Which Medication Should I Add First?

Practical suggestions for medication management in heart failure patients

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1

Statement of Disclosure

- I have no relevant financial relationships with commercial interests pertaining to the content presented in this program.

2

Objectives

1. List medications that should be considered for all heart failure patients with reduced ejection fraction.
2. Describe a patient-centered medication regimen for a complicated patient with heart failure with reduced ejection fraction that cannot receive all guideline recommended medications.

3

Acronyms

- HFrEF (Heart Failure with reduced ejection fraction)
- ACC (American College of Cardiology)
- AHA (American Heart Association)
- LVEF (left ventricular ejection fraction)
- ACEi (angiotensin converting enzyme inhibitor)
- ARB (angiotensin receptor blocker)
- ARNI (angiotensin receptor neprilysin inhibitor)

4

Case #1

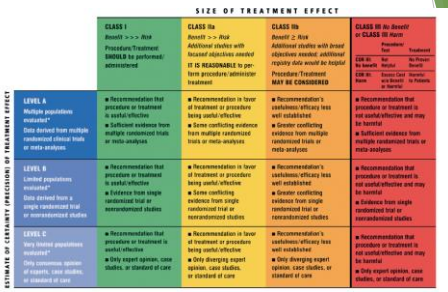
- FD is a 59 year old male who was admitted to the hospital with increased shortness of breath and 2+ edema.
- Chest X-ray: correlates with congestive heart failure.
- Demographics
  - PMH: NIDDM, Hypertension, Coronary artery disease
  - Current Medications:
    - Aspirin 81mg
    - Atorvastatin 40mg nightly
    - Metformin 500mg BID
  - Allergies: NKDA

5

Case #1

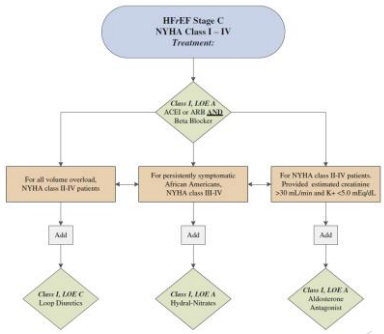
- Pertinent labs/test results
  - BP: 135/85
  - HR: 95 (sinus rhythm)
  - ECHO
    - Moderate to severely reduced LV systolic function (25-30%)
    - Mild to moderate global hypokinesis of the left ventricle
  - Basic Metabolic Panel
    - BUN 11
    - SCr 1.1
    - K 4.3
    - Na 140
    - Pro-BNP > 35,000

6



ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I Benefit >>> Risk Procedure/Treatment SHOULD be performed/administered	CLASS IIa Benefit >> Risk Additional studies with focused objectives needed IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	CLASS III: No Benefit or CLASS III: Harm Procedure/Test: Not Helpful / Treatment: No Proven Benefit COR III: No Benefit COR III: Harm: Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only divergent expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only divergent expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care

Yancy CW et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15; 62(16): e 147-239.



Yancy CW et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15; 62(16): e 147-239.

Diuretics

CLASS I

1. **Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. *(Level of Evidence: C)***

- Most effective: Loop Diuretics
  - Furosemide 20-40mg once daily
  - Bumetanide 0.5-1mg once daily
  - Torsemide 20-40mg once daily

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Diuretics

- Mortality and morbidity with diuretics are unknown
- Bumetanide and torsemide are 100% bioavailable
  - May work better in certain populations
  - Specifically renal patients
  - Malnutrition
- If refractory edema occurs, consider the addition of metolazone with a loop
- Electrolytes and renal function need to be closely monitored

Epstein M, et al. Potentiation of furosemide by metolazone in refractory edema. Cur Ther Res 1977: 656-67

ACE Inhibitors

- Class I recommendation
- ACE inhibitors are recommended for patients with HFrEF and current or prior symptoms (unless contraindicated) to reduce morbidity and mortality
- Should be used in combination with beta blockers
- Used for afterload reduction
- Monitor renal function, blood pressure and potassium
- Dosing
  - Start low and go slow
  - Basic metabolic panel should be monitored approximately 2 weeks after starting the medication or after a dose increase

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ACE Inhibitors

- Dosing for ACE inhibitors

Drug	Initial Daily Dose(s)	Maximum Dose(s)
ACE inhibitors		
Captopril	6.25 mg 3 times	50 mg 3 times
Enalapril	2.5 mg twice	10 to 20 mg twice
Fosinopril	5 to 10 mg once	40 mg once
Lisinopril	2.5 to 5 mg once	20 to 40 mg once
Perindopril	2 mg once	8 to 16 mg once
Quinapril	5 mg twice	20 mg twice
Ramipril	1.25 to 2.5 mg once	10 mg once
Trandolapril	1 mg once	4 mg once

