Another Broken Heart - Understanding and Treating Heart Failure
Shannon Finks, PharmD, FCCP, BCP

Live Activity Handout
2 slides per page
Another Broken Heart - Understanding and Treating Heart Failure

**ACTIVITY DESCRIPTION**

More than 10 million patients visit their physician every year for heart failure. More patients require hospitalization for heart failure than all types of cancer combined. Heart failure usually gets worse with time and approximately 50% of patients with heart failure die within 5 years. Pharmacist involvement in the management of chronic heart failure can improve quality of life and minimize hospitalization. This knowledge-based activity will review the recommendations and updated pharmacotherapy for heart failure to include appropriate candidates, relevant drug interactions and monitoring parameters. Further, the activity will offer pharmacists strategies for educating patients on treatment and encouraging compliance with drug and diet therapy as part of the health care team to reduce further hospitalizations and improve patient outcomes.

**TARGET AUDIENCE**

The target audience for this activity is pharmacists and nurses in hospital, community, and retail pharmacy settings.

**LEARNING OBJECTIVES**

After completing this activity, the pharmacist will be able to:

- Outline the key changes/recommendations identified in the 2017 ACCF/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guidelines for the Management of Heart Failure.
- Describe the current and emerging pharmacotherapies for patients with heart failure with reduced ejection fraction (HFrEF) to include their role in therapy, adverse events, safety concerns, and key counseling points associated with each.
- Identify the pharmacist’s role in educating patients on the importance of HF prevention, hypertension management, and the treatment of comorbid conditions related to managing heart failure.

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Dr. Shannon Finks, PharmD, FCCP, BCPS is a Professor of Clinical Pharmacy at the University of Tennessee College of Pharmacy. She received her Doctor of Pharmacy degree from The University of Tennessee College of Pharmacy and completed a pharmacy practice residency at Methodist Hospitals of Memphis. Dr. Finks has practiced for fifteen years in the area of cardiology. She is a Fellow of the American College of Clinical Pharmacy and a Board Certified Pharmacotherapy Specialist with Added Qualifications in Cardiology. Dr. Finks has served as a national faculty member for the American College of Clinical Pharmacy Updates in Therapeutics: The Pharmacotherapy Preparatory and Recertification Course since 2012. Her current practice includes Cardiology Service at the VA Hospital where she co-precepts students and residents in the cardiology intensive care unit. Throughout her career she has mentored numerous students and residents and takes great pride in fostering continued education among pharmacists. Dr. Finks has received multiple teaching awards, including the Most Influential Professor Award from the University of Tennessee College of Pharmacy and The University of Tennessee Alumni Association Outstanding Teacher Award. Dr. Finks is well published in the medical literature and has been invited to present locally, regionally, and nationally on numerous cardiovascular related topics.

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• None
Objectives

• Outline the key changes/recommendations identified in the 2017 ACCF/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guidelines for the Management of Heart Failure.

• Describe the current and emerging pharmacotherapies for patients with heart failure with reduced ejection fraction (HFrEF) to include their role in therapy, adverse events, safety concerns, and key counseling points associated with each.

• Identify the pharmacist’s role in educating patients on the importance of HF prevention, hypertension management, and the treatment of comorbid conditions related to managing heart failure.

Abbreviations

• Refer to the appendix
Objective 1

- Outline the key changes/recommendations identified in the 2017 ACCF/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guidelines for the Management of Heart Failure

2017 HF Guideline Update

- Part 2 to the 2016 publication
- Introduced guidance on:
  - New therapies (ARNI and Ivabradine) indicated for HFrEF
  - Updates on HFpEF
  - New insights into the prevention of HF
  - New data on important comorbidities
2017 HF Guideline Update

Updates on HFpEF
- No mortality reducing therapies
- TOPCAT results led to recommendation for use of spironolactone in HFpEF is reasonable to reduce HF hospitalizations

Updates on Prevention
- BP goal <130/80 mm Hg

HFrEF Guideline: New Therapies

Sacubitril/Valsrantan (Entresto)
- Angiotensin Receptor Blocker/Neprolysin Inhibitor (ARNI)
- Reduces mortality better than ACEI therapy
- Recommended in preference to ACEI/ARB in appropriate patients

Ivabradine (Corlanor)
- Sinoatrial node modulator
- Reduces hospitalizations related to HF
- Can be added in patients with NSR and HF >70 bpm

Yancy et al. J Am Coll Cardiol. 2017

Objective 2

• Describe the current and emerging pharmacotherapies for patients with heart failure with reduced ejection fraction (HFrEF) to include their role in therapy, adverse events, safety concerns, and key counseling points associated with each.

