Update on Heart Failure

R. Craig Long, MD, PharmD
Assistant Professor of Medicine
Advanced Heart Failure and Transplant Cardiology

Medical Director: Mechanical Circulatory Support Program
Disclosures

- I have no financial disclosures related to this talk/topic
Objectives

• Review epidemiology and burden of heart failure

• Review recent ACC/AHA Heart Failure Guideline Updates
  - Biomarkers
  - New Medications

• Discuss some practical aspects of caring for a HF patient
Abbreviations

- **HFrEF** (heart failure reduced ejection fraction AKA systolic heart failure)
- **HFpEF** (heart failure preserved ejection fraction AKA diastolic heart failure)
- **ACEi** (Angiotensin converting enzyme inhibitor)
- **ARB** (angiotensin receptor blocker)
- **ARNI** (angiotensin receptor neprilysin inhibitor)
I regularly see patients with heart failure in my practice?

A. YES
B. NO
The U.S. Heart Failure Epidemic

- About 6.5 million Americans have HF
- ~960,000 new HF diagnoses each year
- About 1 million HF hospitalization in US each year
- The lifetime risk of developing HF is ~ 1 in 5 (NHLBI)
- About half of people who develop heart failure die within 5 years of diagnosis
- HF is the final common pathway for all cardiac diseases!
MS-highest rate of mortality due to heart failure. ~65 per 100,000 (over 18 yo) which is over twice the national average of 28 per 100,000
Heart Failure Care

• Consumes significant health care resources
  - More Medicare dollars than any other diagnosis

• Significant morbidity and mortality
• Greatly impacts quality of life
Costs of HF Care

- Total annual medical care cost for HF estimated to be $20.9 billion annually.
- By 2030, cost of HF care is projected to increase to $53.1 billion.

Figure 1. The projected increase in direct and indirect costs attributable to HF from 2012 to 2030 is displayed. Direct costs (cost of medical care) are expected to increase at a faster rate than indirect costs because of lost productivity and early mortality. HF indicates heart failure.
Case

- 55 yo woman with nonischemic CMP (EF 25%) presents with 4 week hx of worsening DOE/fatigue, orthopnea/PND and LE swelling

- Home Meds
  - Carvedilol 25 mg bid
  - Lisinopril 40mg daily
  - Spironolactone 25 mg daily
  - Furosemide 80 mg po bid

- Exam: Edema to knees
  - weight up 10 lbs from prior visit
  - S3 noted
  - JVP ~ 12 cm
Case Continued.....

- Labs
  - Na 135
  - K 3.8
  - BUN 32  (14 two months ago)
  - Cr 1.8   (1.2  two months ago)
  - proBNP 1400 (800 two months ago)

- Admitted to hospital for IV diuresis
After hospitalization for heart failure, what is the estimated 1 year mortality rate?

A. 5%
B. 10%
C. 20%
D. 40%
E. 60%
Heart Failure has a Poor Prognosis

• Survival after diagnosis has improved over time; however, the death rate remains high

50% of patients diagnosed with heart failure will die within 5 years.¹

35.8% of patients hospitalized for heart failure die within 1 year of hospital discharge.²

² Dhamarajan, K et al. Trajectories of risk after hospitalization for heart failure, acute myocardial infarction, or pneumonia: retrospective cohort study. BMJ 2015; 350: h411
Repeatepd hospitalizations predict mortality in the community population with heart failure

Soko Setoguchi, MD, DrPH,a Lynne Warner Stevenson, MD,b and Sebastian Schneeweiss, MD, ScD a Boston, MA

Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.
Heart Failure Patient Care

• More involved than ever
• Current care for HFrEF includes no fewer than:
  - 7 evidence based medications
  - 3 evidence based device strategies
• Opportunity to change natural history of HFrEF has never been better
MORE CHOICES

= 

GREATER COMPLEXITY
GUIDELINE UPDATES

Yancy, et. al.
2017 ACC/AHA/HFSA Heart Failure Focused Update

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration with the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

JACC VOL. 68, NO. 13, 2016
SEPTEMBER 27, 2016:1476-88
In Press, Accepted Manuscript, Available online 28 April 2017
Table 1. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)
CASE

- 35 yo woman with no known PMH presents to your office with CC of shortness of breath
- Had a “cold” about 2 months ago and initially got better but since that time has had a cough and DOE
- Has been seen in ED and Urgent care clinics and currently is on antihistamine and albuterol inhaler (has been told she has allergies and bronchitis)
Measurement of which of the following biomarkers is useful to support a diagnosis or exclusion of heart failure?

