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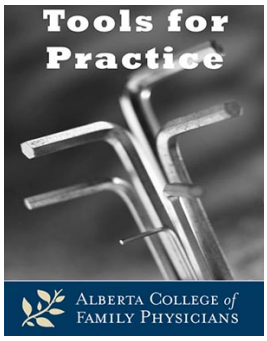

Sacubitril/Valsartan: Getting to the Heart of This Novel Therapy

Clinical Question: Is sacubitril/valsartan (Entresto®) effective for systolic heart failure (HF)?

Bottom Line: Based on one randomized controlled trial (RCT), for every 36 patients with heart failure switched from ACE inhibitors to sacubitril/valsartan, one fewer will die and one fewer will be admitted for heart failure over 27 months. Beta-blockers and aldosterone antagonists should be offered first and continued concurrently.

Evidence:

- One RCT (PARADIGM-HF):[1] 8,399 patients with systolic HF, mean age 64, ~94% Class II/III, B-type natriuretic peptide (BNP) ~250 pg/mL, ~7% North American. Patients switched from their ACE inhibitor to sacubitril/valsartan 200 mg (97 mg/103 mg) BID or enalapril 10 mg BID.
  - At 27 months, sacubitril/valsartan significantly reduced:
    - Cardiovascular death or HF hospitalization: 22% versus 27%, Number Needed to Treat (NNT)=22.
    - Cardiovascular death: 13% versus 17%, NNT=32.
    - HF hospitalization: 13% versus 16%, NNT=36.
    - All-cause mortality: 17% versus 20%, NNT=36.
    - Mean blood pressure ~3 mmHg lower.
    - Fewer discontinuations for renal impairment: 0.7% versus 1.4%, NNT=143.
  - Adverse Effects: Overall fewer with sacubitril/valsartan, 10.7% versus 12.3%, NNT=63. But increased:
    - Symptomatic hypotension: 14% versus 9.2%, Number Needed to Harm (NNH)=20.
    - Angioedema cases: 19 versus 10.
  - Limitations: ~20% withdrew during run-in, stopped early (which can overestimate benefit and underestimate harm), and industry sponsored.

Context:

- The usefulness of initiating therapy based on BNP levels is unknown as most heart failure patients have elevated BNP.[2]
- Concurrent therapy in PARADIGM-HF:[1]
  - ~93% taking beta-blockers.
  - ~Half taking aldosterone antagonists.
- ACE inhibitors, beta-blockers, and aldosterone antagonists each reduce all-cause mortality by ~20-30% versus placebo.[3]
- Based on PARADIGM-HF,[1] guidelines recommend replacing ACE inhibitor/angiotensin receptor blockers with sacubitril/valsartan if on ACE inhibitors, beta-blockers and aldosterone antagonists with elevated natriuretic peptides or hospitalization for heart failure in the previous 12 months.[4,5]
- Starting dose is 50 mg (24 mg/26 mg) to 100 mg (49 mg/51 mg) BID with possible titration to 200 mg in 2-4 weeks.[6]
  - ~40% of patients will need a dose reduction (but 1/3 will be able to go back to full dose).[7]
- Although not currently covered by many insurance plans, it is a recommended benefit.[8]
  - Cost ~$250/month.

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Disclosure:
Authors do not have any conflicts of interest to declare.

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