Heart Failure Pearls in the Ambulatory Care Setting: A Scenario Based Approach

Presented by the ACCP Ambulatory Care PRN and Cardiology PRN

Erika Hellenbart, PharmD, BCPS
Zachary Klick, PharmD, BCPS
Orly Vardeny, PharmD, MS, FCCP, BCACP

Disclosures

- Erika Hellenbart, PharmD, BCPS
  - No financial disclosures related to this activity
- Zachary Klick, PharmD, BCPS
  - No financial disclosures related to this activity
- Orly Vardeny, PharmD, MS, FCCP, BCACP
  - Grant, advisory board: Novartis

Objectives

- To assess choice of therapies for patients with HFrEF with considerations for enhancing medication adherence
- To design titration approaches for optimizing drug therapy in patients with HFrEF
- To discuss the logistics of pharmacists’ roles related to collaborative practice protocols and billing in heart failure clinic
Heart Failure Definition

- **Pathophysiology:** The inability to provide adequate cardiac output to the body at rest or with exertion, or to do so only in the setting of elevated cardiac filling pressures.
  
  -E. Braunwald modified by B. Borlaug and M. Redfield

- **Clinically:** A clinical syndrome characterized by breathlessness, fatigue and edema caused by an abnormality of the heart

The Two Faces of Heart Failure

HFrEF  HfPEF
Treatment of HFrEF

Pathophysiology

Myocardial injury

↓

Left ventricular systolic dysfunction

Perceived reduction in circulating volume and pressure

Neurohumoral activation

• Sympathetic Nervous System
• Renin angiotensin aldosterone system
• Endothelin, arginine vasopressin, etc
• Natriuretic peptides

Systemic vasoconstriction

Renal sodium and water retention

Effect of ACE Inhibition in Patients with HF

CONSENSUS*
NYHA Class IV

Placebo (n = 126)

Enalapril (n = 126)

SOLVD Treatment†
NYHA Class II–III

Placebo (n = 1284)

Enalapril (n = 1285)

Mortality, %

0 20 40 60 80

0 6 12 18 24 30 36 42 48

Months

*Risk reduction 40% (P = 0.002)
†Risk reduction 16% (P = 0.0036)

### Target Doses of ACE Inhibitors & ARBs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Initial Daily Dose</th>
<th>Target Dose Mean</th>
<th>Dose in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Capoten</td>
<td>6.25 mg TID</td>
<td>50 mg TID</td>
<td>122.7 mg/day</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Vasotec</td>
<td>2.5 mg BID</td>
<td>10 mg BID</td>
<td>16.6 mg/day</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Zestril, Prinivil</td>
<td>2.5-5 mg QD</td>
<td>20 mg QD</td>
<td>4.5 mg/day, 33.2 mg/day*</td>
</tr>
<tr>
<td>Candesartan</td>
<td>Atacand</td>
<td>4-6 mg QD</td>
<td>32 mg QD</td>
<td>24 mg/day</td>
</tr>
<tr>
<td>Losartan</td>
<td>Cozar</td>
<td>12.5–25 mg QD</td>
<td>50–150 mg QD</td>
<td>129 mg/day</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan</td>
<td>40 mg BID</td>
<td>160 mg BID</td>
<td>254 mg/day</td>
</tr>
</tbody>
</table>

*No mortality difference between high and low dose groups, but 12% lower risk of death or hospitalization in high dose group vs. low dose group.

### Beta-blockers are the Most Evidence-Based Therapy in Heart Failure

#### MERIT-HF
- Metoprolol Succinate
- Carvedilol
- Bisoprolol

#### CIBIS-2

### Trials Comparing an Aldosterone/MR Antagonist to Placebo (added to an ACE inhibitor) in Systolic HF

#### RALES
- 1663 NYHA class III/IV patients
- 95% ACE-i/10% β-blocker

#### EMPHASIS-HF
- 2737 NYHA class II patients
- 93% ACE-i or ARB/87% β-blocker

ACCF/AHA Guideline for the Management of HF
Beta Blockers & Mineralocorticoid Receptor Antagonists