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ACE Inhibitors

- Enalapril vs. Placebo (SOLVD)
  - 1284 patients in placebo and 1285 in enalapril group
  - Enalapril was dosed between 2.5mg and 20mg per day

	Placebo	Enalapril	P-value
Hospitalization due to HF	736	613	< 0.0001
Total Deaths	510	452	0.0036
Death due to HF	251	209	< 0.0045

The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991 Aug 1; 325(5): 293-302.

13

Angiotensin Receptor Blockers

CLASS I

1. **ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality**

CLASS IIa

1. **ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE inhibitors as first-line therapy for patients with HFrEF, especially for patients already taking ARBs for other indications, unless contraindicated**

CLASS III: Harm

1. **Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF. *(Level of Evidence: C)***

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14

Angiotensin Receptor Blockers

- Start low and go slow
- Reasons to use an ARB
  - Commonly used if intolerant to ACEi
    - Most common reason is ACEi induced cough
    - Bradykinin effect
  - If already on an ARB and transitioning to HF approved per the 2013 guidelines
- Monitoring: patient's volume status, renal function, other concomitant medications

ARBs		
Candesartan	4 to 8 mg once	32 mg once
Losartan	25 to 50 mg once	50 to 150 mg once
Valsartan	20 to 40 mg twice	160 mg twice

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15

Beta Blockers

- Class I Recommendation
- Use of 1 of 3 beta blockers is recommended for all patients with HFrEF, unless contraindicated, to reduce morbidity and mortality
  - Metoprolol succinate, bisoprolol, carvedilol
- HFrEF patients should be stable and it is recommended to start the beta blocker as soon as symptoms improve or if symptoms are mild
- Use with diuretic is optimal to maintain sodium and fluid balance

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16

Beta Blockers

- Start low and go slow
- Titrate up every 2-3 weeks until maximum tolerated dose or target dose is achieved
- Monitor for hypotension, bradycardia and fatigue

Beta blockers		
Bisoprolol	1.25 mg once	10 mg once
Carvedilol	3.125 mg twice	50 mg twice
Carvedilol CR	10 mg once	80 mg once
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once

17

Beta Blockers

- Carvedilol vs. placebo
  - 696 in carvedilol group vs 398 in placebo group
  - Findings led to early termination of the study due to reduced hospitalization and decreased mortality with carvedilol patients

	Placebo	Carvedilol	P-value
Hospitalization	78 (19.6%)	98 (14.1%)	0.036
Death	31 (7.8%)	22 (3.2%)	< 0.001
Combined risk of hospitalization or death	24.6%	15.8%	< 0.001

Packer M, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996 May 23; 334(21): 1349-55.

18

Aldosterone Antagonists

- Class I Recommendation
- Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV HF who have a LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality.
- Patients with NYHA class II HF should have a history of prior CV hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists.

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19

Aldosterone Antagonists

- Creatinine should be 2.5 mg/dL or less in men and 2 mg/dL or less in women.
- Potassium should be less than 5 meq/L.
- Careful monitoring of potassium, renal function and diuretic dosing should be performed at initiation and monitored thereafter to minimize risk of hyperkalemia and renal insufficiency.
- Alternative to spironolactone is eplerenone

20

Aldosterone Antagonists

- RALES study
  - LVEF 35% or less, ACEi, loop diuretic and digoxin (few patients on beta blockers)
  - NYHA class change
    - Placebo
      - 33% improved, 18% did not change, 48% worsened
    - Spironolactone
      - 41% improved, 21% did not change, 38% worsened

	Spironolactone	Placebo	P-Value
Hospitalizations due to cardiac cause	260	336	<0.001
Cardiac deaths	226/822	341/841	< 0.001
Total Deaths	284	386	< 0.001

Pitt B, et al. The effect of spironolactone on morbity and mortality in patients with severe heart failure. N Engl J Med. 1999 Spe 2; 341(10): 709-17.

21

Aldosterone Antagonists

- Alternative to spironolactone
  - Eplerenone
  - 25mg once daily (target dose 50mg daily)
  - Most commonly used when patients experience gynecomastia with spironolactone

	Eplerenone (n= 1364)	Placebo (n=1373)	P-Value
Hospitalization for HF	164 (12%)	253 (18.4%)	< 0.001
Death from CV cause	249 (18.3%)	356 (25.9%)	< 0.001
Death from any cause	171 (12.5%)	213 (15.5%)	< 0.001

22

Zannad F, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011 Jan 6; 364(1): 11-21.

