Heart Failure Workshop

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Patient Case

- BPMH:
  - Ramipril 2.5 mg bid
  - Carvedilol 25 mg bid
  - Apixaban 5 mg bid
  - Diltiazem CD 120 mg daily
- Social history:
  - Non smoker
  - 2 to 3 bottles of beer a week
  - Has been ordering a lot of take-out in the last month

Patient Case

- Mr. AB is a 68 yo male with HFrEF who was admitted to the GIM unit for acute decompensated heart failure
- He reports feeling short of breath at rest. He's been requiring 3 pillows to keep him comfortable and keeps waking up at night feeling short of breath

Patient Case

- On admission:
  - BP 110/70, HR 85
  - RR = 24
  - ++ crackles, bibasilar on chest auscultation
  - JVP = 7 cm ASA, pitting edema 2+
  - Creatinine = 88 µmol/L
  - Na+ = 132 mmol/L
  - K+ = 4.1 mmol/L
  - Weight = 80 kg (dry weight = 75 kg)

Patient Case

- PMH:
  - HFrEF (diagnosed 6 months ago; asymptomatic with no prior hospitalizations)
  - Atrial fibrillation (diagnosed 2 weeks ago)
- Allergies: NKA

Patient Case

- Echocardiogram reveals EF 25%
- Are there any precipitating factors for his heart failure exacerbation?

Precipitating Factors of HF

DISEASE-INDUCED	DRUG-INDUCED
INCREASED CARDIAC DEMAND	
- infection/fever - emotional stress - obesity - anemia - thyrotoxicosis - uncontrolled HTN	- cocaine - amphetamines
INCREASED PLASMA VOLUME	
- increased salt intake - increased fluid intake - renal failure	- NSAIDs, COX-2 inhibitors - corticosteroids - high sodium-content drugs - thiazolidinediones - androgens, estrogens
DEPRESSED CARDIAC FUNCTION	
- cardiac arrhythmias - pulmonary embolism - infiltrative disease (amyloid, sarcoid) - ischemia/MI	- antiarrhythmics - calcium channel blockers (diltiazem, verapamil) - chemotherapeutic drugs (anthracyclines, cyclophosphamide) - itraconazole
POOR PATIENT COMPLIANCE	

Patient Case

- Are there any other medication changes you would like to make for Mr. AB prior to discharge?

Stop beta-blockers in acute HF?

- **B-Convinced study** (RCT)
  - Beta-blocker continuation vs discontinuation during acute HF in patients with HFrEF
  - Non-inferior for primary endpoint of dyspnea and well-being
  - BNP, length of hospital stay, re-hospitalization rate, and death rate were also similar
  - Higher rate of beta-blocker prescription after 3 months in continuation group
  - Excluded patients requiring dobutamine

Jondeau G et al. Eur Heart J 2009;30:2186-2192

Patient Case

- 2 weeks later, you see Mr. AB in the heart failure clinic for follow-up
- You do his BPMH and he continues the same medications from hospital discharge
- He reports that he tries to eat a low-salt diet and cooks most of his meals at home now
- He feels well since his hospital discharge but still feels short of breath when he climbs up the stairs very quickly

CCS HF Guidelines

- Continuation of beta-blocker upon admission for acute HF is safe
- We recommend continuation of chronic beta-blocker therapy with acute HF, *unless the patient is symptomatic from hypotension or bradycardia*

McKelvie RS et al. Can J Cardiol 2013;29:168-181

Patient Case

Physical exam and labs:

- BP 100/60, HR 80
- RR = 12
- Chest clear, no S3 gallop, no ascites
- JVP 3 cm ASA
- Creatinine = 76 µmol/L
- Na+ = 135 mmol/L
- K+ = 4.3 mmol/L
- BNP = 255 pg/ml
- Weight = 75.5 kg (dry weight = 75 kg)

Patient Case

- BPMH:
  - Ramipril 5 mg bid
  - Carvedilol 25 mg bid
  - Furosemide 40 mg daily
  - Apixaban 5 mg bid
- Are there any medication changes you would like to make today?

