Critical Updates in the Management of Chronic Heart Failure

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Chicago State University---College of Pharmacy
Internal Medicine Clinical Pharmacist
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Learning Objectives

At the conclusion of this program, the pharmacist will be able to:

• Differentiate between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

• Compare and contrast therapeutic recommendations from nationally published guidelines on chronic heart failure (HF) management.

• Discuss newer therapies specifically indicated for chronic heart failure treatment and their potential role in practice.

• Illustrate the role of the pharmacist in providing appropriate care in the outpatient setting.
Meet Mr. Johnson

Mr. Johnson is a 65 year old African-American male who presents to family medicine clinic for follow-up from hospitalization about 7 days ago; he was recently diagnosed with new onset heart failure.

PMH: HTN X 30 yrs, DM X 5 yrs, GERD, mild osteoarthritis, NSTEMI with 2 everolimus stents in the LAD artery about 3 years ago.

Meds: Lisinopril 5 mg daily, famotidine 20 mg daily, metformin 1000mg BID, saxagliptin 2.5 mg daily, naproxen 220mg BID, diltiazem CD 120 mg daily, and atenolol 25 mg daily, furosemide 20 mg daily, aspirin 81 mg daily.

Allergies: NKDA
Mr. Johnson...The Interview

Vitals
- BP 150/100 mm Hg (repeat: 152/95 mg), HR 85 bpm (repeat: the same), RR 15 bpm, Tmax WNL

Height
- 75 inches

Weight
- 130 kg

Pertinent Labs (Fasting)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>155 mg/dL</td>
</tr>
<tr>
<td>BUN</td>
<td>35 mg/dL</td>
</tr>
<tr>
<td>SCr</td>
<td>1.0 mg/dL</td>
</tr>
<tr>
<td>CrCL</td>
<td>&gt; 100 mL/min</td>
</tr>
<tr>
<td>Sodium</td>
<td>140 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.0 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>99 mg/dL</td>
</tr>
<tr>
<td>BNP</td>
<td>280 ng/mL</td>
</tr>
</tbody>
</table>

You are tasked with (1) educating Mr. Johnson on his new diagnosis, and (2) making any evidence-based recommendations regarding his heart failure.
CHF: Quick Facts and Stats

• CHF: The “C” is not what you may think.
• Diagnosis is largely clinical in nature.
• Key statistics:
  • By the age of 40 yrs, the lifetime risk of developing HF is 1 in 5.
    • Disparities are certainly present.
  • There are about 650,000 new cases reported annually.
  • Total costs in the US > $40 billion!!!

Heart Failure with Reduced Ejection Fraction (HFrEF)

### Key Characteristics of HFrEF

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>Impaired contractility</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>Depressed</td>
</tr>
<tr>
<td>Abnormal heart sound</td>
<td>( S_3 ) present</td>
</tr>
<tr>
<td>Left ventricular cavity</td>
<td>Typically dilated</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on echocardiograph</td>
<td>Sometimes present</td>
</tr>
<tr>
<td>BNP/NT-proBNP levels</td>
<td>+++</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Cardiomegaly and congestion present</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Prior myocardial infarction or exposure to cardiotoxins</td>
</tr>
<tr>
<td>Evidence base regarding treatment</td>
<td>Well supported</td>
</tr>
</tbody>
</table>

Heart Failure with Preserved Ejection Fraction (HFpEF)

**Key Characteristics of HFpEF**

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Impaired lusitrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection Fraction</td>
<td>Normal or near-normal</td>
</tr>
<tr>
<td>Abnormal heart sound</td>
<td>$S_4$ present</td>
</tr>
<tr>
<td>Left ventricular cavity</td>
<td>Normal, but left ventricle undergoes hypertrophy</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on echocardiograph</td>
<td>Yes</td>
</tr>
<tr>
<td>BNP/NT-proBNP levels</td>
<td>++</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Congestion with or without cardiomegaly</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Individuals are typically obese. May have long-standing history of diabetes, hypertension, atrial fibrillation, or coronary artery disease</td>
</tr>
<tr>
<td>Evidence base regarding treatment</td>
<td>Poorly supported</td>
</tr>
</tbody>
</table>

Mr. Johnson...The Interview

- We know that he was recently diagnosed with chronic HF, but what other key piece of information is needed?
# Categories of Chronic HF

