Chronic Heart Failure: Update on Effective Monitoring and Treatment

Michael G. Shlipak, MD, MPH
Professor of Medicine, UCSF
Chief, Division of General Internal Medicine, SFVA Medical Center
August 12, 2016

Outline

- Diagnosis and Staging
- Diastolic Heart Failure
- Systolic Heart Failure Medications
- Devices and End-Stage Heart Failure

2013 ACCF/AHA Guideline for the Management of Heart Failure
A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines
CIRCULATION, 2013

2016 ACC/AHA/HFS
A Focused Update on New Pharmacological Therapy for Heart Failure
CIRCULATION, 2016

Heart Failure Epidemiology

- Only cardiovascular outcome that continues to increase
- Lifetime risk ~20%
- Complicated to manage with multiple other comorbidities
- Treatments improve survival and reduce morbidity substantially.
  - 5 classes of medications improve survival
  - 3 classes of medications improve symptoms
Why is Heart Failure Challenging to Manage?
- Patients are very complicated and often frail
- CHF travels with many other comorbidities:
  - CAD, hypertension, diabetes, CKD
- Polypharmacy
- Diastolic heart failure becoming more common

Question 1: Which of the following establishes a HF diagnosis?
- a. EF < 35% on echo
- b. BNP > 300 on blood test
- c. S3 on exam
- d. All of the above
- e. None of the above

Heart Failure is a Clinical Diagnosis
- **Essential Symptoms**: dyspnea, fatigue, orthopnea
- **Signs**: rales, edema, JVD, S3
- **Physical exam**: does not distinguish systolic vs. diastolic
- Helpful features include:
  - **Chest X-Ray**: pulmonary congestion
  - Elevated BNP or Nt-proBNP
  - Echo showing diastolic or systolic dysfunction

Diastolic vs. Systolic Heart Failure
- **Diastolic HF**:
  - Official term is “Heart Failure with Preserved Ejection Fraction”
  - Abbreviated as HFpEF
  - Pronounced “huff-puff”
- **Systolic HF**:
  - Official term is “Heart Failure with Reduced Ejection Fraction”
  - Abbreviated as HFrEF
  - Pronounced “huff-ruff”
NYHA Functional Classes

**Classes assume a prior diagnosis of heart failure**

I. No limitation on ordinary physical activity  
II. Slight limitation – ordinary physical activity  
III. Marked limitation- < ordinary physical activity  
IV. Symptoms or discomfort at rest

Problems with these classes:
- Patients vary across stages, going up and down
- All class 4 at time of hospitalization

AHA (2009) Classification of Heart Failure

A. **Risk factors** for heart failure- no clear signs/symptoms  
B. **Asymptomatic LV disease**- LVH, diastolic dysfunction, valve disease, low EF  
C. **Symptomatic heart failure**- dyspnea at rest or exertion, fluid retention  
D. **Advanced heart failure**- inotrope requirement, consideration for assist device or transplant  
  - Can only progress down the classes  
  - Emphasizes prevention over staging

Outline

- Diagnosis and Staging  
- **Diastolic Heart Failure**  
- Systolic Heart Failure Medications  
- Devices and End-Stage Heart Failure

Strategies that apply to all CHF Patients

- Initial ECHO  
- Repeat only if major changes  
- Salt restriction  
- Daily weight monitoring  
- Exercise  
- Diuretics for symptoms  
- Avoid NSAIDS  
- Monitor:  
  - Volume status  
  - Electrolytes, renal function
Question 2: Which of the following improve survival in diastolic heart failure?

a. ACE-I  
b. ARB’s  
c. Beta blockers  
d. Ca-channel blockers  
e. All of the above  
f. None of the above

**What is Diastolic Heart Failure?**

- "Stiff heart syndrome" - heart cannot relax in diastole to allow the left ventricle to fill
- Causes increased pressure in the left atrium, and pulmonary edema
- Defined by EF, yet actual stroke volume may be same as SHF
- Same signs and symptoms as systolic HF
- Especially common in women and elderly

**Diastolic HF: Good and Bad News**

**Good news:**
- More favorable prognosis than SHF
- Simpler regimen, as diuretics cornerstone of therapy

**Bad news:**
- Often progresses to SHF
- No therapies improve DHF survival

**ACC/AHA Guidelines for DHF Treatment**

- BP control (SBP < 130)
- Rate/rhythm control in AF
- Diuretics for pulmonary congestion
- Revascularization and other treatment for coronary ischemia
- European guideline recommends cardiac rehabilitation, though limited evidence
Outline