Sacubitril-valsartan

- 2016 ACC/AHA heart failure guidelines update:
  - Now includes an angiotensin receptor neprilysin inhibitor (ARNI)
  - Class I recommendation
  - Alternative to an ACEi or ARB

23

Yancy CW, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016 Sep 27; 68(13): 1476-88.

Sacubitril-valsartan

- Mechanism
  - Sacubitril
    - Prodrug
    - Inhibits neprilysin
      - Increase natriuretic peptides
      - Increase vasodilation
  - Valsartan
    - Decrease sodium and water retention
    - Decrease vasoconstriction
    - Decrease hypertrophy
    - Decrease fibrosis

24

McMurray JJ, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11; 371(11): 993-1004.

Sacubitril-valsartan

- Must hold an ACEi for 36 hours prior to initiation of an ARNI
  - Increased risk of angioedema if given together
  - Mechanism: thought to be due to the breakdown of bradykinin from both classes
- Dosing
  - Enalapril >10mg, lisinopril >10mg or ramipril >5mg
    - 49/51mg BID
  - Losartan > 50mg, valsartan > 160mg
    - 49/51mg BID
- Monitor for hypotension and renal insufficiency

25

Sacubitril-valsartan

- Sacubitril-valsartan vs. enalapril
  - 4187 in the sacubitril-valsartan group
  - 4212 in the enalapril group
  - Study stopped early due to superior results with sacubitril-valsartan

	LCZ696	Enalapril	P-value
Hospitalizations	537	658	<0.001
Death due to cardiac cause	914	1117	<0.001
Death from any cause	711	835	<0.001

26

McMurray JJ, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11; 371(11): 993-1004.

Case #1

- FD is a 59 year old male who was admitted to the hospital with increased shortness of breath and 2+ edema.
- Chest X-ray is consistent with congestive heart failure.
- Demographics
  - PMH: NIDDM, Hypertension, CAD
  - Current Medications:
    - Aspirin 81mg
    - Atorvastatin 40mg nightly
    - Metformin 500mg BID
  - Allergies: NKDA

27

Case #1

- Pertinent labs/test results
  - BP: 135/85
  - HR: 95 (sinus rhythm)
  - ECHO
    - Moderate to severely reduced LV systolic function (25-30%)
    - Mild to moderate global hypokinesis of the left ventricle
  - Basic Metabolic Panel
    - BUN 11
    - SCr 1.1
    - K 4.3
    - Na 140
    - Pro-BNP > 35,000

28

Case #1

- FD was started on IV furosemide 40mg BID x 3 doses and transitioned to 20mg daily as fluid volume improved.
- What additional therapy should be considered?
  - BB and ACEi
    - Carvedilol 3.125mg BID (need to wait until heart failure is compensated)
    - Lisinopril 5mg daily
  - Spironolactone?
  - Where does sacubitril-valsartan fit in?

29

OTHER AGENTS USED IN HFREF

30

Nitrate/hydralazine

- Class I
  - The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African American with NYHA class III-IV HFrEF receiving optimal therapy with ACEi and beta blockers, unless contraindicated.
- Class IIa
  - A combination of hydralazine and isosorbide dinitrate (unless contraindicated) can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACEi or ARB because of drug intolerance, hypotension, or renal insufficiency.

Yancy CW et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15; 62(16): e 147-239.

31

Nitrate/hydralazine

- Dosing
  - Brand ($$$) vs generic equivalents
  - Compliance

Hydralazine and isosorbide dinitrate		
Fixed-dose combination (424)	37.5 mg hydralazine/20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily
Hydralazine and isosorbide dinitrate (449)	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate: 120 mg daily in divided doses

32

Nitrate/hydralazine

- A-HeFT Study
  - Mostly NYHA class III patients, some class IV
  - 518 patients in Nitrate/hydralazine group
  - 532 in placebo group
  - Did not show the same results in the Caucasian population

	ID/hydralazine	Placebo	P-value
Hospitalization for heart failure	32 (6.2%)	54 (10.2%)	0.02
Death from any cause	85 (16.4%)	130 (24.4%)	0.001

Taylor AL, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004 Nov 11; 351(20): 2049-57.