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Initial Dose</th>
<th>Target Dose</th>
<th>Mean Dose in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>Zebeta</td>
<td>1.25 mg QD</td>
<td>10 mg QD</td>
<td>8.6 mg/day</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Coreg</td>
<td>3.125 mg BID</td>
<td>25 mg BID</td>
<td>37 mg/day</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Coreg CR</td>
<td>10 mg QD</td>
<td>80 mg QD</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Toprol XL</td>
<td>12.5-25 mg QD</td>
<td>200 mg QD</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldactone</td>
<td>12.5-25 mg QD</td>
<td>25 mg QD</td>
<td>26 mg/day</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Inspra</td>
<td>25 mg QD</td>
<td>50 mg QD</td>
<td>42.6 mg/day</td>
</tr>
</tbody>
</table>

Hydralazine and Isosorbide Dinitrate

- **Class I:** The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III-IV HFrEF receiving optimal therapy with ACEIs and β-blockers, unless contraindicated
  
  Level of Evidence = A

- **Class IIa:** A combination of hydralazine and isosorbide dinitrate 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, unless contraindicated

  Level of Evidence = B


Sinus Node Inhibition with Ivabradine

- **MOA:** Blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel in the sinoatrial node, responsible for the I_F current
  - Delays diastolic depolarization

  - Does not affect other ion channels

  - Does not alter myocardial contractility and intra-cardiac conduction
### SHIFT Study Results

<table>
<thead>
<tr>
<th>Number of Events</th>
<th>Outcome</th>
<th>Ivabradine</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death or HF</td>
<td>Hospitalization</td>
<td>793</td>
<td>937</td>
<td>0.82 (0.75, 0.9)</td>
<td>4.2%</td>
</tr>
<tr>
<td>CV Death</td>
<td></td>
<td>449</td>
<td>491</td>
<td>0.91 (0.80, 1.03)</td>
<td>1.1%</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td></td>
<td>514</td>
<td>672</td>
<td>0.74 (0.66, 0.83)</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

The treatment effect reflected only a reduction in the risk of hospitalization for worsening HF; there was no benefit observed for the mortality component of the primary endpoint.

### 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure

- 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 (IIa, B-R)
  - Only 25% of patients studied in SHIFT were on optimal doses of beta-blocker therapy. It is important to initiate and up titrate these agents to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation.

### Sacubitril/valsartan – A First-in-Class Angiotensin Receptor Neprilysin Inhibitor (ARNI) – Simultaneously Inhibits NEP and the RAS

LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio.
**PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)**

Enalapril (n=4212) vs Sac/Val (n=4187)

HR = 0.80 (0.73-0.87)  
*P* = 0.0000004

Number needed to treat = 21

*Kaplan-Meier Estimate of Cumulative Rates (%)*

**2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure**

- The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A), OR ARBs (Level of Evidence: A), OR ARNI (Level of Evidence: B-R) 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

- The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality (IA)

- The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema (IA)

- In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (IB-R)
  - ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (IIIIB-R)
Titration Strategies

Medication Optimization Challenges in HFrEF
- Question of which medication to titrate first
- RAAS blockers and beta blockers reduce blood pressure, leading to tolerability issues with titration to target doses
- RAAS blockers and renal dysfunction and hyperkalemia
- Worsening HF symptoms with beta blockers, affecting adherence
- Dynamic fluid status of the HF patient

Mr. T – First Visit
- 64 year old male
  - PMH: COPD, GERD, PUD, CAD s/p DES to LM and LCx (3 years prior)
    - Recent admission for shortness of air (SOA) two weeks prior, ECHO showed LVEF 20-25%
  - Relevant Labs:
    - SCr = 0.86 mg/dL
    - Na = 137 mmol/L
    - K = 4.1 mmol/L
    - NT Pro-BNP = 1282 pg/mL
- Current Medications:
  - Aspirin 81 mg QD
  - Clopidogrel 75 mg QD
  - Atorvastatin 80 mg QD
  - Carvedilol 6.25 mg BID
  - Lisinopril 2.5 mg QD
  - Furosemide 40 mg QD PRN 2lbs weight gain in 24 hours or 5lbs weight gain in one week
  - Ranitidine 150 mg BID
  - Tiotropium 18 mcg QD
Mr. T – First Visit