<table>
<thead>
<tr>
<th>Category</th>
<th>Ejection Fraction Determined</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure with reduced ejection fraction (HFrEF)</td>
<td>≤ 40%</td>
<td>Previously known as “systolic heart failure”. Most studied groups of patients. Therapies known to improve both morbidity and mortality.</td>
</tr>
<tr>
<td>Heart Failure with preserved ejection fraction (HFpEF)</td>
<td>≥ 50%</td>
<td>Previously known as “diastolic heart failure”. Common form of HF, but no known therapies to improve mortality.</td>
</tr>
<tr>
<td>HFpEF borderline</td>
<td>41-49%</td>
<td>Considered an intermediate category. These patients are managed the same as those with HFpEF.</td>
</tr>
<tr>
<td>HFpEF improved</td>
<td>&gt;40%</td>
<td>Patients who previously had HFrEF, but have had an improvement in EF. More research necessary on how to best manage these individuals.</td>
</tr>
</tbody>
</table>

Mr. Johnson...The Interview

- Before hospitalization: He reported that he would experience SOB from doing regular chores around his home. He likes to garden but hasn’t been able to do so for several weeks. He noticed swelling in his legs that progressively worsened over time. In order for him to sleep, he had to sleep in his recliner chair. Whenever he would lie flat, he mentioned that it felt as if he was drowning.

- In the clinic: He reports that is SOB has improved. While he does experience some limitations in movement when performing chores, it is not as bad as it was prior to hospitalization. He reports that he has started to take walks around the neighborhood, but at this point, he can go a few blocks before feeling winded. Some edema is present in his lower legs...likely 1+. He is concerned that “none of the medications are working.”
# Classification of Chronic Heart Failure

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitations in physical activity</td>
</tr>
<tr>
<td>II</td>
<td>Mild impairment in activity. Able to comfortably rest.</td>
</tr>
<tr>
<td>III</td>
<td>Moderate limitation in movements. Symptoms relieved with rest, but less than ordinary activities can provoke symptoms.</td>
</tr>
<tr>
<td>IV</td>
<td>Inability to perform any activity without marked symptoms. Symptoms occur even during rest</td>
</tr>
</tbody>
</table>

The Criteria Committee for the New York Heart Association.
Classification of Chronic Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Presence of HF risk factors but no structural heart disease or HF symptoms</td>
</tr>
<tr>
<td>B</td>
<td>Development of structural heart disease, but no HF symptoms</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease in addition to current or prior HF history</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF symptoms requiring specialized interventions</td>
</tr>
</tbody>
</table>

## Classification of Chronic Heart Failure

<table>
<thead>
<tr>
<th>ACC/AHA Staging System</th>
<th>Description</th>
<th>New York Functional Class System</th>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Presence of HF risk factors but no structural heart disease or HF symptoms</td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Development of structural heart disease, but no HF symptoms</td>
<td>I</td>
<td></td>
<td>No limitations in physical activity</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease in addition to current or prior HF history</td>
<td>II</td>
<td></td>
<td>Mild impairment in activity. Able to comfortably rest.</td>
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</tr>
</tbody>
</table>

Mr. Johnson...The Interview

• Shx—Divorced. Former smoker, quit immediately after his MI. No illicit drug use. Drinks a glass of red wine with dinner 4-5x/week. Meals typically consists of TV dinners and he loves canned foods because “they are easy.” Once per week, he drinks about 1L of “pop” over the course of several days.
General Recommendations

• Patient education
• Sodium restriction
• Fluid restriction
• Exercise/Wellness
• Avoidance of specific drugs
## General Recommendations: Patient Education

### Recommendations Regarding Patient Education

<table>
<thead>
<tr>
<th>Publication</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013 ACCF/AHA HF Management Guideline</td>
<td>Expanded details regarding the importance of patient education and self care. Explicit recommendation developed—<em>Patients with HF should receive specific education to facilitate HF self-care (Class I, LOE: B).</em></td>
</tr>
</tbody>
</table>