Baseline Therapy for HFrEF

Yancy et al. J Am Coll Cardiol. 2017
Initial HFrEF Treatment

ACEI/ARB

Initial dose selected on newness to therapy; most start low dose

Consider increasing dose of ACEI/ARB every 2 weeks until maximum tolerated or target dose is achieved
Monitor blood pressure, renal function, and potassium after initiation and during titration

Beta blockers

Consider increasing dose of beta blocker every 2 weeks until maximum tolerated or target dose is achieved
Monitor heart rate, blood pressure, and for signs of congestion after initiation and during titration

Diuretics

Titrate dose to relief of congestion over days to weeks. In some instances, it may be necessary to reduce diuretic dosing in the setting of increasing doses of ACEI/ARB/ARNI
Monitor blood pressure, electrolytes, and renal function after initiation and during titration

ACEI-Benefits in HFrEF

• Block production of angiotensin II
  • Decrease sympathetic stimulation
  • Decrease production of aldosterone and vasopressin
  • Decrease vasoconstriction

• Increases bradykinins
  • Increases vasodilatory prostaglandins
  • May affect myocardial remodeling

• Clinical utility
  • Reduces mortality 25-30% RRR
  • Reduces hospitalizations ~30% RRR
  • Improves symptoms, exercise capacity, and quality of life

Yancy et al. J Am Coll Cardiol. 2017
ACEI/ARB: In whom and when?

- ACE inhibitors are recommended in all patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality.

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

- Routine combined use of ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF.


ACEI Dosing and Monitoring

**Initiation**
- Initiate at low dose and titrate slowly
- Titrate to target for maximal benefit

**Monitoring**
- Monitor SCr, K, and BP
  - within 1-2 weeks of initiation
- Common adverse events*
  - Cough in ~5-35%;
  - SCr > 30% in ~>26%
  - Hyperkalemia in 1-20%

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
<th>Target Dose</th>
<th>Max Dose</th>
<th>Mean Dose Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>2.5mg BID</td>
<td>10mg BID</td>
<td>10-20mg BID</td>
<td>16.6mg/day</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5mg QD</td>
<td>20mg QD</td>
<td>20-40mg QD</td>
<td>32.5-35.0mg/day</td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25mg 3x/D</td>
<td>50mg 3x/D</td>
<td>50mg 3x/D</td>
<td>122.7 mg/day</td>
</tr>
</tbody>
</table>

*angioedema occurs in up to ~0.7% of patients*
Concerning ACEI Adverse Events

**SCr Elevations**
- Normal physiology
- Rise is proportional to baseline SCr
- Usually occurs within the 1st 4 weeks; stabilizes w/i 2 months
- Reversible upon discontinuation
- Significant = 0.5 mg/dL change or > 30% from baseline

**Hyperkalemia**
- Usually mild (1-20%)
- Severe elevations rare (<3%)
- Risk factors
  - Baseline K, SCr, multiple RAS agents

**Angioedema**
- Can occur at any time
- 2-4 times more likely in AA
- Switching
  - To ACEI- Not recommended
  - To ARB- cross reactivity ~10%


ARB Dosing and Monitoring

- ARB effect same as ACEI on SCr and BP
  - Less cough and angioedema
  - Conflicting results on hyperkalemia

- Recommended in those who are ACEI intolerant
  - Reasonable to use 1st line in HFrEF instead of ACEI in patients, especially if already taking for other indication

- Specific ARBs that have shown benefit in clinical trials include:

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Target Dose</th>
<th>Max Dose</th>
<th>Mean Dose Achieved in Clinical Trials</th>
</tr>
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<tbody>
<tr>
<td>Candesartan</td>
<td>4-8mg QD</td>
<td>32mg QD</td>
<td>32mg QD</td>
<td>24mg/day</td>
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<tr>
<td>Losartan</td>
<td>25-50mg QD</td>
<td>150mg QD</td>
<td>50-150mg QD</td>
<td>129mg/day</td>
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<tr>
<td>Valsartan</td>
<td>20-40mg BID</td>
<td>160mg BID</td>
<td>160mg BID</td>
<td>254mg/day</td>
</tr>
</tbody>
</table>