- **Vitals**
  - HR = 89 BPM
  - BP = 137/86 mm Hg
  - O2 = 98% Room Air
  - Wt = 76.7 kg
  - Ht = 70"
  - RR = 14

- **Symptoms**
  - No orthopnea, PND
  - No SOA at rest, SOA during normal ADLs
  - No edema

- **HF Physical Exam**
  - Neck – No JVD or HJR
  - Cardiac – Normal rate and rhythm, normal S1 & S2, no S3 or S4
  - Pulmonary – No crackles, no wheezes
  - Abdomen – Non-tender, non-distended, no hepatosplenomegaly
  - Extremities – No cyanosis, no clubbing, no edema
  - Skin – Warm and dry

- **Plan**
  - Increase carvedilol
  - Start spironolactone

ACEI/ARB vs Beta-blocker

- **Which to increase first?**
  - Looking at clinical trials
    - ACEI studied as addition to vasodilation therapy w/out Beta-blockers
    - CONSENSUS, SOLVD
    - Beta-blockers added on to ACEI/ARB therapy in trials
  - Patient considerations
    - Volume status
    - Renal function and electrolytes
    - Blood pressure and heart rate
  - Drug considerations
    - Time to reach maximum tolerated dose or target dose
    - Side effects
  - Answer?
    - Beta-blocker based on feasibility of titration, obstacles and outcomes

Aldosterone Antagonists

- **When to start?**
  - EMPHASIS-HF
    - Significant difference in mortality early in the first year of therapy
  - RALES
    - Difference in mortality within one year of therapy
  - Patient considerations
    - Can start prior to discharge – especially if renal function and electrolytes WNL
    - Was an ACEI/ARB started or uptitrated?
    - Can wait until first outpatient visit to assess renal function and serum potassium
  - Two thoughts: start after ACEI/ARB titration complete or start during titration
  - If symptoms persistent
  - Criteria:
    - INR=1–1.4
    - LVEF ≤ 35%
    - SCr < 2.5 mg/dL; K+ < 5 mEq/l
    - Background therapy of ACEI/ARB plus BB or intolerant to prior therapy

Mr. T – Second Visit

- 64 year old male seen in clinic 2 weeks ago
  - Current Labs:
    - SCr – 0.91 mg/dL
    - Na – 139 mmol/L
    - K – 4.5 mmol/L
    - NT Pro-BNP – 1148 pg/mL
  - Complaint: Feeling tired and feet a little swollen

- Current Medications:
  - Aspirin 81 mg QD
  - Clopidogrel 75 mg QD
  - Atorvastatin 80 mg QD
  - Carvedilol 12.5 mg BID
  - Lisinopril 2.5 mg QD
  - Furosemide 40 mg PRN 2lbs weight gain in 24 hours or 5lbs weight gain in one week
  - Ranitidine 150 mg BID
  - Spironolactone 25 mg QD
  - Tiotropium 18 mg QD

Mr. T – Second Visit

- Vitals
  - HR – 81 BPM
  - BP – 130/81 mm Hg
  - O2 – 98% Room Air
  - Wt – 77.5 kg
  - Ht – 70"
  - RR – 13

- Symptoms
  - Some edema on bilateral lower extremities
  - No PND, orthopnea, improved SOA during ADLs
  - No abdominal distension

- HF Physical Exam
  - Neck – No JVD
  - Cardiac – Normal rate and rhythm, normal S1 & S2, no S3 or S4
  - Pulmonary – No crackles, no wheezes
  - Abdomen – Non-tender, non-distended, no hepatosplenomegaly
  - Extremities – BLE edema
  - Skin – Warm and dry

Mr. T – Second Visit

- Next steps for Mr. T
  - Increase ACEI dose
  - Keep beta-blocker dose at same dose due to signs and symptoms of fluid retention
    - Educate on daily weights, sodium and fluid restrictions
    - Schedule diuretic; consider diuretic titration
Beta-Blocker Dose Titrations

- Many issues may need to be addressed
  - Fluid status
    - Can cause fluid retention
  - Side effects
    - Common to feel fatigued, foggy mentally
    - Heart rate and blood pressure

- How to resolve then?
  1. Titrate slowly over longer periods of time
  2. Choice of beta-blocker
  3. Optimize diuretic strategy