LOE=Level of Evidence

### Spectrum of Patient Education

- **Hospital**
- **Clinics/Community Pharmacies**

# General Recommendations: Sodium Restriction

## Recommendations Regarding Sodium Restriction

<table>
<thead>
<tr>
<th>Publication</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009 ACC/AHA HF Management Guideline--Focused Update of 2005 guideline</td>
<td>Moderate restriction is recommended (3-4 gms daily).</td>
</tr>
<tr>
<td>2010 HFSA Comprehensive HF Practice Guideline</td>
<td>Dietary sodium restriction (2-3 g daily) is recommended. Further restriction (&lt;2 g daily) may be considered in moderate to severe HF. (SOE=C).</td>
</tr>
<tr>
<td>2013 ACCF/AHA HF Management Guideline</td>
<td>Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms. (Class IIa, LOE: C). Clinicians should recommend some degree of restriction (&lt; 3 gms) in stage C or D HF patients.</td>
</tr>
</tbody>
</table>

LOE= Level of Evidence, SOE=Strength of Evidence
## General Recommendations: Fluid Restriction

### Recommendations Regarding Fluid Restriction

<table>
<thead>
<tr>
<th>Publication</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2009 ACC/AHA HF Management Guideline--Focused Update of 2005 guideline</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>2010 HFSA Comprehensive HF Practice Guideline</strong></td>
<td>Fluid restriction (&lt;2 L/day) is recommended in patients with moderate hyponatremia (serum sodium &lt;130 mEq/L) and should be considered to assist in treatment of fluid overload in other patients. (SOE=C) In patients with severe (serum sodium &lt;125 mEq/L) or worsening hyponatremia, stricter fluid restriction may be considered. (SOE=C).</td>
</tr>
<tr>
<td><strong>2013 ACCF/AHA HF Management Guideline</strong></td>
<td>Fluid restriction (1.5-2 L/daily) is reasonable in stage D, especially in patients with hyponatremia, to reduce congestive symptoms. (Class IIa, LOE: C).</td>
</tr>
</tbody>
</table>

LOE= Level of Evidence,      SOE=Strength of Evidence

# General Recommendations: Exercise

## Recommendations Regarding Exercising

<table>
<thead>
<tr>
<th>Publication</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009 ACC/AHA HF Management Guideline--Focused Update of 2005 guideline</td>
<td>Exercise training is beneficial as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF and reduced LVEF (Class I, LOE: B).</td>
</tr>
<tr>
<td>2010 HFSA Comprehensive HF Practice Guideline</td>
<td>Patients with HF undergo exercise testing to determine suitability for exercise training. If deemed safe, exercise training should be considered (while in a supervised setting). If tolerated, patients should increase duration and intensity with a goal of 30 minutes of moderate activity/exercise, 5 days per week with warm up and cool down exercises (SOE: B).</td>
</tr>
<tr>
<td>2013 ACCF/AHA HF Management Guideline</td>
<td>Exercise training (or regular physical activity) is recommended as safe and effective who are able to participate to improve functional status (Class I, LOE:A).</td>
</tr>
</tbody>
</table>

LOE= Level of Evidence, SOE=Strength of Evidence

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*J Card Fail* 2010;16:e475-e539.  
General Recommendations: Avoiding Certain Drugs

<table>
<thead>
<tr>
<th>Publication</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2009 ACC/AHA HF Management Guideline--Focused Update of 2005 guideline</strong></td>
<td>Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF should be avoided or withdrawn whenever possible (NSAIDs, most antiarrhythmic drugs, and most calcium channel blocking drugs). (Class I, LOE: B).</td>
</tr>
<tr>
<td><strong>2010 HFSA Comprehensive HF Practice Guideline</strong></td>
<td>NSAIDs, including cyclooxygenase-2 inhibitors, are not recommended in patients with chronic HF. (SOE:B)</td>
</tr>
<tr>
<td><strong>2013 ACCF/AHA HF Management Guideline</strong></td>
<td>Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF are potentially harmful and should be avoided or withdrawn whenever possible (e.g., most antiarrhythmic drugs, most calcium channel blocking drugs (except amlodipine), NSAIDs, or thiazolidinediones) (Class III, LOE: B)</td>
</tr>
</tbody>
</table>

LOE= Level of Evidence, SOE=Strength of Evidence
## General Recommendations: Avoiding Certain Drugs