-- Yancy et al. J Am Coll Cardiol. 2017
ACEI/ARB Counseling Points

**Specific benefit from ACEI/ARB**
- Reduce mortality, hospitalization, and improve quality of life
- Work by blocking stressful hormones, which allows blood to flow more easily
- Delays the progression to worsening heart failure
- Symptoms improve=weeks

**Specific risk from ACEI/ARB**
- May increase K concentrations
  - K and SCr will be monitored
  - Limit salt substitutes
- Appreciate angioedema risk
  - Report swelling/tingling ASAP
- Contraindications
  - Pregnancy
  - Bilateral RAS
- Avoid Drug Interactions
  - NSAIDs
  - K sparing diuretics, suppl, or Na substitutes


β-blocker- Benefits in HFrEF

- Blocks the effect of NE and other sympathetic neurotransmitters
  - Decreases risk for sudden cardiac death and arrhythmias
  - Decreases cardiac hypertrophy and cell death
  - Decreases vasoconstriction and HR
- Clinical Utility:
  - Decreased mortality (~35% RRR compared with placebo)
  - Decreased hospitalizations (~25% RRR compared with placebo)
  - Symptom improvement (3-6 months)
  - Improved clinical status
  - Improved EF
**β-blockers: In whom and when?**

- Use of 1 of the 3 beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
<th>Target Dose</th>
<th>Max Dose</th>
<th>Mean Dose Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25mg QD</td>
<td>10mg QD</td>
<td>10mg QD</td>
<td>8.6mg/day</td>
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<tr>
<td>Carvedilol</td>
<td>3.125mg BID</td>
<td>25mg BID</td>
<td>50mg BID</td>
<td>37mg/day</td>
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<tr>
<td>Metoprolol succinate XL/ER</td>
<td>12.5-25mg QD</td>
<td>200mg QD</td>
<td>200mg QD</td>
<td>159mg/day</td>
</tr>
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</table>

**β-blocker Dosing and Monitoring**

**Initiation**
- Added when HF symptoms are **stable (euvoletic)**
  - Symptom improvement is **slow** (months)
- Initiate at **low dose** and increase (double) dose every 2 weeks (or slower) to target dose
  - Aim to reach target dose in 8-12 weeks
- **Avoid abrupt discontinuation**
  - Can precipitate clinical deterioration

**Monitoring**
- BP, HR, and symptoms of hypotension
  - Monitor 1-2 weeks
- **Weakness, fatigue**
  - Usually resolves w/i weeks
- Significant ADEs occur
  - If not titrated slowly
  - If patient not euvoletic
  - Can reduce dose of ACEI/diuretic if needed to achieve target dose
Concerning β-blocker ADEs

**Fluid retention and worsening HF**
- Not generally a reason to permanently withdraw treatment
- May need to decrease dose or intensify conventional tx

**Bradycardia or heart block**
- Usually asymptomatic
- Severe bradycardia will require dose reduction

**Hypotension**
- Can separate βB from ACEI
- Hypotension may resolve after dose ↓ of diuretic in volume depleted patients
- If hypoperfusion, decrease or discontinue βB until evaluation

**Fatigue**
- Multifactorial
- Consider sleep apnea, overdiuresis, depression

β-blocker Counseling Points

**Specific benefit from β-blocker**
- Reduce mortality, hospitalization, and improve quality of life
- Reverse the remodeling process and can ↑ strength and function of heart
- Decrease heart workload and can regulate rhythm
- Delay the progression to worsening heart failure
- Temporary side-effects

**Specific risk from β-blocker**
- May increase risk for decompensation
  - Monitor for worsening HF, edema
  - Daily weights
- Fatigue
  - Dose related; 4-6 weeks resolve
- Orthostasis/Bradycardia
- Can worsen wheezing
  - Monitor use of asthma rescue tx
- Blood glucose control


Diuretics: In Whom and When?

- Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms.
- Short term benefit (days) includes decreased symptoms for volume overload.
- Intermediate term benefit (weeks to months) includes improvement in HRQOL.