Mr. T – Subsequent Visit

- 64 year old male seen in clinic 16 weeks ago
  - Current Labs:
    - Scr – 1.13 mg/dL
    - Na – 141 mmol/L
    - K – 4.6 mmol/L
    - NT Pro-BNP – 1114 pg/mL

- Complaint: Feeling lightheaded, fatigued; edema resolved

- Current Medications:
  - Aspirin 81 mg
  - Clopidogrel 75 mg QD
  - Atorvastatin 80 mg
  - Carvedilol 12.5 mg BID
  - Lisinopril 40 mg
  - Furosemide 40 mg BID
  - Ranitidine 150 mg BID
  - Spironolactone 25 mg
  - Tiotropium 18 mcg

Mr. T – Subsequent Visit

- Vitals
  - HR – 78 BPM
  - BP – 88/63 mm Hg
  - O2 – 98%
  - Wt – 76.2 kg
  - Ht – 70”

- Symptoms
  - No PND, orthopnea
  - No abdominal distension
  - No peripheral edema

- HF Physical Exam
  - Neck – No JVD
  - Cardiac – Normal rate and rhythm, normal S1 & S2, no S3 or S4
  - Pulmonary – No crackles, no wheezes
  - Abdomen – Non-tender, non-distended, no hepatosplenomegaly
  - Extremities – No cyanosis, no clubbing, no edema
  - Skin – Warm and dry
Mr. T – Subsequent Visit

- **Assessment:**
  - Patient experiencing symptomatic hypotension

- **Plan:**
  - Switch to metoprolol succinate 100 mg daily
    - Discontinue carvedilol 12.5 mg BID
  - Consider reducing diuretic dose if continually euvolemic

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Medication Titration and Vitals

- **One wall clinicians hit is hypotension or bradycardia**
  - Balance between quality of life and mortality benefit

- **Strategies**
  - Switching agents
    - Losing alpha activity of beta blockers
    - Taking away additional medications that do not confer mortality benefit but lower blood pressure
  - Continual assessment of fluid status
    - Temporarily holding diuretics or decreasing dose if possible
  - Start low, go slow
    - Try to only titrate one medication at a time

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Switching Beta-Blockers

- **Different strategies!**
  - Discontinuation-initiation or overlapping titration
  - Most patients tolerate discontinuation-initiation

- **Considerations**
  - Beta-blocking effect and alpha effect
    - Arrhythmia suppression and ventricle function
    - Anti-hypertensive effect
  - Patient adherence and understanding

Abraham WT. CHF. 2003; 8, 275-278
ACEI to ARB Switching

- ACEI first line unless unable to tolerate ACEI therapy
  - Not all ARBs are indicated for heart failure
    - Valsartan, candesartan, losartan
- Side effect profile
  - Mostly similar
  - Cough
  - ACEI induced angioedema
- Setup for newer therapies
  - ACEI discontinuation prior to sacubitril/valsartan

Wait! What About When to Add...

- Digoxin
  - Can consider adding on if repeated hospitalizations
  - Patients with HF and AF - possible increase in mortality with use
- Hydralazine/Isosorbide Dinitrate
  - First line therapy for African-American patients or those intolerant of ACEI/ARB therapy
- Sacubitril/Valsartan
  - Option to switch to/add if requiring further reduction in mortality
  - Switching options: hold ACEI for 36 hours or transition to ARB first then to sacubitril/valsartan
- Ivabradine
  - Can be added to patients on max tolerated beta-blocker therapy or intolerant of beta-blocker therapy who have a heart rate ≥ 70 BPM in normal sinus rhythm and HFrEF

Summary

- For titration:
  - Go slow!
  - If given the choice between ACEI/ARB and BB
    - BB first – will take longer to get to target dose, ADRs to overcome
  - Watch for side effects
    - Vitals and signs/symptoms
  - Switching considerations
    - End goal – reaching target doses
    - Physiologic profile of the drugs involved
    - Consideration for adherence
Pharmacists’ Roles in the Heart Failure Clinic

Heart Failure Clinic Domains

- Disease management
- Functional assessment
- Quality of life assessment
- Medical therapy and drug evaluation
- Device evaluation
- Nutritional assessment
- Follow-up
- Advanced planning
- Communication
- Provider education
- Quality Assessment