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention of Sodium and Water</td>
<td>NSAIDs, Cox II Inhibitors, Corticosteroids, Thiazolidinediones</td>
</tr>
<tr>
<td>Negative Inotropic Effects</td>
<td>Calcium channel blockers (verapamil, diltiazem), Itraconazole, Most antiarrhythmic agents (except amiodarone and dofetilide)</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>Anthracyclines, Sunitinib, Trastuzumab, Paclitaxel, Ifosfamide, Excessive amounts of ethanol</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Biologic response modifiers (infliximab, etanercept), Clozapine, Illicit drugs (cocaine, amphetamines), Decongestants (pseudoephedrine, phenylephrine), Saxagliptin</td>
</tr>
</tbody>
</table>

[Am J Health-Syst Pharm. 2011; 68:1791-804.]
Role of Device Therapies

- Cardiac resynchronization therapy
- AICDs
- Specialized interventions
  - LVADs
  - Cardiac Transplantation

Knowing what we know that this point...

• What would you recommend for Mr. Johnson regarding the following:
  • Patient education?
  • Sodium restriction?
  • Fluid restriction?
  • Exercise/Wellness?
  • Avoidance of specific drugs?
Management of Heart Failure with Reduced Ejection Fraction

Stage A

Treat per nationally published guidelines:
- Hypertension
- Diabetes
- Dyslipidemia
- Ischemic Heart Disease
- Obstructive Sleep Apnea

Manage conditions that could incite HF exacerbation

Evaluate drug regimen if potential agents are present that can induce HF

Management of Heart Failure with Reduced Ejection Fraction

Maintain all stage A recommendations

Acute Coronary Syndrome
Secondary Prevention Measures:
If reduced EF—ACEI or ARB + appropriate BB indefinitely
If preserved EF—ACEI or ARB indefinitely, BB X 3 yrs, then reevaluate

Left Ventricular Hypertrophy:
Manage blood pressure per nationally published guidelines

Valvular Malfunction:
Repair or replacement may be warranted

Stage B

ACEI=Angiotensin Converting Enzyme Inhibitor
ARB=Angiotensin Receptor Blocker
BB= Beta Blocker

JAMA 1997;278(3):212-216.
Management of Heart Failure with Reduced Ejection Fraction

Stage C

*Ensure routine use of Guideline-Directed Medical Therapy (GDMT)
  Maintain Stage A and B recommendations

*ACEI or ARBs (Any agent is acceptable)

Symptomatic relief from hypervolemia: Loop Diuretics

*BBs (Either metoprolol succinate, carvedilol bisoproprolol)

Other Considerations/Thoughts
*Goal should be to attain same target doses of ACEI (or ARBs) or BB used in trials.
*Think about your individual patient when considering GDMT.
*Carvedilol CR listed as an option in 2013 guidelines, not the others.

Management of Heart Failure with Reduced Ejection Fraction

Stage D

- Continue all recommendations from stage A, B, and C
- IV inotropic agents can be administered as a temporary measure
- Cardiac transplantation Placement of LVAD Long term IV inotropic administration as a palliative measure

Knowing what we know that this point...

- What would you recommend for Mr. Johnson regarding his HF regimen?
After about 9 months, Mr. Johnson RTC. He reports that he has been adhering to all recommendations regarding exercising and sodium intake. He even keeps an organized log of physical activities. He no longer uses the naproxen for his mild OA. Additionally, he reports no missed doses of any meds. All of his HF meds currently are at target doses. Despite this news, he still experiences mild SOB and is not able to exercise for a full session without getting winded. He can perform most chores around his home.
Management of Heart Failure with Reduced Ejection Fraction—Stage C

Stage C with persistent symptoms

- African-American patients, can consider hydralazine/isosorbide dinitrate
- Dual RAAS blockade
- Digoxin

RAAS=Renin-Angiotensin-Aldosterone System

Management of Heart Failure with Reduced Ejection Fraction—Stage C

Story Behind Hydralazine/Nitrate Combination

V-HeFT I
(Hydr/Nitrate vs. Placebo)

V-HeFT II
(Hydr/Nitrate vs. Enalapril)

A-HeFT
(Hydr/Nitrate vs. Placebo)


Hydr=Hydralazine
Management of Heart Failure with Reduced Ejection Fraction—Stage C

**A-HeFT Trial**

1050 self identified black patients with NYHA III-IV and reduced EF (Mean age 56 yrs, Mean EF 23%)