Diuretics:

- **Class I, LOE A**
  - ACEI or ARB AND Beta Blocker
  - For patients with persistent volume overload, NYHA class II-IV
  - Titrate

**Class I, LOE A**
- Loop Diuretics

Diuretic Dosing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Oral Bioavailability (%)</th>
<th>Initial Daily Dose (mg)</th>
<th>Maximum Dose</th>
<th>Duration of action (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop Diuretics: 25-30% increase in sodium excretion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>10-67</td>
<td>20-40 mg/day or BID</td>
<td>600</td>
<td>6-8</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>80-100</td>
<td>0.5-1 mg/day or BID</td>
<td>10</td>
<td>4-6</td>
</tr>
<tr>
<td>Torsemide</td>
<td>80-100</td>
<td>10-20 mg/day</td>
<td>200</td>
<td>12-16</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>100</td>
<td>25-50 mg/day or BID</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td><strong>Thiazide Diuretics: 5-8% increase in sodium excretion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>65-75</td>
<td>25 mg/day or BID</td>
<td>100</td>
<td>6-12</td>
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<tr>
<td>Metolazone</td>
<td>40-65</td>
<td>2.5 mg/day</td>
<td>20</td>
<td>12-24</td>
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<tr>
<td>Chlorthalidone</td>
<td>64</td>
<td>12.5-25 mg/day</td>
<td>100</td>
<td>24-72</td>
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<tr>
<td>Chlorothiazide (IV)</td>
<td>30-50</td>
<td>250-500 mg/day</td>
<td>2000</td>
<td>6-12</td>
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</table>
Diuretic Strategies and Monitoring

Inpatient
- IV - 2-2.5 times oral maintenance dose
- Titrate to a weight loss of 1-2 pound weight loss/day
- Ceiling effect ~160 mg
- Combination therapy may be needed

Outpatient
- Start with low dose, may double and titrate upwards
- Chronic therapy adjusted to maintain euvolemia
  - Daily weights necessary
  - Sliding scale if necessary
- Should be combined with ACEI, β-blockers

Monitoring
- K+ and Mg (desire K of 4.0 mEq/L and Mg of 2.0 mEq/L
- Replacement commonly needed

Diuretic Counseling Points

Specific benefit from Diuretic
- Reduce accumulation of fluid
- Improve overall comfort
- Short- and intermediate-term benefit in symptom control
- Do not alter underlying disease process
- Keeps you out of the hospital and symptom free

Specific risk from Diuretic
- May increase risk for dehydration
  - Daily weights
  - Monitor for K, Mg, SCr
  - Report dizziness
- Increased urination
  - Dosing should be strategically timed (avoid bedtime doses)

Add On Mortality Reducing Therapies

Choices are not mutually exclusive and one therapy is not preferred in all scenarios.

- **MRA**
  - For NYHA Class II-IV, provided est CrCl >30 ml/min and K<5.0 mEq/L

- **Hydral/Nitrate**
  - For NYHA Class III-IV, in black patients.

- **ARNI**
  - For NYHA Class II-III HF with adequate BP on ACEI or ARB, NO C/I to ARB or sacubitril

Add on therapies in green are Class I GDMT.

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Aldosterone Antagonist- Benefits in HFrEF

- Slows progression of cardiac remodeling
  - Blocks the direct fibrotic actions on the myocardium
  - Decreases loss of K and Mg
  - Decreases Na retention
  - Eliminates catecholamine potentiation

- Clinical Utility:

<table>
<thead>
<tr>
<th>Spironolactone (NYHA III and IV)</th>
<th>Eplerenone (NYHA II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased mortality ~30% RRR</td>
<td>Decreased mortality ~25% RRR</td>
</tr>
<tr>
<td>Decreased HF hospitalizations ~35% RRR</td>
<td>Decreased HF hospitalizations ~42% RRR</td>
</tr>
<tr>
<td>Symptom improvement</td>
<td>Data in Post MI patients with LVEF &lt; 40 with h/o DM with S/S HF</td>
</tr>
</tbody>
</table>
Aldosterone Antagonists: In whom and when?

- Recommended in NYHA Class II-VI patients with an LVEF ≤ 35%
  - Patients with NYHA Class II should have a history of CV hospitalization or elevated BNP
- Recommended in all patients after an acute MI, with signs and symptoms of HF, or a history of DM, with a LVEF < 40%
- Inappropriate use of aldosterone receptor antagonists is potentially harmful when
  - SCr > 2.5 mg/dL in men or > 2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/1.73m²), and/or
  - K⁺ >5.0 mEq/L.

