The Dark Side of the Moon: Heart Failure with Preserved Ejection Fraction

Felix K. Yam, Pharm.D., M.A.S., BCPS-AQ Cardiology
Associate Clinical Professor
UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences
Disclosure

I have no relevant conflicts of interest to disclose.
Objectives

1. Know the prevalence and risk factors for heart failure with preserved ejection fraction.

2. Differentiate the pathophysiology and pharmacologic treatment options between heart failure patients who have reduced ejection fraction and those who have preserved ejection fraction.

3. Apply pharmacotherapy principles and knowledge of published evidence to optimize medication use and improve outcomes in patients who have heart failure with preserved ejection fraction.
Heart Failure: Burden of Disease

Life-time risk of developing HF for Americans age ≥ 40

One-half of patients diagnosed with HF dead within 5 years

### Heart Failure: Comparative Mortality

<table>
<thead>
<tr>
<th>Disease State</th>
<th>1-year mortality (men)</th>
<th>1-year mortality (women)</th>
<th>5-year mortality (men)</th>
<th>5-year mortality (women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1950-1969</td>
<td>30%</td>
<td>28%</td>
<td>70%</td>
<td>57%</td>
</tr>
<tr>
<td>1970-1979</td>
<td>41%</td>
<td>28%</td>
<td>75%</td>
<td>59%</td>
</tr>
<tr>
<td>1980-1989</td>
<td>33%</td>
<td>27%</td>
<td>65%</td>
<td>51%</td>
</tr>
<tr>
<td>1990-1999</td>
<td>28%</td>
<td>24%</td>
<td>59%</td>
<td>45%</td>
</tr>
<tr>
<td>All Cancer</td>
<td></td>
<td></td>
<td>38%</td>
<td>37.3%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td></td>
<td></td>
<td>14.1%</td>
<td></td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td></td>
<td></td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>Colon Cancer</td>
<td></td>
<td></td>
<td>38.6%</td>
<td></td>
</tr>
</tbody>
</table>

Heart Failure: Morbidity and Cost

- Hospitalization, 53%
- Drugs/Other, 18%
- Physician/Provider, 6%
- Nursing Home, 12%
- Lost productivity/mortality, 11%

Estimated 2010 total heart failure costs: $39.2 billion

In 2030, projected U.S. Heart Failure Costs: $70 billion

HF is the primary diagnosis in > 1 million hospitalizations annually

All-cause mortality after each subsequent hospitalization for heart failure

Slides adapted from AHA Target:HF Presentation 2010.
Established benefits of guideline-recommended heart failure therapies

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>Relative Risk Reduction in Mortality</th>
<th>Relative Risk Reduction in Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17%</td>
<td>31%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>34%</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>30%</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>43%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Slides adapted from AHA Target:HF Presentation 2010
Trends in the Proportion of Cardiovascular Deaths in Clinical Trials

Mortality Benefits Only Found in Heart Failure Patients with Reduced Ejection Fraction

Mortality and Hospitalization in OPTIMIZE-HF Registry: HFrEF vs. HFpEF

Increasing Hospital Admissions for HFP EF

Comparative Survival: HFrEF vs. HFpEF

Survival has improved in HFrEF but NOT HFpEF

Different Phenotypes of Heart Failure

- **HFrEF**
  - EF ≤ 40
  - The ventricles fill normally with blood
  - The enlarged ventricles fill with blood

- **HFpEF**
  - EF ≥ 50
  - The stiff ventricles fill with less blood than normal

Epidemiology: Heart Failure with Preserved Ejection Fraction

\[ r = 0.92, \quad P < 0.001 \]
How do patients with heart failure die?