How to Begin

- Obtain data from your institution
  - HF population
  - HF readmissions
  - HF specialist vs. general cardiologist vs. APN
- Include evidence from literature
- Find a physician champion
  - Increase buy-in over time
  - Less frequent provider visits
Define Your Role

**Physician Clinic**
- Medication reconciliation
  - Focus on new patients and recent hospitalizations
  - Identify access issues
- Medication recommendations
  - Guideline directed
  - Avoid drug interactions
- Team discussion regarding treatment plan
- Further education on adjustments to patient/family
  - Updated medication list
- Lab follow-up as necessary

**PharmD Titration Clinic**
- HFrEF and HFrpEF with stable volume
- Medication reconciliation
- Optimize HF regimen prior to follow-up MD visit
- Education and adherence
- Lab follow-up as necessary

Collaborative Practice Agreement

- Define targeted patients
  - Who should be referred? How?
  - Internal and/or external patients?
- Guideline-driven recommendations
- Include a mechanism for:
  - Medication titration
  - Lab ordering and follow-up
  - Prescription refills
  - MD availability if acute issue
  - Communication with patient and provider

All encounters documented in EMR

HF Team at UIH

- Two HF Specialists
  - Four clinics per week
- Two APNs
  - Transitions of Care & Outpatient
  - IV Osmesis
- Two RNs
  - Transitions of Care and Outpatient
- Two PharmDs
  - Full-time & part-time
  - Physician and titration clinics
  - Developed educational materials
  - Medication flow sheets
- Interprofessional research
- Weekly team meetings
  - Admitted patients
  - Advanced HF patients
- HF Hotline
  - Voicemail for patients to reach HF team directly
  - PharmDs and APNs rotate coverage
Reimbursement Options: “Incident to”

- Physician/Provider – based clinic
  - Individual or group
- Provider initiates treatment
- Auxiliary personnel provide integral services or supplies
- Under direct supervision of provider
  - Immediately available to provide assistance
  - Billing provider may differ from provider ordering service
- Referred back to provider if new problem identified
- Low level of reimbursement
  - Restricted to CPT code 99211
- Must represent an expense to the practice
  - Salary or non-salary (exam room, office supplies, staff support, etc)
  - Ex. College of Pharmacy with physician-based clinical practice

Kliethermes MA et al. ASHP.org

Reimbursement Options: “Facility Fee”

- Governed by Hospital Outpatient Prospective Payment System (HOPS)
- Hospital-based clinic
  - Professional Fee – Providers
  - Technical Fee (Facility Fee) – Auxiliary Personnel
- Cost of using the facility to provide services
- Similar requirements to “incident to” billing
- Reimbursement is made to the hospital/clinic

Kliethermes MA. Updates in Therapeutics: Ambulatory Care Pharmacy. Review and Resertification Course. 2015: 2-450 – 2-454

Reimbursement Options: Transitional Care

- Transitional Care Management (TCM)
- Physicians, NP, PA, clinical nurse specialist, certified nurse-midwife
- First 30 days following discharge
  - Interactive contact within 2 days
    - Telephone, email, or face-to-face
  - Face-face-visit
    - Moderately complex decision-making within 14 days of discharge (CPT code 99495)
    - Highly complex decision-making within 7 days of discharge (CPT code 99496)
- Pharmacist can:
  - Provide interactive contact within 2 days of discharge
  - Provide non-face-to-face care
  - Assist provider with face-to-face visits
  - “Incident-to” requirements with “general” supervision versus “direct”

Kliethermes MA et al. ASHP.org
Measuring Success

- Collect data before and after interventions
  - Patients on guideline-directed medication therapy
  - Adherence
  - Readmissions
- Present benefit to administration
  - Billing will not cover PharmD salary
  - Decreased office visits for provider
  - Prior authorization assistance
  - Improved metrics
    - Increase value-based reimbursement
- Expand services as need arises
  - PCSK9 Inhibitor Consult service

Summary

- Pharmacists have a role on HF team
- Role can vary and evolve based on needs of the institution
- Training site for students and residents
- Known to improve patient outcomes

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