• Diagnosis and Staging
• Diastolic Heart Failure
• Systolic Heart Failure Medications
• Devices and End-Stage Heart Failure

ACE Inhibitors

• Improve symptoms and reduce hospitalizations
• Decrease mortality risk for all heart failure stages
• Class effect- all ACE inhibitors
• Aim for target dose (ATLAS finding)

Meta-Analysis of ACE Trials

• 30 RCTs- ACE-I vs. placebo
• Mortality
  - 0.77 (0.67-0.88)
• Death or hospitalization for heart failure
  - 0.65 (0.57-0.74)
• Specific ACE-I’s with benefits in RCT’s:
  - Benzapril -Enalapril -Ramipril
  - Captopril -Lisinopril

Kidney Function and ACE Inhibitors in Heart Failure

• Clinical trials show benefit if estimated GFR > 30
• No evidence for lower GFR levels
• Expect the creatinine to rise at least 30%
• Even creatinine doubling is OK- typically returns near baseline
• Worry about K increase (keep < 5.5); balance the K with diuretic dose.
• Continue ACE-Is as eGFR declines unless cannot control K.

Shlipak MG, Ann Intern Med 2003
**ARBs in Systolic Heart Failure**

- Generally equivalent to ACE inhibitors
- Use for patients with cough on ACE inhibitors
- Combination of ACE and ARB?
  - Decreases hospitalization risk; increases adverse effect risk (increased K)
  - No survival difference
  - Generally, not recommended, as safety probably lower in actual practice


---

**Question 3: What is an “ARNI”?**

A. A novel heart failure agent that slows down the SA node to allow greater ventricular filling
B. B. New class of heart failure drugs that prevents arrhythmias so patients will not require an ICD
C. C. A combination of an Angiotensin Receptor Blocker with a medication that blocks neprilysin
D. D. A novel beta-blocker that has the ability to increase ejection fraction
E. E. All of the above

---

**PARADIGM-HF Trial: Angiotensin-Receptor blocker/Neprilysin Inhibitor (ARNI) vs. Enalapril**

*The NEW ENGLAND JOURNAL of MEDICINE*

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

- John J.V. McMurray, M.D., Milena Fietkau, M.D., Mahdy S. Ostad, M.D., M.P.H., Jianlian Cao, Ph.D.
- Martin P. Lehmkuhl, M.D., Adiel R. Estahle, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D.,
- Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D.,
  for the PARADIGM-HF Investigators and Committees

**PARADIGM-HF Trial**

- N=8,442
- Class 2-4 HF symptoms
- EF< 40%
- The new drug:
  - LCZ696
  - Valsartan/Sacubitril
  - Entresto
  - 2015 FDA approval
- Sacubitril- blocks Neprilysin ➔
- ↓ vasoconstriction, ↓ Na retention, ↓ remodeling
- Prior ARNI- Omipatrilat (caused ↓ BP, angioedema, and cognitive dysfunction)
PARADIGM-HF Trial

Inclusion Criteria:
- EF < 40%
- BNP > 150
- Prior ACE/ARBs

Exclusion Criteria:
- SBP < 95
- eGFR < 30
- K > 5.2
- ACE/ARB angioedema

Baseline Characteristics of Patients

Mean Age 64
% Female 22%

Race
- White 66%
- Black 5%
- Asian 18%
- Other 11%

Mean BP 122/72
Mean Creatinine 1.12
% eGFR < 60 36%
Class 2 70%
Class 3 24%

Enrollment in 3 Phases

1.) Enalopril 10mg 2x/day: 2 weeks (N= 10,513)
   - 10% drop out (5.6%- adverse effects)

2.) LCZ696: 4 weeks (N=9,419)
   - 100 mg and 200 mg
   - 10% drop out (5.8%- adverse effect)

3.) RCT: Enalopril (10 mg 2x/day) vs. ARNI (200 mg 2x/day) (N=8,442)
   - trial stopped early
   - median follow-up 27 months

Medications

<table>
<thead>
<tr>
<th>Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE/ARB</td>
<td>100%</td>
</tr>
<tr>
<td>BB</td>
<td>93%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>80%</td>
</tr>
<tr>
<td>Aldo-Antagonist</td>
<td>55%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>30%</td>
</tr>
<tr>
<td>Devices</td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>15%</td>
</tr>
<tr>
<td>CRT</td>
<td>7%</td>
</tr>
</tbody>
</table>
**PARADIGM Trial**