Minimize Risk for Hyperkalemia

- Risk of hyperkalemia ↑ progressively when SCr > 1.6 mg/dL
- Do not initiate in patients with K⁺ > 5.0 mEq/L
- Start at typical doses—then, uptitrare to target
  - Typical is 12.5-25 mg spironolactone or 25 mg eplerenone
  - QOD dosing upon initiation when eGFR 30-50 ml/min/1.73 m²
    - Daily dosing after 1 month if K⁺ ≤ 5 and CrCl > 30 ml/min
- Risk for hyperkalemia increases with higher doses of ACEI/ARB
  - Enalapril or lisinopril > 10mg daily
- In most cases, discontinue K⁺ supplementation when starting AA
- Close monitoring is required
  - Day 3, 1 week, and at least monthly x first 3 months
  - Decrease dose by 50% or discontinue if K⁺ > 5.5 mEq/L
Aldosterone Antagonist Counseling

**Specific benefit from AA**
- Reduce mortality, ↓hospitalizations, and QOL improvement in patients with symptoms of HFrEF
- Same benefit with HFrEF immediately following MI
- Work by blocking “a harmful stress hormone”

**Specific risk from AA**
- Increased risk for hyperkalemia
  - Monitor for K, Mg, SCr
  - Limit additional K in diet
  - Avoid NSAIDs
  - Daily weights
- Avoid dehydration
  - Caution with excessive sweating or diarrhea
- Gynecomastia
  - Report breast tenderness


Hydral/Nitrate: In whom and when?

- Useful for morbidity and mortality reductions in African Americans with HFrEF who remain symptomatic despite concomitant use of ACE inhibitors, beta blockers, and aldosterone antagonists
- Useful for morbidity and mortality reductions in those with current or prior symptoms of HFrEF who can not be given ACEI/ARB due to intolerance, hypotension, or renal insufficiency

Class I, LOE A
ACEI or ARB AND Beta Blocker

For persistently symptomatic African Americans, NYHA class III-IV

Add

Class I, LOE A
Hydralazine + Isosorbide dinitrate
Hydral/Nitrate- Considerations

Dosing and Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
<th>Target Dose</th>
<th>Max Dose</th>
<th>Mean Dose Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-dose combination</td>
<td>37.5mg hydralazine/20mg isosorbide dinitrate TID</td>
<td>75mg hydralazine/40mg isosorbide dinitrate TID</td>
<td>75mg hydralazine/40mg isosorbide dinitrate TID</td>
<td>~175mg hydralazine/90mg isosorbide dinitrate daily</td>
</tr>
<tr>
<td>Hydralazine &amp; isosorbide dinitrate</td>
<td>hydralazine: 25-50mg TID-QID &amp; isosorbide dinitrate: 20-30mg TID-QID</td>
<td>Hydralazine: 75mg QID &amp; isosorbide dinitrate: 40mg QID</td>
<td>hydralazine: 300mg daily, divided doses &amp; isosorbide dinitrate: 120mg daily, divided doses</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Monitoring and Counseling

- **Common SE:**
  - headache, dizziness/hypotension, and nausea
- **Rare SEs:**
  - Arthralgias and ↑ANA
  - Adherence concerns

Hydralazine/Nitrate Counseling

**Specific Benefit from H/N**
- Reduce mortality, ↓hospitalizations, and QOL improvement in African American patients with symptoms of HFrEF
- Marginal benefit in those who cannot take ACEI/ARB

**Specific Risks from H/N**
- Stress adherence for 3 x daily dosing
  - Reflect tachycardia and rebound hypertension
- Avoid PDE-5 inhibitors
  - Severe hypotension
- Nitrate free interval not needed
- Report any rash and arthralgias
**ARNI: In Whom and When?**

- **Class I, LOE A**
  - ACEI or ARB AND Beta Blocker

  For patients stable on ACEI/ARB with chronic symptoms, NYHA class II-III

  - Switch

- **Class I, LOE B**
  - ARNI

- Inhibition of the RAS with ACE inhibitors, or ARBs, or ARNI in conjunction with evidence based beta blockers and aldosterone antagonists in selected patients is recommended for patients with chronic HFrEF *to reduce morbidity and mortality*

  - In patients with chronic symptomatic HFrEF NYHA Class II or III who tolerate ACEI/ARB, replacement by ARNI is recommended for further morbidity and mortality.

