Heart Failure Medication Titration

By: Tom Babb Pharm D., BCCP
North Central Heart a Division of Avera Heart Hospital

Disclosures

• I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation.

Learning Objectives

Pharmacists:
1. Determine the appropriate medication therapies to start on a patient with heart failure with reduced ejection fraction;
2. Identify special considerations that apply to certain patient populations, and evaluate how to most effectively treat their HFrEF.

Pharmacy Technicians:
1. Identify medications used to treat HFrEF;
2. Identify the correct brand/generic names for heart failure medications.
Heart Failure Prevalence/Burden

- Worldwide
  - 26 million people
  - 5.7 million in US with projections of 46% increase by 2030
  - Improved treatment on HTN, CAD, and valvular disease
- Significant mortality/morbidity
- Cost
  - $31 billion in 2012
  - 10% of total health care cost for cardiovascular care in United States

Clinic Work Flow

- New Patient
  - Physician sees in hospital or clinic
  - Diagnosis with NYHA class
  - MD or CNP will see 1 week after discharge if hospitalized for initial HF diagnosis.
  - Orders GDMT and recommendations
  - Heart failure nurse educates on lifestyle modifications
  - Pharmacist/Rn
    - Sees patient in 2 weeks after physician or during physician visit
    - Education of medications/home medication review/titration

Work Flow Continued

- Titration
  - Occurs every 2 weeks or sooner if needed
  - Visits in clinic with RN/pharmacist at least once a month for reeducation and titrations.
  - Follow up after 3 months of titration
    - Medications at goal or optimized
      - ECHO, ECG. Sees physician or CNP
      - EP consult if EF still <35% after titration.
### Classification of Heart Failure

<table>
<thead>
<tr>
<th>NYHA Functional Classification</th>
<th>ACCF/AHA Stages of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>A</td>
</tr>
<tr>
<td>No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
<td>B</td>
</tr>
<tr>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.</td>
<td>C</td>
</tr>
<tr>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
<td>D</td>
</tr>
<tr>
<td>Stable in any physical activity without symptoms of HF; or symptoms of HF at rest.</td>
<td>D</td>
</tr>
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</table>

### GDMT: How do we titrate?

- Start patient on low dose ACE I/ARB and Beta blocker
  - Start low and titrate slow
  - Titrated based on SBP and heart rate. Goal >90 sbp and pulse>50
- ACE or Beta blocker titration first?
  - Beta blockers may improve mortality/morbidity when titrated first
  - ACE inhibitors only decrease morbidity (hospitalizations etc...)

### Mortality Benefits for HFrEF

- Drugs that inhibit the renin-angiotensin system have modest effects on survival

### Special Considerations

- Pregnancy
  - No ACE. Start Beta Blocker (caution with breast feeding)
- Symptomatic HF or Acute HF
  - Hold BB titration until stable
- MI/Angina
  - ACE and BB needed but BB titration best choice.
- Atrial Fibrillation
  - BB can help rate control and should be titrated first.
- Ventricular Ectopy
  - BB can suppress Ventricular arrhythmias and reduce sudden cardiac death
Special Considerations Cont

- Diabetes/chronic kidney disease
  - ACE inhibitors may have protective effects on kidneys
  - Carvedilol may be a better BB (does not blunt insulin sensitivity)
- Asian/African Americans
  - ACE tend to have higher rates of cough and angioedema. ARB first line?

Are all heart failure meds created equal?

- ACE I or ARB (guideline Class IA)
  - Start with ACE inhibitor first usually based on cost
  - If intolerant (cough?) switch to ARB
  - Class effect no differences in efficacy
- Beta Blockers
  - ![Not created equal!!!
  - GDMT includes: carvedilol, metoprolol XL, and bisoprolol.
    - Switch patients to one of these beta blockers if on another beta blocker and is diagnosed with HFrEF.

When to add Aldosterone antagonists (K sparing diuretics)?