33

Digoxin

- Class IIa
  - Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF
- Potential areas to utilize digoxin
  - Patients remaining symptomatic despite current treatment with first line therapies
  - Patients in atrial fibrillation who cannot tolerate a BB
  - Therapeutic drug levels: 0.5-0.9 ng/mL
  - Watch electrolytes!

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34

Ivabradine

- Class IIa
- Ivabradine can be beneficial to reduce hospitalizations for the following patients:
  - Symptomatic, stable, chronic, NYHA class II-III HFrEF
  - Receiving GDEM (guideline-directed evaluation and management) including a beta blocker at maximum tolerated doses
  - In sinus rhythm with heart rate of 70 bpm or greater at rest

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35

Ivabradine

- Novel agent
- Selectively inhibits the I_f current in the SA node, providing heart rate reduction
- NYHA Class II-IV
- Cannot use if patient is in atrial fibrillation
- Can cause phosphenes (important counseling point)

36

Ivabradine

- SHIFT study
  - 3241 in ivabradine group
  - 3264 in placebo group
  - Not statistically significant for mortality

	Ivabradine	Placebo	P-value
Hospital admission for worsening heart failure	514	672	< 0.0001
Cardiovascular mortality	449	491	0.128
Death from heart failure	113	151	0.014

Swedberg K, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010 Sep 11; 376(9744): 875-85.

37

Overview

- Medications decreasing mortality and hospitalizations
  - ACEi/ARB/ARNI
  - BB (specifically carvedilol, metoprolol XL and bisoprolol)
  - Spironolactone/epleronone
- Other agents to consider
  - Ivabradine
  - Digoxin
  - Isosorbide dinitrate/hydralazine
    - First line in African American patients taking BB and ACEi
    - NYHA Class III-IV
    - Consider for patients unable to take ACEi/ARB/ARNI due to renal insufficiency

38

Use of Patiromer?

- Indication: Hyperkalemia
  - 8.4g once daily
- Pros
  - Possible for patients who experience hyperkalemia with ACEi and/or AA
  - May help achieve target dosing per the 2013 ACC/AHA heart failure guidelines
- Cons
  - Cost
  - Package insert states: administer patiromer 3 hours before or 3 hours after (when first approved it was 6 hours) other medications due to risk of binding
  - Compliance?

Veltassa (patiromer) [prescribing information]. Redwood City, CA: Relypsa Inc; November 2016.

39

Case #2

- CS presents to the heart failure clinic for a first time visit. He was recently hospitalized for an acute heart failure exacerbation.
  - ECHO: LVEF 20%
  - Discharge cardiac medications
    - Furosemide 40mg PO BID
    - Potassium chloride 20meq PO daily
    - Carvedilol 3.125mg PO BID
    - Diltiazem XR 120mg daily

40

Case #2

- Demographics:
  - 39 year old female
  - Caucasian
- Physical Exam
  - Weight 135 kg (discharge weight 120kg)
  - Height 162.56 cm
  - 3+ edema
  - BP 145/65
  - HR 100 (regular)
  - NYHA Class III
- Labs
  - SCr 1.75 (baseline)
  - BUN 35
  - K 4.9
  - Na 141
  - Mg 2.1

41

Case #2

- What pharmacologic recommendations would you make based on this information?

42

Case #2

- Consider during heart failure clinic visit:
  - Diltiazem was discontinued
    - Negative inotropic effect
    - Can increase risk of heart failure exacerbation
  - Furosemide IV 80mg times one given in the clinic and furosemide 80mg PO BID
    - Focus on fluid
  - History of non-compliance?
    - Is she taking all the medications correctly?
    - How is she taking the furosemide?

43

Case #2

- Other future considerations
  - Isosorbide dinitrate/hydralazine
    - Compliance with TID dosing?
    - BP tolerance
  - ACEi/ARB/ARNI
    - Unstable renal function
    - Future consideration
  - Ivabradine or digoxin
    - Elevated HR
    - Decreased BP

44

Conclusion

- Focus on the class I recommendations per the 2013 ACC/AHA guidelines and 2016 update
  - ACEi/ARB/ARNI
  - BB
  - Spironolactone/eplerenone
- Outlying factors could lead to using alternative therapies
  - Nitrate + hydralazine
  - Digoxin
  - Ivabradine
- Importance of diuretics and symptom management
  - Utilizing IV furosemide in an outpatient setting to prevent an ER visit
  - Multi-disciplinary clinic
  - Educate on the importance of these medications
    - Is patient going to take due to cost?
    - Side effects
    - Frequency

45

Thank you

References

- 1. Yancy CW et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15; 62(16): e147-239.
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