- **Hydr/ISDN (2 tabs TID) +SOC**
- **Placebo +SOC**

**Primary Endpoint:** Composite of all cause death, change in quality of life, and first HF hospital admission

ISDN=Isosorbide Dinitrate
SOC=Standard of care

# Management of Heart Failure with Reduced Ejection Fraction—Stage C

<table>
<thead>
<tr>
<th>Component</th>
<th>Hydr/ISDN</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>6.2%</td>
<td>10.2%</td>
<td>0.02</td>
</tr>
<tr>
<td>Δ in QOL in 6 months</td>
<td>-5.6±20.6</td>
<td>-2.7±21.2</td>
<td>0.02</td>
</tr>
<tr>
<td>1st HF hospital admission</td>
<td>16.4%</td>
<td>24.4%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

QOL=Quality of Life

![Graph showing overall survival over days since baseline visit](image)

Management of Heart Failure with Reduced Ejection Fraction—Stage C

- Considerations for Hydralazine/Isosorbide Dinitrate
  - In African-American patients, the combination does not take precedence over ACEI (or ARB)/BB.
    - Other ethnic groups
  - Pill burden
  - Cost
Management of Heart Failure with Reduced Ejection Fraction—Stage C

- Dual RAAS Blockade
  - Standard Therapy + Aldosterone Antagonist
  - Standard Therapy + ARB
Management of Heart Failure with Reduced Ejection Fraction—Stage C

<table>
<thead>
<tr>
<th>Landmark Studies Involving Aldosterone Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td><strong>RALES (N=1663)</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>EPHESUS (N=6632)</strong></td>
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<td></td>
</tr>
</tbody>
</table>

Management of Heart Failure with Reduced Ejection Fraction—Stage C

EMPHASIS-HF Study

*Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure*

(Pts ≥ 55 yrs old, EF ≤ 30-35%, NYHA II)

- 1364 patients received standard treatment plus eplerenone 25-50 mg/day
- 1373 patients received standard treatment plus placebo

Primary Endpoint: Death from CV causes or hospitalization
Secondary Endpoint: Many including hospitalization for HF or death from any cause, etc.

*N Engl J Med*

Management of Heart Failure with Reduced Ejection Fraction—Stage C

• Primary Outcomes
  • CV causes or hospitalization for HF: HR 0.63 (95% CI 0.54-0.74); p<0.001
  • All cause mortality: HR 0.76 (95% CI 0.62-0.93); p<0.008

• Secondary Outcomes
  • Death from any cause or hospitalization for HF: HR 0.65 (95% CI 0.55–0.76); p<0.001

## Management of Heart Failure with Reduced Ejection Fraction—Stage C

### Recommendations Regarding Aldosterone Antagonists

<table>
<thead>
<tr>
<th>Publication</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2009 ACC/AHA HF Management Guideline--Focused Update of 2005 guidelines</strong></td>
<td>Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Required labs: SCr ≤ 2.5 mg/dL in men or ≤ 2.0 mg/dL in women and potassium &lt;5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks of therapy may outweigh the benefits (Class I, LOE: B).</td>
</tr>
<tr>
<td><strong>2010 HFSA Comprehensive HF Practice Guideline</strong></td>
<td>Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (&lt;35%) while receiving standard therapy, including diuretics. (SOE=A).</td>
</tr>
<tr>
<td><strong>2013 ACCF/AHA HF Management Guideline</strong></td>
<td>Aldosterone antagonists are recommended in patients with NYHA class II-IV and who have EF of 35% ≤, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone antagonists. (Class I, LOE:A).</td>
</tr>
</tbody>
</table>

LOE=Level of Evidence  
SOE=Strength of Evidence
Management of Heart Failure with Reduced Ejection Fraction—Stage C

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</thead>
<tbody>
<tr>
<td>2009 ACC/AHA HF Management Guideline—Focused Update of 2005 guidelines</td>
<td>The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. (Class IIB, LOE: B)</td>
</tr>
<tr>
<td>2010 HFSA Comprehensive HF Practice Guideline</td>
<td>The addition of an ARB should be considered in patients with HF due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and beta blocker. (SOE=A).</td>
</tr>
<tr>
<td>2013 ACCF/AHA HF Management Guideline</td>
<td>Addition of an ARB may be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACE inhibitor and a beta blocker in whom an aldosterone antagonist is not indicated or tolerated (Class IIB, LOE:A).</td>
</tr>
</tbody>
</table>