- Spironolactone or Eplerenone
- NYHA Class I
  - No indication for heart failure
- EPHESUS Trial (Post MI NYHA II-IV with EF<40) and EMPHASIS-HF trial (NYHA II EF<30%)
  - Start eplerenone 25 mg daily may increase to max of 50 mg daily
  - Both trials found significant reduction in cardiac mortality and hospitalization benefit.
- RALES Trial (NYHA III-IV with EF <35%)
  - Start spironolactone 12.5 mg daily and titrate to 25 mg daily (max 50 mg)
  - Risk reduction of 30% for mortality after 2 years of treatment
  - 36% risk reduction in hospitalization
- Precautions
  - GFR<30, increased risk of hyperkalemia
  - Baseline K >5.0

African American Population

- Lower renin production
  - ACE/ARBs don’t work as well
  - Increased risk of Angioedema with ACE/ARBs
- Do we use ACE I/ARBs?
  - Yes but may need to add other medications to get to a goal SBP <130
- Hydralazine/isosorbide dinitrate
  - Added to ACE I/ARB
  - Or if intolerant to ACE I/ARB
  - Improves survival and decrease hospitalizations
  - Efficacy seen more in African American Population
  - Dosing is times three daily (Adherence ?)
Statins

- Heart Failure?
  - No indication
- CAD, hyperlipidemia (LDL>190), High ASCVD risk, Diabetes
  - YES PLEASE!
- Addition of statin when indicated as above
  - Reduces the likelihood of damaging the heart from MI.
  - MI → increase chance of heart failure

Sacubitril/valsartan (Entresto®)

- PARADIGM-HF trial (randomized double blind trial)
  - Enalapril vs sacubitril/valsartan
  - 8442 patients randomized
- Results
  - Decrease all cause mortality
  - Reduced hospitalizations
  - Improved KCCQ patient score
  - Class IB-R recommendation for HF guidelines

Dosing Sacubitril/valsartan

- Dosing
  - If on ACE inhibitor, allow for 36 hour washout period before starting
  - Not on ACE/ARB - start dose at 24/26 mg twice daily
  - If on ACE/ARB, start at 49/51 mg twice daily
  - Titrate dose, doubling dose every 2 to 4 weeks until target dose of 97/103 mg twice daily, as tolerated.
- In practice
  - Significant hypotension
    - Start at lowest dose and titrate slowly
Digoxin?

• Place in therapy?
  • Digoxin can be considered to help reduce hospitalizations
• Benefits
  • Improve symptoms
  • Increase exercise tolerance
  • Decrease hospitalizations
  • Greatest effect is in EF<25 % or NYHA III or IV
• No Mortality Benefit

Digoxin dosing

• 0.125 mg/day is adequate to achieve the desired serum concentration.
• Consider dosing 0.125 mg every other day in patients older than 70 years, those with impaired renal function.
• Dig level should be < 1
  • Levels >1.2 had increased mortality
• Check level in 5-7 days
  • Steady state

Ivabradine

• Place in therapy
  • For patients with symptomatic NYHA functional classes II and III.
  • Stable,chronic HFrEF(LVEF of 35% or less)
  • Receiving GDTM
  • Including maximum tolerated β-blocker dose
  • NSR with a heart rate of 70 beats/minute or greater at rest.

Ivabradine

• SHIFT trial
  • Reduced hospitalizations
  • No mortality benefit
• Mechanism: Selectively inhibits the If current in the sinoatrial node, providing heart rate reduction.
• Adverse effects: New onset Afib, should not be used on demand pacemaker patients set at 60 beats/min or greater.
Diuretics

- **Loop diuretics**
  - Furosemide, torsemide, bumetanide
  - Potency: 40mg:20mg:1mg
  - Ethacrynic acid
  - Option if truly allergic to sulfa moiety in other loop diuretics
  - VERY EXPENSIVE!

- **Thiazide diuretics for HF**
  - Metolazone
  - Adjunct to loop
  - Chlorthiazide IV
    - No difference between PO metolazone and Chlorthiazide IV in loop resistant patients.
  - Chlothalidone
    - Option if need more blood pressure control

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**Adherence? Use of Seattle Heart Failure Model?**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Meds</th>
<th>Diuretics</th>
<th>IV</th>
<th>Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>Furosemide</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>Torsemide</td>
<td></td>
<td>IV catheter</td>
</tr>
<tr>
<td>KNYA Class</td>
<td></td>
<td>Bumetanide</td>
<td></td>
<td>IV catheter</td>
</tr>
<tr>
<td>EF</td>
<td></td>
<td>Ethacrynic acid</td>
<td></td>
<td>IV catheter</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td></td>
<td>Chlorthiazide</td>
<td></td>
<td>IV catheter</td>
</tr>
</tbody>
</table>