**REDUCED EJECTION FRACTION**
- Coronary heart deaths, 43%
- Non-CV deaths, 36%
- Other CV deaths, 21%

**PRESERVED EJECTION FRACTION**
- Coronary heart deaths, 29%
- Non-CV deaths, 49%
- Other CV deaths, 22%

Modes of Cardiovascular Death in I-PRESERVE Trial

Mode of CV Death

- Sudden Death: 44%
- Pump Failure: 24%
- Stroke: 14%
- MI: 8%
- Other: 10%

Risk Factors and Comorbidities Associated with HFpEF

Heart Failure with Preserved Ejection Fraction Pathophysiology

- Obesity
- Hypertension
- Diabetes
- Chronic Kidney Disease
- Atrial Fibrillation

Systemic Inflammation (release of interleukin-6 and tumor necrosis factor α)

Coronary Vascular Endothelial Dysfunction and Reduced Vasodilator Response

- Diastolic dysfunction
- Arterial stiffness
- Chronotropic incompetence
- Abnormal LV systolic function
- Pulmonary HTN

Distinct Pathophysiology: HFrEF vs. HFpEF
End diastolic pressure volume relationship

Exercise intolerance and peripheral edema are hallmark clinical symptoms.
Clinical Presentation of HFpEF vs. HFrEF

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>HFpEF</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea on exertion</td>
<td>60%</td>
<td>73%</td>
</tr>
<tr>
<td>Nocturnal dyspnea</td>
<td>55%</td>
<td>50%</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td>35%</td>
<td>46%</td>
</tr>
<tr>
<td>Rales</td>
<td>72%</td>
<td>70%</td>
</tr>
</tbody>
</table>

# 2013 ACC/AHA/HFSA HFpEF Recommendations

## Table 21. Recommendations for Treatment of HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to</td>
<td>I</td>
<td>B (27,91)</td>
</tr>
<tr>
<td>published clinical practice guidelines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>demonstrable myocardial ischemia is present despite GDMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>for HFpEF to improve symptomatic HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>Iib</td>
<td>B (589)</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>
Treatment Patterns HFpEF vs. HFrEF

Pharmacologic Treatment Strategies in HFP EF

- **Treatment of volume overload and congestion**
- **Treatment of hypertension**
- Renin-angiotensin-aldosterone blockade
- Aldosterone receptor antagonists
- Angiotensin Receptor Neprilysin Inhibitor
- β – blockade
- Digoxin
Treatment of volume overload and congestion

- Class I recommendation (LOE C) for symptomatic management
- No mortality benefit
- Sudden decreases in LV volumes may result in decrease in cardiac output
- Diuretic resistance is common
Managing Diuretic Resistance

- **↓ Cardiac Output**
- **↑ CVP**

- **↓ Plasma albumin**

Reduced absorption of loop diuretic

Unable to bind to albumin

Distal Na reabsorption

- **↓ RBF and GFR**

- **↓ Plasma albumin**

- **↑ RAAS and SNS**

- **Braking phenomenon**

- **Reduced filtration**
  - **Organic acids compete with active transport**

Switch loop diuretic
(furosemide, bumetanide, torsemide)

Combination diuretic therapy
(add metolazone, acetazolamide or mineralocorticoid antagonist)

Intravenous administration
(ED admission or infusion clinic)

Reduced absorption of loop diuretic

Unable to bind to albumin

Distal Na reabsorption

Braking phenomenon

↑ RAAS and SNS

Reduced filtration

- Organic acids compete with active transport
# Loop diuretic selection

<table>
<thead>
<tr>
<th></th>
<th>Furosemide (Lasix®)¹ ³</th>
<th>Torsemide (Demadex®)²</th>
<th>Bumetanide (Bumex®)¹ ²</th>
<th>Ethacrynic Acid (Edecrin®)²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV loading doses</strong></td>
<td>40 mg</td>
<td>20 mg</td>
<td>1 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td><strong>Max total daily dose</strong></td>
<td>600 mg</td>
<td>200 mg</td>
<td>10 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>10 – 100%</td>
<td>80 – 100%</td>
<td>80 – 90%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Duration of action</strong></td>
<td>6 – 8 hours</td>
<td>12 – 16 hours</td>
<td>4 – 6 hours</td>
<td>6 hours</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>diuresis w/in 10 – 20 minutes; peak diuresis in 1.5 hours</td>
<td>diuresis w/in 10 minutes of IV dose; peak diuresis at 60 minutes</td>
<td>peak diuresis w/in 75 minutes</td>
<td>usually reserved for pts with documented sulfa allergy</td>
</tr>
</tbody>
</table>