  - ARNI *should not be* administered concomitantly with ACE inhibitors or within 36 hours of last dose of ACE inhibitor

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**Sacubitril/Valsartan, Entresto® In Whom and When?**

- **Indication (FDA approval 7/7/2015)**
  - To reduce risk *of CV death and HF hospitalization* in patients with chronic HF (NYHA Class II-IV) and reduced EF
  - Identified as LCZ696 in studies prior to FDA approval

  - Combines an ARB (valsartan) with the novel compound sacubitril, which is a neprilysin (or NEP) inhibitor

  - Combination sometimes referred to as an ARNI (angiotensin receptor and neprilysin inhibitor)

  - Administered in conjunction with other HF therapies, in place of ACE inhibitor or ARB

**Natriuretic Peptide System**
- pro-BNP
- BNP
- NT-pro BNP
- Neprilsin
- Inactive fragments
  - Vasodilation
  - ↓ blood pressure
  - ↓ sympathetic tone/aldosterone
  - ↓ fibrosis/hypertrophy
  - Natriuresis/diuresis

**Renin Angiotensin System**
- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II
- AT$_1$ receptor
- Vasoconstriction
- ↑ blood pressure
- ↑ sympathetic tone/aldosterone
- ↑ fibrosis/hypertrophy

**Heart Failure**
- LCZ696
- Sacubitril
- Valsartan

**PARADIGM HF Trial (2015)**
- Included: Patients with HFrEF (EF ≤40%) NYHA II-IV (70%-Class II)
- N=8442 patients
- Randomized to either Entresto or enalapril
- Patients treated for up to 4.3 yrs; median f/u 27 mo
- Results:
  - Primary endpoint was composite CV death or HF hospitalization ↓ 20%
  - Also in ↓ 20% HF hospitalizations and ↓ 16% all cause mortality
Double dose every 2-4 weeks, as tolerated to target dose 97/103mg= 100 mg BID

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*Washout period of 36 hours required if switching from ACEI, none needed for ARB

Entresto® Considerations

Safety and Monitoring
- Greater symptomatic hypotension than ACEI
- Less hyperkalemia, SCr ≥ 2.5 mg/dL, and cough than ACEI
  - Correct volume or Na prior to initiation
  - Monitor renal function/K+
- Less discontinuation rates than ACEI

Contraindications
- Concomitant ACE inhibitor
  - Angioedema risk
  - Washout period needed, 36 hours
- History of angioedema to prior ACE inhibitor or ARB
- Concomitant aliskiren in patients with diabetes
- Pregnancy
  - Can cause fetal toxicity

Entresto® Considerations

Drug Interactions
- ACEI/ARB
- Aliskiren
  - Contraindicated if diabetes
  - Avoid use if eGFR <60mL/min/1.73 m²
- Potassium-sparing diuretics
- NSAIDs/COX-2 inhibitors
- Lithium – increased concentrations

Cost
- 30 day supply for
  - 24/26mg=50 mg BID ~$476
  - 49/51mg=100 mg BID ~$476
  - 97/103mg=200 mg BID ~$476
- ACEI/ARB $4 generic

Entresto® Counseling Points

Specific Benefit from Entresto
- Works by blocking a stressful hormone that causes heart damage
- Reduces mortality and hospitalizations more than standard ACEI/ARB
- Full benefit may not be fully realized

Specific Risk from Entresto
- Do not take ACEI/ARB with Entresto
- May cause hypotension and renal insufficiency
- Report swelling or airway compromise immediately
- Not for use in pregnancy
Other Add On Therapies

Digoxin

- Usually reserved for patients with atrial fibrillation requiring additional rate control
- Controversial use as risks may outweigh benefit in most
- For morbidity improvement

Ivabradine (Corlanor)

- For NYHA Class II-IV, on maximally tolerated and/or target doses of beta blockers
- For reduction in HF related hospitalizations

Digoxin- Benefit in HFrEF

Morbidity Benefit
- Improved symptoms
- Improved exercise tolerance
- Decreases hospitalizations

Mechanism
- Decreasing sympathetic outflow (central)
- Some increase in cardiac contractility

In whom and when?
- Only after appropriate neurohormonal antagonists initiated
  - In patients with symptomatic HF and AF for rate control
  - In patients with sinus rhythm with symptomatic HFrEF

Digoxin Considerations

Dosing and Monitoring
- 0.125 mg daily
  - No load in HF
- Risk of toxicity increases
  - age, renal dysfunction, hypokalemia, and hypomagnesemia
- Monitor SCr and Mag
- Goal < 1 ng/ml
- Drug interactions
  - Clarithromycin, dronedarone, amiodarone, itraconazole, propafenone

Counseling
- S/S toxicity
  - Anorexia, nausea, vomiting, visual changes, bradycardia, hyperkalemia, arrhythmias

Digoxin Counseling Points

Specific Benefit from digoxin
- Reduce hospitalizations and ↓ symptoms in patients with symptoms of HFrEF despite target doses of other neurohormonal agents
- Marginal benefit in those who can not take ACEI/ARB

Specific Risks from digoxin
- Narrow therapeutic window
- ↑mortality if >1.0 ng/mL
- Withdrawal of therapy may cause symptom worsening
- Needs monitoring if status changes
- Report signs of toxicity
Ivabradine: In Whom and When?