**Intensifying Outpatient Diuresis**

- Double daily loop diuretic dose
- Triple daily loop diuretic dose
- Twice daily loop diuretic dosing
- Transition to an alternative loop diuretic (torsemide or bumetanide)
- Add a thiazide
- Outpatient IV diuresis

**Outpatient diuretic infusion?**

- Fluid management for patients unable to pull fluid off with oral titration at home
- Goal to manage patients outpatient
- IV infusion or push depends on home dose
  - Usually 2 x oral home dose for IV dose
- Goal urine output of >500 ml in 2 hrs
  - Re-bolus if urine output <500 after 2 hrs
  - If creatinine >1.5 goal is 250 cc in 2 hrs
- Labs to be drawn prior and 3 hrs after infusion
  - BMP
  - Replace potassium as needed
Drug interactions

- Average HF patient takes 6.8 prescription medications according to AHA.
- does not include OTC's
- NSAID's with ACE/ARB
- Renal compromise
- Carvedilol with food (Orthostasis)
- Calcium Channel blockers (exception amlodipine is HF Neutral)
- Dilidatam and verapamil contraindicated

Medication that cause heart failure or exacerbate HF

- Anticancer medications
  - Trastuzumab, bevacizumab
  - Doxorubicin, Daunorubicin, 5-fluorouracil, paclitaxel, cyclophosphamide,
  - NEW TYPES of patients classified as cardio-oncology.
- Interferon can cause myocardial ischemia
- Rheumatology medications
  - Hydroxychloroquine, Enbrel
  - Thiazolidinediones (Pioglitazone, Rosiglitazone)
  - DDP-4 inhibitors (alogliptin, saxagliptin)
  - Clostazol
  - Intraconazole
  - Pregabalin and gabapentin
  - NSAID's!!

Devices

- **CardioMems**
  - Indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure
  - Captures the following data: PA pressure waveform; systolic, diastolic, and mean PA pressures and HF
  - reduce HF hospital admissions and improve QoL.
  - After insertion of device,
    - Aspirin 81-325 mg daily for life
    - Clopidogrel 75 mg daily for 1 month

Cardio Mems Reports
EP Referrals

- 3 month titration
- Goal of EF >35%
- If fail on GDMT, then refer for EP evaluation and discussion of ICD, Bi-V ICD
- LBBB

HFpEF

- Spironolactone
  - Only med with any evidence at improved mortality and reduced hospitalizations in HFpEF
  - TOPCAT trial
- HFpEF management
  - Control Blood pressure <130/80
  - Diuretics!!!
  - CardioMems
  - Manage Atrial Fibrillation
  - Coronary revascularization as needed per cardiology.

RN Teaching Focus

- S/S to Report
  - SOB, Cough, Swelling, Orthopnea, CP, Dizziness
- Weight Monitoring
  - Same time, clothing
- Diet 2000mg Sodium
- Fluid Restriction 64 oz
- ETOH Restriction
  - 1-2 drinks/week
- Quit Tobacco
- Activity
  - Daily program
  - 150 minutes/week goal
- Cardiac Rehab

Green Zone

- You feel well
- No shortness of breath
- No swelling of legs or stomach
- No weight gain
- No chest pain
- Your plan:
  - Stable: This zone is your goal
  - Continue to follow your treatment plan

Yellow Zone

- You feel poorly
- Weight gain of 3 lbs overnight or 5 lbs over your baseline weight
- Noticeable swelling in feet, legs, or stomach
- More short of breath than usual
- Weight drop of 2 lbs, associated with light-headedness or dizziness
- Your plan:
  - Caution: This zone is a warning
  - Review your sodium intake
  - Review your fluid intake
  - Call our office if your symptoms do not improve in 1 or 2 days

Red Zone

- Significant shortness of breath unrelieved with rest
- Severe or concerning chest heaviness or pain
- Your plan:
  - Seek emergency evaluation at the nearest ER or call 911
Decompensated HF/Refractory HF

Treatment for Subset IV
- Cold and wet (CI < 2.2, PCWP > 18)

Use IV Loop diuretic first. Then MAP < 50

Yes

IV diuresis (keep PCWP between 15-18 mm Hg). Once this goal is achieved, reassess for use of inotropes or vasodilators.