LOE=Level of Evidence   SOE=Strength of Evidence

Management of Heart Failure with Reduced Ejection Fraction—Stage C

- **Digoxin**
  - Recommendations remain consistent across guidelines.
  - Does not improve mortality, but can reduce hospitalization rates.
  - Other considerations:
    - Can be added to symptomatic patients with GDMT or its addition can be delayed.
    - Useful for patients with concomitant atrial fibrillation.
    - Doses should not exceed 250 mcg daily.
    - Be cognizant of drug-drug interactions.
Management of Heart Failure with Reduced Ejection Fraction—Stage C

### Recommendations Regarding Adjunctive Use of Dyslipidemic Agents

<table>
<thead>
<tr>
<th>Publication</th>
<th>Statins</th>
<th>Omega 3 Fatty Acids (O3FAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009 ACC/AHA HF Management Guideline--Focused Update of 2005 guidelines</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2010 HFSA Comprehensive HF Practice Guideline</td>
<td>There is no indication to use statins specifically for the treatment of HF, but statins are indicated to treat hyperlipidemia in HF patients.</td>
<td>None</td>
</tr>
<tr>
<td>2013 ACCF/AHA HF Management Guideline</td>
<td>Not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use (Class III, LOE: A)</td>
<td>Reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations (Class IIa, LOE: B)</td>
</tr>
</tbody>
</table>

Management of Heart Failure with Reduced Ejection Fraction—Stage C

**GISSI Prevenzione trial**—
Patients s/p MI
21% reduction in death in those taking 1 gm O3FA (850-882 mg EPA/DHA) vs. placebo

*Post hoc* analysis

**GISSI Prevenzione trial**—
2,000 patients in treatment group had reduced EF

**GISSI HF trial**—
6,975 Patients NYHA Class II-IV HF
Reductions in all cause death, CV death and hospitalizations in those taking 1 gm O3FA (850-882 mg EPA/DHA) vs. placebo

---

Knowing what we know that this point...

- What would you recommend for Mr. Johnson regarding his HF regimen:
  - Add digoxin?
  - Add hydralazine/isosobide dinitrate?
  - Add spironolactone?
  - Add candesartan?
Management of Heart Failure with Preserved Ejection Fraction

• Overall treatment principles
  • Maintain adequate blood pressure
  • Reduce tachycardia
  • Maintain euvolemia
  • Treat and prevent myocardial ischemia

Management of Heart Failure with Preserved Ejection Fraction

• Key caveats to consider with managing blood pressure in these patients:
  • No restrictions on which BB to use.
  • Broader array of calcium channel blockers can be used.
  • While ACEIs/ARBs may be used to manage blood pressure, data have demonstrated a small reduction in HF hospitalizations with the use of ARBs in a population of patients with HFpEF.
  • Loop diuretics should be used carefully.

Newer Agents for Managing Chronic Heart Failure

- Ivabradine (Corlanor®)
  - Hyperpolarization-activated cyclic nucleotide-gated channel blocker.
    - Slows down heart rate by inhibition of the I_f current.
  - Indicated for persistently symptomatic HF patients with resting pulse ≥ 70 bpm.
  - Patient-specific criteria for use include:
    - Reduced EF (≤ 35%)
    - Stable disease with continued symptoms
    - Sinus rhythm
    - Max tolerated dose of BBs/contraindication for BB therapy.

Newer Agents for Managing Chronic Heart Failure (Ivabradine)

**SHIFT**
(Systolic heart failure treatment with the I_f inhibitor ivabradine Trial)

- 6,000 patients with EF ≤ 35%, initial HR > 70 bpm, prior HF admission.
- All received standard therapies.
- Ivabradine groups had 2% reduction in all-cause readmissions (1,231 readmissions), compared to placebo (1,356 hospitalizations); p=0.003.

**BEAUTIFUL**
(morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction)

- 10,917 stable CAD patients with EF ≤40%, initial HR ≥ 60 bpm, with a prior HF hospital admission.
- All received standard therapies.
- HR ↓ in the ivabradine group compared to placebo, there was no difference in the primary outcomes (composite of CV death, hospitalization for MI or HF).
- Patients with HR > 70 bpm demonstrated no difference in primary outcomes, but differences were detected in secondary endpoints (admission due to MI or revascularization).