A. Troponin
B. Natriuretic peptide
C. Galectin
D. Soluble ST2 Receptor
Natriuretic peptides

• Assist in diagnosis or exclusion of HF as cause of symptoms
  - chronic HF
  - acute decompensated HF
• Role in population screening for HF is emerging
• Useful for establishing prognosis or disease severity in chronic HF
Selected Potential Causes of elevated natriuretic peptide levels

**Cardiac**
- HF, including RV syndromes
- Acute coronary syndromes
- Heart muscle disease, including LVH
- Valvular heart disease
- Pericardial disease
- Atrial fibrillation
- Myocarditis
- Cardiac surgery
- Cardioversion
- Toxic-metabolic myocardial insults, including cancer chemotherapy

**Noncardiac**
- Advancing age
- Anemia
- Renal failure
- Pulmonary: obstructive sleep apnea, severe pneumonia
- Pulmonary hypertension
- Critical illness
- Bacterial sepsis
- Severe burns
Staging of Heart Failure

New York Heart Association Classification

IV

ACC/AHA Staging

D
Refractory End-Stage HF
Marked symptoms at rest despite maximal medical therapy

C
Symptomatic HF
Known structural heart disease
Shortness of breath and fatigue
Reduced exercise tolerance

B
Asymptomatic HF
Previous MI
LV systolic dysfunction
Asymptomatic valvular disease

A
High Risk for Developing HF
Hypertension
CAD
Diabetes mellitus
Family history of cardiomyopathy
### Biomarkers: Recommendation for Prevention of HF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>For patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF (85, 86).</td>
<td>NEW: New data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF.</td>
</tr>
</tbody>
</table>

See Online Data Supplements A and B.

### Biomarkers: Recommendation for Diagnosis

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF (15-24, 28-30).</td>
<td>MODIFIED: 2013 acute and chronic recommendations have been combined into a diagnosis section.</td>
</tr>
</tbody>
</table>

See Online Data Supplements A and B.

### Biomarkers: Recommendations for Prognosis

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (16, 87-92).</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF (27, 93-100).</td>
<td>MODIFIED: Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers that are useful.</td>
</tr>
</tbody>
</table>
- Troponin, galectin-3, soluble ST2 receptor

- “A combination of biomarkers may ultimately prove to be more informative than single biomarkers”
Figure 1. Biomarkers Indications for Use

- **ACC/AHA Stage A/B HF**
  - Prevention: BNP or NT-proBNP (COR IIa)
  - Diagnosis: BNP or NT-proBNP (COR I)
  - Prognosis or added risk stratification: Other biomarkers of myocardial injury or fibrosis* (COR IIb)

- **ACC/AHA Stage C/D HF**
  - Prevention: BNP or NT-proBNP (COR IIa)
  - Diagnosis: BNP or NT-proBNP (COR I)
  - Prognosis or added risk stratification: Other biomarkers of myocardial injury or fibrosis* (COR IIb)

- **ACC/AHA Acute/Hospitalized HF**
  - Prevention: BNP or NT-proBNP (COR I)
  - Diagnosis: BNP or NT-proBNP, and cardiac troponin (COR I)
  - Prognosis or added risk stratification: PredischARGE BNP or NT-proBNP (COR IIa)

*Denotes biomarkers of myocardial injury or fibrosis.
Patient Case

• 40 year old white man with no known PMH before being diagnosed with systolic HF 6 months ago
• Improved to NYHA class II with initial therapy
  - Furosemide 40 mg bid
  - Carvedilol 12.5 mg bid
  - Spironolactone 25 mg daily
  - Stopped taking enalapril 5 mg bid due to dry cough
• Physical Exam
  - BP 116/70, HR 68
  - JVP 6 cm H2O, lungs clear, no edema, +S3 gallop
• Creatinine 1.4, K 4.1, proBNP 1250
• Echo - LVEF 20%, mod LVE, mild MR
• Cardiac MRI - no ischemia, infarction, inflammation or infiltration, EF 22%, mild MR
What therapy would you now recommend?