No

In any of the following present:
1) SBP < 90
2) Symptomatic Hypotension
3) Worsening RF / end organ failure (Hypoperfusion)

Use inotropes
Milrinone or Dobutamine

Use Vasodilators
3 “Ns” - Nitro, NTG, NPH or Mensa

Success Story!!

- 71 yo Male
- Severe Ischemic Cardiomyopathy
  - HTN
  - CVA 2004
  - Ex Smoker
  - Type II diabetes
  - OSA
  - CKD stage II-III
  - Supportive Wife

- 10/16 admit cough/SOB
- 11/16 diagnosed EF 15-20%
- 1/17 Syncope/ Fall> subdural hematoma
  - Cathe> JVD
- 3/17 PCI
- 7/17 ICD
- 8/17 Near Syncope low BP
- 8/17 HF clinic monitoring
  - ARB/BB/diuretic fluctuates
- 8/17- current: No Hospitalizations!!
Patient Cases

- MS a 65 yo male presents to HF clinic for up titration of HF medications Post AMI with EF 25-30%. He currently is wearing a life vest. On exam he has no edema or noticeable shortness of breath. Weight has been stable at 211 lbs. Current medications are
  - Lisinopril 2.5 mg daily, carvediolol 3.125 mg bid, ASA 81 mg daily, spironolactone 12.5 mg daily, Clopidogrel 75 mg daily, NTG SL as needed, Ibuprofen 600 mg tid
- Vitals/labs:
  - Blood pressure outpatient have been 130’s/80’s, pulse 85.
  - Scr: 1.1 BUN: 18, K: 4.8, Na: 135, Cl: 95, Cr: BUN ratio Normal
  - Weight today is 213 lbs

How should we treat this patient in the outpatient clinic?

A. Discontinue ibuprofen and titrate Lisinopril up to 10 mg daily  
B. Discontinue Ibuprofen and titrate carvedilol to 6.25 mg bid  
C. Discontinue ibuprofen and titrate spironolactone to 25 mg daily  
D. Discontinue ibuprofen and add isosorbide dinitrate 10 mg tid and hydralazine 10 mg tid

Patient Case

- BB 68 yo female HFrEF patient presents to the clinic after 2 months of GDMT titration. She complains of increasing shortness of breath and decreased exercise capacity. Medications include:
  - Lisinopril 40 mg daily, metoprolol XL 100 mg bid, spironolactone 25 mg daily, Digoxin 0.125 mg daily, furosemide 40 mg bid, KCL 10 mEq daily
  - Vitals/labs: BP 128/76 HR 63; Scr 1.1mg/dl K 4.5 mEq/L. ECG: NSR, QRS 105 QTC 448. LVEF=25-30% Euvolemic with dry weight of 145 lbs
What is next step for treatment of BB HFrEF

A. Stop metoprolol and switch to carvedilol 25 mg bid
B. Increase spironolactone to 50 mg daily
C. Stop Digoxin
D. Switch lisinopril to sacubitril/valsartan after appropriate washout period.

Patient Cases

• SE 58 yo male presents to heart failure clinic with a newly diagnosed dilated cardiomyopathy in the hospital, his EF on ECHO was 20%. While in hospital they pulled 20 lbs of fluid off over 3 days, he is 210 lbs at discharge and he was considered euvoletic. Current medications:
  • New meds: Lisinopril 2.5 mg, carvedilol 3.125 mg 12h, spironolactone 12.5 mg daily, furosemide 40 mg bid,
  • Home meds: aspirin 81 mg daily, amlodipine 10 mg daily,
• Vitals today
  • BP Left arm 135/95 right arm 140/100 Pulse 61
  • Orthostatics 105/70 and 104/69
  • Scr:1.4 (up from 1.0 in hospital), BUN: 40, Na: 141, K: 5
• Weight today: 204 lbs
• Symptoms/Complaints
  • Dry mouth
  • Dizziness when standing up
  • Fatigue

Which intervention would provide best option to manage SE's Heart failure?

A. Decrease furosemide dose to 40 mg daily and have patient increase fluids until weight back to normal.
B. Increase carvedilol to 6.25 mg bid
C. Increase Lisinopril to 5 mg daily
D. Discontinue amlodipine due to risk of edema.
**Which intervention would provide best option to manage SE’s Heart failure?**

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**Questions?**

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**References**