- Of benefit in:
  - Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA Class II-III) stable chronic HFrEF (LVEF ≤ 35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.
- Contraindications:
  - ADHF, BP <90/50 mm Hg, sick sinus syndrome, SA node block, 3rd degree AVB without PPM, resting HR < 60, pacemaker dependence, severe hepatic impairment, strong 3A4 inhibitors

Ivabradine- Corlanor®

- Adjunct to standard of care for HF patients
- Approved in the US (April 2015) for the reduction of hospitalization in patients with chronic heart failure and:
  - Stable, symptomatic heart failure
  - LVEF of ≤ 35%
  - Stable sinus rhythm with HR ≥ 70 bpm
  - On maximum tolerated doses of BB or CI to BB
- Novel agent that reduces HR by inhibiting the cardiac pacemaker, AV node, I_{f} current
Why be concerned about ↑HR?

- Accelerated atherosclerosis
  - *Int J Cardiol* 2008;126:302-12
- Coronary plaque disruption
  - *Circulation* 2001;126:1477-82
- Increases in all-cause and CV mortality in those with antecedent HR in Framingham study
  - *Am Heart J* 1987; 113:1489-94
- Increased mortality in ACS starting at HR >70 bpm

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Dosing and Monitoring Corlanor®

**Dosing**

- Initiate at 5 mg BID
  - with meals
  - Or, 2.5 mg BID in those ≥ 75
- After 2 weeks if HR is
  - between 50-60, keep dose
  - >60, increase to 7.5 mg BID
  - <50, decrease to 2.5 mg BID
- For 30 days treatment, 5 mg BID, costs ~$375.00

**Monitoring**

- Avoid CIs and DIs
- Caution if pregnancy age
  - Fetal toxicity
- Monitor HR and rhythm
  - May increase risk for AF
  - Sinus arrest and heart block
- Other ADE:
  - Bradycardia, hypotension or increased BP, AF, luminous phenomena or visual brightness
Drug Interactions- Corlandor®

**Strong CYP3A4 inhibitors**
- Contraindicated
  - Azole antifungals, macrolide antibiotics, HIV protease inhibitors, nefazadone

**Moderate CYP3A4 inhibitors**
- Avoid
  - Diltiazem, verapamil, grapefruit juice

**CYP3A4 inducers**
- Avoid
  - St. John’s wort, rifampicin, barbiturates, phenytoin

**Negative Chronotropes**
- Monitor HR
  - Digoxin, amiodarone

Corlandor® Counseling Points

**Specific Benefit from Corlandor**
- Reduces hospitalizations in those that have HR>70 bpm who are already receiving BB therapy
- No mortality reduction
- May improve EF/QOL (symptoms)
- Works by slowing heart rate

**Specific Risk from Corlandor**
- Can cause bradycardia, hypertension, atrial fibrillation and transient increases in brightness
- Can cause fetal toxicity
- Many drug interactions
Heart Failure Undertreated

ACC IN THE NEWS

Gaps Remain In Use And Dosing Of Evidence-Based, Guideline-Recommended Medications For HFrEF, Analysis Indicates.

Medscape (7/17, Brooks, Subscription Publication) reports that an “analysis of data from the Change the Management of Patients with Heart Failure (CHAMP-HF) registry” indicates “major gaps remain in use and dosing of evidence-based, guideline-recommended medications for heart failure with reduced ejection fraction (HFrEF).” The findings were published online in the Journal of the American College of Cardiology. To view the full JACC article, click here.

