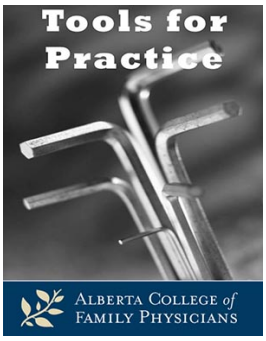
Tools for Practice is proudly sponsored by the Alberta College of Family Physicians (ACFP). ACFP is a provincial, professional voluntary organization, representing more than 4,400 family physicians, family medicine residents and medical students in Alberta. Established over sixty years ago, the ACFP strives for excellence in family practice through advocacy, continuing medical education and primary care research. www.acfp.ca

November 7, 2016



Target/higher dosing of medications in heart failure—is it necessary?

Clinical Question: Does getting to target/higher doses of heart failure (HF) medications improve outcomes and/or increase side effects?

Bottom-line: In HF patients, higher dose angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and angiotensin receptor blockers (ARB) versus lower doses result in non-significant improvements in mortality, and inconsistent decreases in HF hospitalizations. Higher doses cause more dizziness or hypotension (4-15%), dose reductions (20%), and stopping (2-8%). Starting on low doses and focusing on tolerability is essential.

Evidence:

- Largest randomized controlled trials (usually Class 2 HF), comparing high versus low dose.
  - Beta-blockers:
    - MOCHA:[1] 345 patients; BID carvedilol 25 mg versus 6.25 mg x6 months.
      - No statistical difference in:
        - Mortality: 1% versus 6%.
        - Cardiovascular hospitalizations: Both 11%.
        - Dizziness: 24% versus 38%.
      - Bradycardia: 12% versus 1%, Number Needed to Harm (NNH)=10.
    - J-CHF:[2] 364 patients; BID carvedilol 10 mg versus 1.25 mg x3 years.
      - No statistical difference in death/hospitalization for HF/cardiovascular disease (21% versus 23%).
      - More required dose reduction (23% versus 0.7%), NNH=5.
    - Meta-regression confirms lack of increased dose benefit.[3]
  - ACE inhibitors:
    - ATLAS:[4] 3,164 patients (77% class 3 HF); lisinopril 32.5-35 mg versus 2.5-5 mg x4 years:
      - No statistical difference in:
        - Mortality: 43% versus 45%.
        - Any hospitalization: 37% versus 39%.

        - Decreased mortality plus hospitalization (80% versus 84%), NNT=25.
        - More dizziness (19% versus 12%) and hypotension (11% versus 7%).
    - NETWORK:[5] 1,532 ACE naïve patients, BID enalapril 10 mg versus 2.5 mg x6 months:
        - No statistical difference in:
            - Death/HF hospitalization or worsening symptoms: 15% versus 13%.
        - More treatment withdrawals (27% versus 19%), NNH=13.
- ARBs:
    - HEAAL:[6] 3,846 patients; losartan 150 mg versus 50 mg x4.7 years:
        - Death/HF admission: 43% versus 47%, NNT=30.
            - HF admission: 23% versus 26%, NNT=35.
            - Similar overall mortality: 33% versus 35%.
        - More hypotension and hyperkalemia: NNH~30 each.
- Smaller studies report similar.[7-9]

Context:

- Evidence supports "triple therapy" in HF: Beta-blocker, ACE/ARB, and aldosterone antagonists.[10]
- Target doses often unattainable, even in clinical trials.
    - Only ~50% achieve 50% of target doses.[11]
- Despite inconsistent RCT evidence, guidelines still recommend trying to achieve target/higher doses[12] based in part on non-dose response HF studies (CONSENSUS[13] MERIT[14] and VALIANT[15]).

Authors:
James McCormack BSc Pharm Pharm D, Michael R. Kolber BSc MD CCFP MSc

Disclosure:
Authors do not have any conflicts to disclose.

References:

1. Bristow MR, Gilbert EM, Abraham WT, *et al*. Circulation. 1996; 94:2807-16.
2. Okamoto H, Hori M, Matsuzaki M, *et al*. Int J Cardiol. 2013; 164:238-44.
3. McAlister FA, Wiebe N, Ezekowitz JA, *et al*. Ann Intern Med. 2009; 150:784-94.
4. Packer M, Poole-Wilson PA, Armstrong PW, *et al*. Circulation. 1999; 100:2312-8.
5. Poole-Wilson PA on behalf of NETWORK Investigators. Eur Heart J. 1998; 19:481-9.
6. Konstam MA, Neaton JD, Dickstein K, *et al*. Lancet. 2009; 374:1840-8.
7. Hori M, Sasayama S, Kitabatake A, *et al*. Am Heart J. 2004; 147:324-30.
8. Clement DL, De Buyzere M, Tomas M, *et al*. Acta Cardiol. 2000; 55(I):1-7.
9. Nanas JN, Alexopoulos G, Anastasiou-Nana MI, *et al*. J Am Coll Cardiol. 2000; 36:2090-5.
10. Lindblad AJ, Allan GM. Can Fam Physician. 2014; 60:e104.
11. Tavazzi L, Maggioni AP, Borer JS. Eur Heart J. 2013; 34:2792-4.
12. McKelvie RS, Moe GW, Ezekowitz JA, *et al*. Can J Cardiol. 2013; 29:168-81.
13. The CONSENSUS Trial Study Group. N Engl J Med. 1987; 316;1429-35.
14. MERIT-HF Study Group. Lancet. 1999; 353:2001-7.
15. Pfeffer MA, McMurray JJV, Velazquez EJ, *et al*., for the Valsartan in Acute Myocardial Infarction Trial Investigators. N Engl J Med. 2003; 349:1893-906.

Tools for Practice is a biweekly article summarizing medical evidence with a focus on topical issues and practice modifying information. It is coordinated by G. Michael Allan, MD, CCFP and the content is written by practising

family physicians who are joined occasionally by a health professional from another medical specialty or health discipline. Each article is peer-reviewed, ensuring it maintains a high standard of quality, accuracy, and academic integrity. If you are not a member of the ACFP and would like to receive the TFP emails, please sign up for the distribution list at http://bit.ly/signupfortfp. Archived articles are available on the ACFP website.

This communication reflects the opinion of the authors and does not necessarily mirror the perspective and policy of the Alberta College of Family Physicians.