1. bioavailability adversely affected by food  
2. IV : PO conversion is 1:1  
3. IV : PO conversion is 1:2
PA Pressures and Pathophysiology of Congestion

Adamson PB, et al. Curr Heart Fail Reports 2009
CardioMEMS™ HF System

PATIENT TRANSMISSION

SECURE WEBSITE

CLINICIAN REVIEW
Hemodynamic Management of Patients with HFpEF

Treatment of hypertension

Ventricular-arterial stiffening in HFpEF leads to dramatic elevations in blood pressure

Treating hypertension can lower risk of developing HF by > 50%

Renin-angiotensin aldosterone system inhibitors

2003: CHARM Study: Candesartan

2006: PEP-CHF Study: Perindopril

2008: I-PRESERVE: Irbesartan

PEP-CHF. Eur Heart J 2006;27:2338-45.
ALLHAT Study: Chlorthalidone

Risk of developing HFpEF compared to chlorthalidone

- vs. lisinopril: 0.74 (95% CI, 0.56 to 0.97)
- vs. amlodipine: 0.69 (95% CI, 0.53 to 0.91)
- vs. doxazosin: 0.53 (95% CI, 0.38 to 0.73)

Blood pressure effects and achievement of BP goals in ALLHAT

Systolic Blood Pressure Over Time

- Chlortalidone
- Amlodipine
- Lisinopril

% Achieved BP Goal

- Chlorthalidone
- Amlodipine
- Lisinopril

vs. amlodipine, p < 0.03
vs. lisinopril, p < 0.001

vs. amlodipine, p < 0.09
vs. lisinopril, p < 0.001
<table>
<thead>
<tr>
<th>Trial</th>
<th>Δ in systolic blood pressure, mm Hg</th>
<th>Δ in diastolic blood pressure, mm Hg</th>
<th>compared to placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>11.4</td>
<td>8.9</td>
<td>--</td>
</tr>
<tr>
<td>HYVET</td>
<td>15</td>
<td>6.1</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>CHARM</td>
<td>6.9</td>
<td>2.9</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>PEP-CHF</td>
<td>3</td>
<td>--</td>
<td>$p &lt; 0.03$</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>3.8</td>
<td>2.1</td>
<td>$p &lt; 0.05$</td>
</tr>
</tbody>
</table>

PEP-CHF. Eur Heart J 2006;27:2338-45.
Intensive Blood Pressure Control and Outcomes: SPRINT Study

**1st Occurrence of CV Event**
- **Heart Failure**: 0.62 (95% CI, 0.45 to 0.84)
- **Myocardial Infarction**: 0.83 (95% CI, 0.64 to 1.09)
- **Stroke**: 0.89 (95% CI, 0.63 to 1.25)

*intensive treatment arm = goal SBP < 120 mm Hg; standard treatment arm = goal SBP < 140

Summary: Inhibition of RAAS and Intensity of Blood Pressure Reduction

• No evidence of mortality benefit when using RAAS inhibitors
• Use of RAAS inhibitors should be guided by comorbidities
• ARB’s may reduce hospitalizations in patients with HFpEF (Class IIa, LOE C)
• Blood pressure reduction strongly correlated with HFpEF prevention
  • evidence with chlorthalidone
• More stringent BP goals may be warranted in patients with HFpEF
Mineralocorticoid Receptor Antagonists

ALDO-DHF Trial

- **E/e’ medial velocity ratio**
  - Placebo and Spironolactone groups compared at 6 and 12 months.
  - **P < .001** for Spironolactone vs Placebo at 6 months, **P < .001** at 12 months.

- **Left ventricular mass index**
  - Placebo and Spironolactone groups compared at 6 and 12 months.
  - **P = .16** for Spironolactone vs Placebo at 6 months, **P = .009** at 12 months.