EMPHASIS

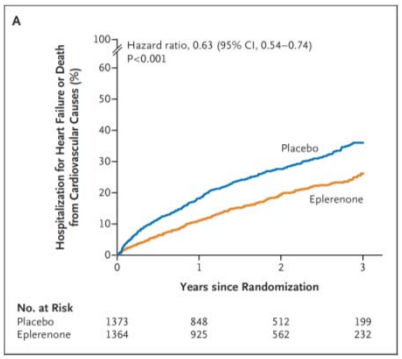
- Key exclusion criteria:
  - serum K+ > 5 mmol/L
  - eGFR < 30 mL/min
- More hyperkalemia (K+ > 5.5 mmol/L) in the eplerenone group (11.8% vs 7.2%)

Zannad F et al. New Engl J Med 2011;364:11-21

CCS HFrEF Treatment Algorithm

Howlett JG et al. Can J Cardiol 2016;32:296-310

EMPHASIS



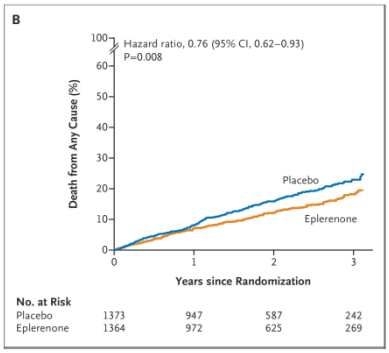
Zannad F et al. New Engl J Med 2011;364:11-21

EMPHASIS

- Eplerenone (up to 50 mg daily) vs placebo
- NYHA class II
- 69 yo, 83% white, 22% females, EF 26%
- 53% had previous hospitalizations for HF
- Baseline medications
  - ACE inhibitor / ARB / or both 93%
  - Beta-blocker 87%
  - Diuretic 85%
  - Digoxin 27%

Zannad F et al. New Engl J Med 2011;364:11-21

EMPHASIS



Zannad F et al. New Engl J Med 2011;364:11-21

RALES

- Spironolactone (up to 50 mg daily) vs placebo
- NYHA class III or IV (70% NYHA class III)
- 65 yo, 87% white, 27% females, EF 25%
- Baseline medications
  - ACE inhibitor 95%
  - Beta-blocker 11%
  - Diuretic 100%
  - Digoxin 74%

Pitt B et al. New Engl J Med 1999;341:709-717

MRAs – CCS HF Guidelines

- MRA such as *eplerenone* for patients > 55 years with mild to moderate HF during standard HF treatments with EF ≤ 30% (or ≤ 35% if QRS duration >130 ms) and recent (6 months) hospitalization for CV disease or with elevated BNP or NT-proBNP (EMPHASIS)
- MRA such as *spironolactone* for patients with an EF < 30% and severe chronic HF (NYHA IIIB-IV) despite optimization of other recommended treatments (RALES)
- MRA such as *eplerenone* in patients after an MI with EF ≤ 30% and HF or EF ≤ 30% alone in the presence of diabetes (EPHESUS)

McKelvie RS et al. Can J Cardiol 2013;29:168-181

RALES

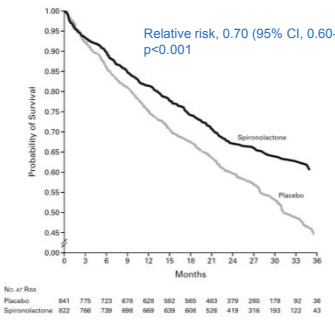
- Key exclusion criteria
  - serum K+ > 5 mmol/L
  - serum creatinine > 221 µmol/L
- More gynecomastia or breast pain in the spironolactone group (10% vs 1%)
- No difference in serious hyperkalemia (2% spironolactone vs 1% placebo)
  - Serious hyperkalemia defined as serum K+ ≥ 6 mmol/L

Pitt B et al. New Engl J Med 1999;341:709-717

Differences between MRAs

	Spironolactone	Eplerenone
Receptor affinity	Blocks the mineralocorticoid receptor as well as androgen and progesterone receptors	More selective – low affinity for androgen and progesterone receptors (lower incidence of gynecomastia, impotence, and menstrual irregularities)
Metabolism	Hepatic Active metabolites	Hepatic – CYP3A4 Inactive metabolites
Half-life	1.4 hrs (active metabolites 12-20 hrs)	4-6 hrs
Availability & drug plan coverage	Generics Private plan ODB	No generics Private plan ODB with LU code
Cost	$ 0.11	$ 2.75

RALES



Pitt B et al. New Engl J Med 1999;341:709-717

Eplerenone now covered by ODB

- LU code 458:
  - For NYHA class II chronic HF with EF ≤ 35%, as a complement to standard therapy
  - Note: Patients must be on optimal therapy with an ACE inhibitor, an ARB, or both and a beta-blocker (unless contraindicated) at the recommended dose or maximal tolerated dose

Patient Case

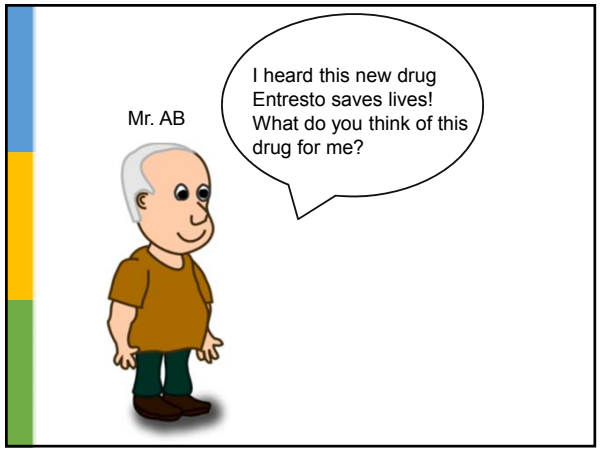
- Which MRA would you add?
- Do you believe the MRAs are interchangeable?