Use of Guideline Directed Therapies in
Objective 3

• Identify the pharmacist’s role in educating patients on the importance of HF prevention, hypertension management, and the treatment of comorbid conditions related to managing heart failure.
Pharmacist’s Role

Pharmacists can improve HF outcomes in HF by:

Global goals
• Identifying patients at risk and risk reduction
  • BP < 130/80 mm Hg
  • Control of Risk Factors
• Improving quality of life
• Minimize hospitalization

Specific Interventions
• Medication reconciliation and education
• Medication adherence and access
• Prevention of adverse drug event and medication errors, especially at times of transitions of care
• Target dose titration

HFrEF Medication Reconciliation

• Beta Blocker (carvedilol, metoprolol succinate, bisoprolol)
• ACEI/ARB/ARNI
• Spironolactone/Eplerenone
• Iosorbide dinitrate/hydralazine
• Lasix


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Patient Education

• All patients should understand the importance of standard therapy for HF
  • Importance leads to adherence
  • As to not confuse ACEI or BB with blood pressure control
  • Give patients specific benefits/risks to empower self care
• All patients should understand that select drugs may need to be titrated and may need to be continued for an indefinite time
• All patients should understand risks of each drug therapy and when to call health care professional

Medications to Avoid in HFrEF

• Thiazolidinediones (glitazones):
  • cause worsening HF
  • Increase the risk of HF hospitalization
• Most CCBs:
  • Have a negative inotropic effect and can cause worsening HF
  • Exceptions: amlodipine and felodipine
• NSAIDs and COX-2 inhibitors:
  • may cause sodium and water retention, worsening renal function and worsening HF
• ARB (or renin inhibitor) + ACE inhibitor AND a mineralocorticoid antagonist is NOT recommended:
  • because of the risk of renal dysfunction and hyperkalaemia.
Communication

**Shared Decision Making**
- Improved engagement
- Ownership of one's health
- Improved satisfaction

**Partnership**
- Improved health outcomes
- Quality improvement

Case Studies
Case #1

A 72 year old white man has been recently diagnosed with heart failure. He has recently been discharged from the hospital where he was treated for shortness of breath and edema. His most recent ejection fraction was 65%. His medications include lisinopril 10 mg daily, carvedilol 25 mg twice daily, and furosemide 40 mg twice daily. What should this patients BP goal be?

a. 130/80
b. 135/85
c. 140/80
d. 140/90

This is NOT a poll question.

Case #1 Answer

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Case #1

Which medication has been shown to reduce hospital admissions for heart failure with preserved ejection fraction and could be safely added in this patient if all laboratory values are within normal limits?

a. Digoxin  
b. Spironolactone  
c. Diltiazem  
d. Valsartan

This is NOT a poll question.

2017 HF Guideline Update

Updates on HFpEF
- No mortality reducing therapies
- TOPCAT results led to recommendation for use of spironolactone in HFpEF is reasonable to reduce HF hospitalizations

Updates on Prevention
- BP goal <130/80 mm Hg

Yancy et al. J Am Coll Cardiol. 2017

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Case #1 Answer

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Case #2

A physician contacts you for help in changing a patient from losartan 100 mg daily to sacubitril/valsartan. The patient is 55 years old, is white, and has a history of angioedema on lisinopril but has tolerated losartan without problem. She is also taking carvedilol 25 mg twice daily, furosemide 40 mg twice daily, spironolactone 12.5 mg daily. Her BP is 125/70 mm Hg; HR 70 bpm; K= 5.0 mEq/L. SCr=1.2 mg/dL. Which is best to recommend?
Case #2

• Which is best to recommend?
  a. Start at 49/51 mg twice daily 36 hours after the last dose of losartan
  b. Start at 97/103 mg twice daily at the next dosing interval
  c. Do not start sacubitril/valsartan because of history of angioedema
  d. Do not start sacubitril/valsartan because of K 5.0 mEq/L

Double dose every 2-4 weeks, as tolerated to target dose 97/103mg = 200 mg BID

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  c. Do not start sacubitril/valsartan because of history of angioedema
  d. Do not start sacubitril/valsartan because of K 5.0 mEq/L

This is NOT a poll question.
Case #3

An 87 year old man with known HFrEF (EF 15-20%) comes to the pharmacy for refills on lisinopril and carvedilol and to pick up a new prescription ivabradine. His other medications include apixaban for atrial fibrillation and levothyroxine for hypothyroidism. His heart rate is 80 and blood pressure is 100/80 mm Hg. Which is the most important reason to call the physician regarding the ivabradine prescription in this patient?

Case #3

• Which is the best reason to call the physician regarding stopping the ivabradine prescription in this patient?
  a. The beta blocker should be tapered first
  b. Ivabradine will increase risk for bleeding
  c. Ivabradine should not be used in atrial fibrillation
  d. The patient’s heart rate does not need ivabradine

This is NOT a poll question.
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This is NOT a poll question
What questions may I answer?...