Newer Agents for Managing Chronic Heart Failure (Ivabradine)

<table>
<thead>
<tr>
<th>Ivabradine (Corlanor®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Patient-specific criteria for usage</strong></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td><strong>Disease State considerations</strong></td>
</tr>
<tr>
<td><strong>Drug-drug interactions</strong></td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
</tr>
</tbody>
</table>

ADHF=Acute decompensated heart failure

Newer Agents for Managing Chronic Heart Failure

Angiotensin-Neprilysin Inhibition

RAAS

Angiotensinogen → Angiotensin I → Angiotensin II

Aldosterone

Vasoconstriction

Bradykinin

Natriuretic Peptide System

Natriuretic Peptides (B-type natriuretic peptide)

Vasodilation

Adrenomedullin

Neprilysin

Inactive Fragments
Newer Agents for Managing Chronic Heart Failure (Sacubitril/Valsartan)

PARADIGM-HF
8442 patients with NYHA class II-IV disease with an EF ≤ 40%, either a BNP > 150 pg/mL or prior HF hospitalization within past yr (Mean age 64 yrs, 71% of patients had NYHA II HF)

Sacubitril/Valsartan 200 mg BID + SOC

Enalapril 20 mg BID + SOC

Primary endpoints—Composite of death for CV causes or HF hospital admission
Secondary endpoints—Change in QOL scores from baseline to 8 months, time to reduction in renal function, and time to new onset atrial fibrillation.

SOC=Standard of care
QOL=Quality of life

Newer Agents for Managing Chronic Heart Failure (Sacubitril/Valsartan)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo†</td>
<td>−2.99±0.36</td>
<td>−4.63±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation‡</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function§</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

* Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons.
† Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as the least-squares mean (±SE) of the between-group difference.
‡ A total of 2670 patients in the LCZ696 group and 2638 patients in the enalapril group who did not have atrial fibrillation at the randomization visit were evaluated for new-onset atrial fibrillation during the study.
§ A decline in renal function was defined as end-stage renal disease or a decrease of 50% or more in the estimated glomerular filtration rate (eGFR) from the value at randomization or a decrease in the eGFR of more than 30 ml per minute per 1.73 m², to less than 60 ml per minute per 1.73 m².

**Newer Agents for Managing Chronic Heart Failure (Sacubitril/Valsartan)**

<table>
<thead>
<tr>
<th><strong>Sacubitril/Valsartan (Entresto™)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Reduce the risk of CV death and HF hospitalization in patients with heart failure with reduced ejection fraction.</td>
</tr>
<tr>
<td><strong>Patient-specific criteria for usage</strong></td>
<td>If on an ACEI, it must be discontinued 36 hours prior to the initiation.</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>49/51 mg PO BID. Titrate after 7-14 days to target dose of 97/103 mg PO BID. Dose adjust in both renal/hepatic impairment.</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Concomitant use of ACEI, history of angioedema with ACEI or ARB, concomitant use with aliskiren in diabetic patients.</td>
</tr>
<tr>
<td><strong>Drug-drug interactions</strong></td>
<td>Potassium-sparing diuretics, potassium supplements</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Cough, hypotension, angioedema</td>
</tr>
</tbody>
</table>

Something to Think About

• Could Mr. Johnson be a candidate for...
  • Ivabradine?
  • Sacubitril/Valsartan?
Role of The Outpatient Pharmacist

• VITAL!!!!!!
• Remember the essential non-pharmacological measures.
  • Patient education!!
  • Dietary needs
  • Daily weights
• Ensure mortality-saving agents are on board.
• Remain cognizant of drug-induced causes.
• Recommend other key therapies to manage other HF associated disease states (if necessary).
• Provide immunizations.
Other Recommendations for Mr. Johnson

• Any other needed interventions for Mr. Johnson?
Conclusions

• Chronic HF continues to be a common medical issue suffered by many.
• Nonpharmacological and pharmacotherapy are both key in improving QOL and extending life!
• Our role is instrumental in ensuring reduction in hospitalizations and improving mortality.
Critical Updates in the Management of Chronic Heart Failure

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