*Primary and Secondary Outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N=4,187)</th>
<th>Enalapril (N=4,212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome – (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death or HF Hospitalization</td>
<td>21.8%</td>
<td>26.5%</td>
<td>0.80 (0.73-0.87)</td>
</tr>
<tr>
<td>Death</td>
<td>13.3%</td>
<td>16.5%</td>
<td>0.80 (0.71-0.89)</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>12.8%</td>
<td>15.6%</td>
<td>0.79 (0.71-0.89)</td>
</tr>
<tr>
<td>Secondary outcomes – (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>17.0%</td>
<td>19.8%</td>
<td>0.84 (0.76-0.93)</td>
</tr>
</tbody>
</table>

**PARADIGM Trial**

*Adverse Events during Randomized Treatment*

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N=4,187)</th>
<th>Enalapril (N=4,212)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Symptomatic</td>
<td>14.0%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>≥2.5 mg/dl</td>
<td>3.3%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td>&gt;6.0 mmol/liter</td>
<td>4.3%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Cough</td>
<td>11.3%</td>
<td>14.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema</td>
<td>0.5%</td>
<td>0.2%</td>
<td>0.19</td>
</tr>
</tbody>
</table>

**Controversies around Entresto**

- Cost- $4,560/year
  - Pay for performance models?
- Single trial
  - Only 5% Blacks
  - Low % with devices
  - Run in period required tolerance to the drug
- Potential “off target” effects?
  - Hypotension
  - Cognitive decline a concern (with Omipatrilat)

**Recommendations around Entresto**

**Recommendations**

1.) Class 1 agent for systolic HF
2.) For use in patients who are stable on maximum ACE or ARB
3.) Never use in combination with ACE or ARB
Beta Blockers in Systolic Heart Failure

- Beta blockers improve symptoms and increase ejection fraction by 5-10%
- Beta blockers decrease mortality in systolic heart failure, from both pump failure and arrhythmic causes
- Unlike ACE inhibitors, not a class effect
- Metoprolol or Carvedilol (U.S.)
- Bisoprolol in Europe

Heart Failure Survival

![Graph showing relative risk reductions and 95% confidence intervals](image)

Challenge of Titrating Beta Blockers in Heart Failure Patients

- Both metoprolol and carvedilol require subtle dose increases at 2 week intervals
- Can take up to 6 visits to reach target
- Hypo-tension is not a contra-indication unless symptomatic (even if SBP<90)
- Carvedilol may be more difficult to titrate dose up.
- Benefit greatest at maximum dose
- Unfortunately, many patients left at the low starting dose

Other Therapies in Systolic Heart Failure

- Diuretics
- Aldosterone Antagonists- spironolactone, eplerenone
- Hydralazine/Nitrates
- Invabradine

Ramani G et al., Mayo Clin Proc 2010
**Diuretics**
- Rapid relief of dyspnea and fluid retention
- Aim for lowest dose that reaches “dry weight”
- Therapeutic goals:
  - Improved dyspnea and orthopnea
  - Minimal pre-tibial edema
- Patients can manage the dose and schedule

**Diuretic Refractory Patients**
- Periodic thiazide (metolazone)
  - e.g. 3x/week doses
  - watch for hypo-Na+, hypo-K+
- Change the loop diuretic- furosemide (Lasix), bumetanide (Bumex), Torsemide (Demadex)
- Long-acting nitrates also useful for symptoms
- Occasional IV diuretics may be required- intestinal edema can block po absorption

**Aldosterone Antagonists**
(spironolactone, eplerenone)
- Improve survival and reduce hospitalization- RALES trial
- Only studied in NYHA class 3-4 heart failure patients on ACE inhibitors
- K allowed up to 5.6; very few hyper-K complications
- 1/3 on beta blockers

**Enormous Rise in Spironolactone Use**

**Rales Trial**

HR = 0.70

Pitt B. et al., NEJM 1999

Juurlink DN et al., NEJM 2004
Epidemic of Hyper-K Followed

![Graph showing the rate of hospital admissions for hyperkalemia among patients receiving ACE inhibitors.](image)

Juurlink DN et al., NEJM 2004

What Happened?