Patient Case

- EF 25% (from last hospital admission)
- BPMH:
  - Ramipril 5 mg bid
  - Carvedilol 25 mg bid
  - Furosemide 40 mg daily
  - Eplerenone 50 mg daily (titrated up from 25 mg daily)
  - Apixaban 5 mg bid

Patient Case

- 3 months later, you see Mr. AB in the heart failure clinic for follow-up
- He still feels short of breath when he climbs up the stairs very quickly



Patient Case

Physical exam and labs:

- BP 105/65, HR 80
- RR = 14
- Chest clear, no S3 gallop, no ascites
- JVP 3 cm ASA
- Creatinine = 80 µmol/L
- Na+ = 137 mmol/L
- K+ = 4.1 mmol/L
- BNP = 205 pg/ml
- Weight = 75.3 kg (dry weight = 75 kg)

Patient Case

What is in your assessment to ensure that sacubitril/valsartan is appropriate for Mr. AB?

PARADIGM-HF

	Sacubitril /Valsartan (n = 4187)	Enalapril (n = 4212)	Hazard Ratio (95% CI)	P Value
Death from cardiovascular causes or 1st hospitalization for heart failure	914 (21.8%)	1117 (26.5%)	0.80 (0.73-0.87)	<0.001
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71-0.89)	<0.001
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71-0.89)	<0.001
Death from any cause	711 (17.0%)	835 (19.8%)	0.84 (0.76-0.93)	<0.001

McMurray JJV et al. N Engl J Med 2014;371:993-1004. Adapted from http://www.clinicaltrialresults.org

Who are the patients?

- 64 yo, 22% females, 66% white, 7% North America
- SBP 122 mm Hg
- HR 73 bpm
- SCr 100 µmol/L
- EF 30%
- Mostly NYHA class II (70%)
- Prior HF hospitalization 63%

McMurray JJV et al. N Engl J Med 2014;371:993-1004

Adverse Event	Sacubitril /Valsartan (N = 4187)	Enalapril (N = 4212)	P Value
	No. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	**<0.001**
Symptomatic with SBP < 90 mm Hg	112 (2.7)	59 (1.4)	**<0.001**
Elevated SCr			
≥ 2.5 mg/dl (221 µmol/L)	139 (3.3)	188 (4.5)	**0.007**
≥ 3.0 mg/dl (265 µmol/L)	63 (1.5)	83 (2.0)	0.10
Elevated K+			
> 5.5 mmol/L	674 (16.1)	727 (17.3)	0.15
> 6.0 mmol/L	181 (4.3)	236 (5.6)	**0.007**
Cough	474 (11.3)	601 (14.3)	**<0.001**
Angioedema			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	----

McMurray JJV et al. N Engl J Med 2014;371:993-1004

Who are the patients?

- Baseline medications
  - ACE inhibitor 78%
  - ARB 23%
  - Diuretic 80%
  - Digoxin 30%
  - Beta-blocker 93%
  - MRA 56%

McMurray JJV et al. N Engl J Med 2014;371:993-1004

PARADIGM-HF Patients

- NYHA class II to IV
- EF ≤ 40% (≤ 35% after protocol amendment)
- Plasma BNP ≥ 150 pg/ml (or NT-proBNP ≥ 600 pg/ml) or if hospitalized for HF within previous 12 months a BNP of ≥ 100 pg/ml (or an NT-proBNP ≥ 400 pg/ml)
- On a stable dose of a beta-blocker (unless contraindicated or not tolerated) and an ACE inhibitor (or ARB) equivalent to at least 10 mg of enalapril daily for at least 4 weeks before screening

Excluded:

- Symptomatic hypotension, SBP < 100 mm Hg
- eGFR < 30 mL/min
- K+ > 5.2 mmol/L

McMurray JJV et al. N Engl J Med 2014;371:993-1004

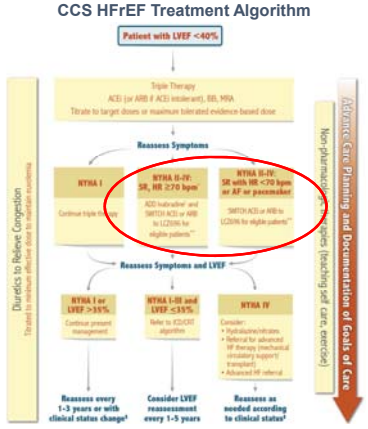
Limitations

- Controlled run-in period
  - 12% of patients withdrew because of an adverse event (most frequently cough, hyperkalemia, renal dysfunction, or hypotension)
- Prior use of ACE inhibitor / ARB
- Few NYHA class IV patients (0.7%)
- Few patients with ICD (15%) / CRT (7%)
- Few black patients (5%)
  - 5 times the rate of angioedema in black patients (2.4%) vs. non-black (0.4%)

Drug Cost and Coverage

- $7.24/day (twice daily dosing)
- Covered by private drug plans
- Not covered by ODB
- Patient assistance cards cover up to 100% of the drug cost

CCS HFrEF Treatment Algorithm



Howlett JG et al. Can J Cardiol 2016;32:296-310

Back to Mr. AB

- Would you use sacubitril/valsartan in him?

Sacubitril/Valsartan Care Plan

- What dose?
- How to switch?
- What to monitor for?

CCS HF Guidelines

Patients with mild to moderate HF, an EF ≤ 40%, an elevated natriuretic peptide level or hospitalization for HF in the past 12 months, a serum potassium < 5.2 mmol/L, and an eGFR ≥ 30 mL/min and treated with appropriate doses of guideline-directed medical therapy should be treated with LCZ696 [sacubitril/valsartan] in place of an ACE inhibitor or an angiotensin receptor blocker, with close surveillance of serum potassium and creatinine.

Moe GW et al. Can J Cardiol 2015;31:3-16

Dosage Strengths

- Available in 3 different strengths:
  - 24.3 mg sacubitril / 25.7 mg valsartan **(50 mg)**
  - 48.6 mg sacubitril / 51.4 mg valsartan **(100 mg)**
  - 97.2 mg sacubitril / 102.8 mg valsartan **(200 mg)**

Initial Dose and Titration

High Dose RAAS inhibitor		Initial Dose	Titration
ACEI	ARB		
enalapril ≥10mg/d lisinopril ≥10 mg/d perindopril ≥4 mg/d ramipril ≥5 mg/d	candesartan ≥16mg/d irbesartan ≥150 mg/d losartan ≥50 mg/d olmesartan ≥10 mg/d telmisartan ≥40 mg/d valsartan ≥160 mg/d	100 mg po bid	Increase in 3 to 6 weeks to target 200 mg po bid
Low Dose RAAS inhibitor		50 to 100 mg po bid	Over 6 weeks, increase to target 200 mg po bid
RAAS inhibitor naïve		50 mg po bid	
Higher risk of hypotension (e.g. low baseline SBP)			

Monitoring

- Same as RAAS inhibitors
  - Blood pressure
  - Serum potassium
  - Serum creatinine
- Angioedema: stop sacubitril/valsartan, contact physician, do not re-challenge
- Expected to raise BNP levels, but not NT-proBNP
  - only NT-proBNP can be used as a suitable biomarker for monitoring

Switching from ACEI/ARB

Switching from ACEI:

- Stop ACEI, **wait at least 36 h** after last dose, then start sacubitril/valsartan

Switching from ARB:

- Stop ARB, no washout period necessary, start sacubitril/valsartan when next dose would have been due

Must not be administered concomitantly or within 36 hours of ACE inhibitors (risk of angioedema)

What-if scenarios

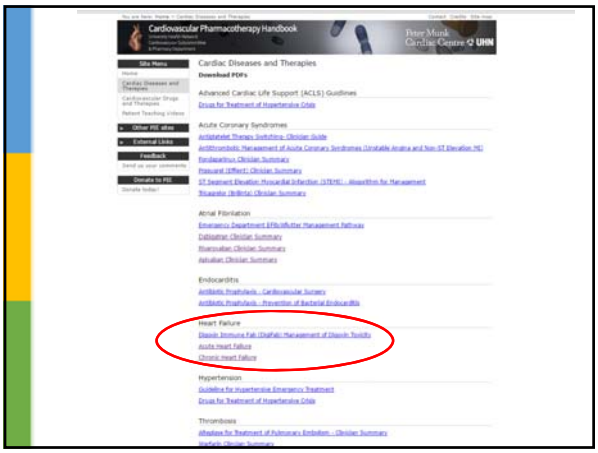
- If Mr. AB was on ramipril 2.5 mg bid, would you consider titrating up his ramipril dose or switch to sacubitril/valsartan?
- What if Mr. AB's a newly diagnosed HF patient? Would you start sacubitril/valsartan de novo?

Patient Case

- What will you monitor for?

Resources

https://pie.med.utoronto.ca/CVmanual/index.htm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