Mineralocorticoid Receptor Antagonists: TOPCAT study

No difference in death from CV causes

Lower incidence of HF hospitalization
Regional differences in TOPCAT: Post-hoc analysis

North and South Americas (n=1767)

- Primary outcome: 0.82 (95% CI, 0.69 to 0.98)
- Cardiovascular mortality: 0.74 (95% CI, 0.57 to 0.97)
- Hospitalization for HF: 0.82 (95% CI, 0.67 to 0.99)

Total events: 522
MRA vs. placebo event rate: 10.5% vs. 12.6%, \( p = 0.026 \)

Russia/Georgia (n=1678)

- Primary outcome: 1.10 (95% CI, 0.79 to 1.51)
- Cardiovascular mortality: 1.31 (95% CI, 0.91 to 1.90)
- Hospitalization for HF: 0.76 (95% CI, 0.44 to 1.32)

Total events: 149
MRA vs. placebo event rate: 2.5% vs. 2.3%, \( p = 0.58 \)

Patients enrolled in Russia/Georgia were younger, had less atrial fibrillation and diabetes

Pfeffer MA et al. Circulation. 2014;131:00-00.
Place in therapy: Mineralocorticoid Receptor Antagonists

- No overall mortality benefit, but consider regional variation
- May reduce HF hospitalizations
- May improve hemodynamic parameters and structural heart abnormalities
- Useful to maintain potassium homeostasis in patients on diuretic therapy
- May be useful in resistant hypertension
Beta-blocker therapy in HFpEF

OPTIMIZE-HF Registry: Propensity Matched Cohort Study of 1,099 Pairs of HFpEF Patients

One small prospective study demonstrates improvement in overall mortality with propranolol compared to placebo (56% vs. 75%, \( p < 0.007 \)). No difference in cardiac mortality and all patients had a history of MI.

Place in therapy: Beta-blockers in HFpEF

• No evidence for reduction in CV related mortality in HFpEF
• Effect blunted by chronotropic incompetence?

• Rate control issues
  • Dependent upon baseline HR’s
    • Improve symptoms in patients with baseline tachycardia
    • Worsen symptoms in patients with bradycardia due to chronotropic incompetence

• Use of β-blockers should be guided by comorbidities
  • History of MI/CAD
  • Atrial fibrillation
Place in therapy: Calcium channel blockers

• Not recommended in HFrEF (Class III (LOE A))

• Theoretical benefit in HFpEF
  • Rate control
  • Improving diastolic filling time

Exercise intolerance and nitrates

• In HFpEF, increase in LV volumes result in dramatic increases in LV pressures.

Nitrates are commonly used to improve symptoms of exercise intolerance and orthopnea.

NEAT-HFPEF: Activity levels fall on nitrates in HFpEF

Place in therapy: Digoxin in HFpEF

- No mortality or hospitalization benefit
- May be used as an adjunctive agent for improved rate control
- Increasing data suggesting higher mortality in patients with atrial fibrillation

Circulation. 2006;114:397-403.
Place in therapy: Neprilysin inhibitors in HFpEF

PARAMOUNT Trial: LCZ696 lowers NT-proBNP

Phase III PARAGON Trial: Expected to complete in 2019

Place in therapy: Ivabradine in HFpEF

Ivabradine improves peak VO$_2$

Larger studies evaluating clinical outcomes are needed

Ongoing clinical trials in patients with HFpEF

- Phosphodiesterase-5 inhibitors
  - Sildenafil
  - Udenafil
- Soluble guanylate cyclase stimulator
  - Riociguat
  - Vericiguat
- Ranolazine
- Nifedipine
Summary: Treatment of HFpEF

Symptoms of HFpEF (normal EF)

- Volume Overload
  - Diuretics

- HR Control
  - β-blockers
    - verapamil
    - diltiazem

- Hypertension
  - Anti-hypertensives

- Atrial Fibrillation
  - Maintain sinus rhythm, amiodarone
1. Which of the following drugs has a class I indication for the treatment of heart failure with preserved ejection fraction?
   a. bumetanide
   b. candasartan
   c. Isosorbide mononitrate
   d. carvedilol

2. Which of the following drugs is associated with a decreased risk of developing heart failure with preserved ejection fraction?
   a. aspirin
   b. chlorthalidone
   c. amlodipine
   d. metoprolol

3. Non-dihydropyridines calcium channel blockers (verapamil, diltiazem) should be avoided in HFpEF?
   a. True
   b. False
Session Code:

1. Write down the course code. Space has been provided in the daily program-at-a-glance sections of your program book.

2. To claim credit: Go to www.cshp.org/cpe before December 1, 2016.