- It’s in the fine print...
- RALES methods- inclusion if patients Cr < 2.5
- 2005 AHA Guidelines- spironolactone recommended in NYHA III heart failure if Cr < 2.5
- RALES table 1- actual Cr levels 1.2 ± 0.3
  - ~80% had Cr ≤ 1.5
  - ~ all had Cr < 2.0
  - average furosemide dose of 80mg

Shlipak MG et al., Ann Intern Med 2003

Case Details of Hyper-K on Spironolactone

- Case reviews of critical or fatal hyper-K (≥ 6.5) Schepkers et al., Am J Med 2001
- Mean Cr of 2.1; all on ACE-I also
- Often in setting of other illness- decreased oral intake
- Lessons learned:
  - Caution in using spironolactone if eGFR < 45, or Cr ≥1.5
  - Stop spironolactone in acute illness

Guideline Recommendations on Aldosterone Antagonists

- AHA HF guidelines (2005, 2009, 2013) have vacillated on aldosterone antagonists
  AHA Class I:
  - Recommended for HF patients EF< 35%
  - eGFR> 30; K < 5.0
  AHA Class III (harmful):
  - eGFR< 30, K > 5.0
  **My recommendation:** Use extreme caution if eGFR 30-45
  - QOD dosing: cutting dose by 1/2
  - Advise patients to stop using when PO intake is reduced or acutely ill
Hydralazine and Nitrites


• 1,040 African American patients
• Hydralazine vs. Placebo
• Trial halted early
• HR= 0.57, p= 0.01

Hydralazine/Nitrates

• Recommended (Class I) for “self-described” African Americans
  – Reduced EF
  – Class III/IV symptoms
  – Already treated with ACE, BB
• Consider (Class 2A) in patients who cannot tolerate ACE/ARB

Ivabradine (Corlanor)

SHIFT Trial

• New class of HF drug
• Slows HR at SA node (I_f current)
• Patients EF<35%, HR>70, on BB
• Results:
  – ↓ HF Hospitalization: 16% vs 21% (0.74; 0.66-0.8)
  – No difference in mortality risk
• AHA recommendation: class 2A for patients with HF and EF<35%
• Opinion: no clear role for this drug in most patients

Outline

• Diagnosis and Staging
• Diastolic Heart Failure
• Systolic Heart Failure Medications
• Devices and End-Stage Heart Failure
Rationale for Implantable Cardiac Defibrillators (ICDs) in CHF

- Ventricular arrhythmia - common cause of heart failure death
- ICDs can reverse VT/VF and save the patient
- VT/VF risk is highest in end-stage CHF patients; but those patients unlikely to survive to gain benefit
- Challenge for selecting ambulatory patients for ICDs:
  - VT/VF risk high enough to benefit
  - CHF moderate, so patient might live a few years

ICD’s in Secondary Prevention

- Studied in Systolic HF patients
- Patients who survived prior sudden death or unstable VT event
- ICD’s clearly improve survival
- Must be consistent with goals of care for patient/family – critical role for the PCP

ICDs in Primary Prevention

- Risk/benefit tradeoff
- Recommended for patients with EF < 35% AND:
  - moderate HF symptoms on appropriate treatment
  - expectation of survival > 1 year
  - Not for class 4 HF - prognosis too poor to benefit, unless as a bridge to transplant
- Prior MI patients appear to have higher SCD risk, among those with Systolic HF

Rationale for CRT (Cardiac Resynchronization Therapy)

- Cardiac dys-synchrony:
  - Concern in patients with EF< 35%
  - RV and LV may not be in harmony
  - Suspect dysynchrony in patients with persistent symptoms despite ideal treatment
- Causes: decrease ventricle filling, decrease EF, increase MR
- CRT: activates LV/RV together with bi-ventricular pacer
- Meta-analysis:
  - decrease in mortality by 25%
  - detectable after 3 months McAlister FA, JACC 2004
Ideal Candidates for CRT

- EF < 35% and persistent symptoms
- 3 additional ECG criteria:
  - Sinus rhythm
  - LBBB
  - QRS > 150mg
- Class I: all 3 ECG criteria
- Class 2A: 2 of 3 ECG criteria
- Class 2B: 1 of 3 ECG criteria

End-Stage Heart Failure

**European Definition of Class D/Advanced HF**
- Severe symptoms at rest or with minimal exertion
- Hospitalized in last 6 months
- Treatment already optimized
- Poor functional status

**Clinical correlates of Advanced HF**
- Weight loss
- Worsening kidney function
- SBP<90
- Intolerance to ACE and/or BB
- Na<133
- Increasing diuretic requirement
- Frequent ICD shocks

Additional Support for End-Stage Heart Failure Patients

Consider:

- Specialized strategies (HF specialist):
  - Mechanical circulatory support
  - Inotrope infusions
  - Transplant or surgery referral

- Hospice/End-of-Life Care (Palliative care)
  - Comfort care
  - Turn off the ICD

Thank you! Any Questions?