predictive factors for responsiveness to carvedilol: Japanese Chronic Heart Failure (J-CHF) study. *Int J Cardiol* 2013;164:238-44.
3. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: β-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009;150:784-94.
4. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999;100:2312-8.
5. Poole-Wilson PA; NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. *Eur Heart J* 1998;19:481-9.
6. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009;374:1840-48.
7. Tavazzi L, Maggioni AP, Borer JS. Should we revise our approach to 'optimal medical therapy'? The case of chronic heart failure. *Eur Heart J* 2013;34:2792-4.
8. McKelvie RS, Moe GW, Ezekowitz JA, Heckman GA, Costigan J, Ducharme A, et al. The 2012 Canadian Cardiovascular Society heart failure management guidelines update: focus on acute and chronic heart failure. *Can J Cardiol* 2013;29:168-81.
9. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;316:1429-35.
10. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.
11. Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-906.
12. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail* 2016;18:891-975.
13. Lindblad AJ, Allan GM. Aldosterone antagonists in systolic heart failure. *Can Fam Physician* 2014;60:e104.

Tools for Practice articles in *Canadian Family Physician (CFP)* are adapted from articles published on the Alberta College of Family Physicians (ACFP) website, summarizing medical evidence with a focus on topical issues and practice-modifying information. The ACFP summaries and the series in *CFP* are coordinated by **Dr G. Michael Allan**, and the summaries are co-authored by at least 1 practising family physician and are peer reviewed. Feedback is welcome and can be sent to **toolsforpractice@cfpc.ca**. Archived articles are available on the ACFP website: **www.acfp.ca.**