A. digoxin 0.125 mg q day
B. valsartan 40 mg bid
C. lisinopril 10 mg q day
D. sacubitril/valsartan 24/26 mg bid
E. no change in medications
## 2016 ACC/AHA/HFSA Guideline Update

### Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (<em>Level of Evidence: A</em>) (9-14), <strong>OR</strong> ARBs (<em>Level of Evidence: A</em>) (15-18), <strong>OR</strong> ARNI (<em>Level of Evidence: B-R</em>) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFREF to reduce morbidity and mortality.</td>
</tr>
</tbody>
</table>

**ARNI-** angiotensin receptor neprilysin inhibitor

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**UMMC University Heart**
2016 ESC HF Guidelines
Is “Stable” HF really stable?

Patients with mild symptoms and physical limitations (NYHA class II) were still at risk

69% of patients randomized to enalapril were NYHA class II¹ (n=2921/4212)

25.4% of these NYHA class II patients experienced CV death or HF hospitalization² (n=742/2921)

Patients with no prior history of HF hospitalization were still at risk

37% of patients randomized to enalapril had no prior history of HF hospitalization¹ (n=1545/4212)

22.5% of these patients experienced CV death or HF hospitalization² (n=348/1545)

Angiotensin–Nepriylysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, 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*

N ENGL J MED 371;11   NEJM.ORG   SEPTEMBER 11, 2014

- Entresto®- chemical combination of valsartan and sacubitril (a nepriylysin inhibitor)
Neprilysin

- Neutral endopeptidase
- Degrades several endogenous vasoactive peptides
  - Natriuretic peptides (ANP/BNP)
  - Bradykinin
  - Adrenomedullin
- Inhibition of neprilysin increases level of the above which counters the neurohormonal activation
- Neprilysin also degrades beta-amyloid in the brain
PARADIGM-HF: Study Design

NYHA class II-IV
LVEF < 35-40%

Randomization

Single-blind run-in period

Double-blind period

LCZ696 200 mg BID

(1:1 randomization)

Enalapril 10 mg BID

Enalapril

10 mg BID

100 mg BID

200 mg BID

2 weeks

1-2 weeks

2-4 weeks
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Enalapril (n=4212)

LCZ696 (n=4187)

HR = 0.80 (0.73-0.87)

P = 0.0000002

Number needed to treat = 21

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>249</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>236</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>896</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>853</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>1544</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>853</td>
<td>1488</td>
<td>1488</td>
</tr>
</tbody>
</table>
**PARADIGM-HF: Cardiovascular Death**

HR = 0.80 (0.71-0.89)  
P = 0.00004  
Number need to treat = 32

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696</td>
<td>4187 4056 3891 3282 2478 1716 1005 280</td>
</tr>
<tr>
<td>Enalapril</td>
<td>4212 4051 3860 3231 2410 1726 994 279</td>
</tr>
</tbody>
</table>
## PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>449 (10.3)</td>
<td>516 (12.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29 (0.7)</td>
<td>59 (1.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Angioedema (adjudicated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications, no hospitalization</td>
<td>16</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>----</td>
</tr>
</tbody>
</table>
Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
PARADIGM-HF Actuarial Analysis

Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure

Gregg C. Fonarow, MD; Adrian F. Hernandez, MD, MHS; Scott D. Solomon, MD; Clyde W. Yancy, MD

Table. Demonstrated Benefits of Evidence-Based Therapies for Patients With Heart Failure and Reduced Ejection Fraction

<table>
<thead>
<tr>
<th>Evidence-Based Therapy</th>
<th>Relative Risk Reduction in All-Cause Mortality in Pivotal Randomized Clinical Trial(s), %</th>
<th>NNT to Prevent All-Cause Mortality Over Time</th>
<th>NNT for All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17</td>
<td>22 over 42 mo</td>
<td>77</td>
</tr>
<tr>
<td>ARNI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16</td>
<td>36 over 27 mo</td>
<td>80</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>34</td>
<td>28 over 12 mo</td>
<td>28</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30</td>
<td>9 over 24 mo</td>
<td>18</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>25 over 10 mo</td>
<td>21</td>
</tr>
<tr>
<td>CRT</td>
<td>36</td>
<td>12 over 24 mo</td>
<td>24</td>
</tr>
<tr>
<td>ICD</td>
<td>23</td>
<td>14 over 60 mo</td>
<td>70</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; NNT, number needed to treat.

<sup>a</sup> Standardized to 12 months.

<sup>b</sup> Benefit of ARNI therapy incremental to that achieved with ACEI therapy. For the other medications shown, the benefits are based on comparisons to placebo control.
RESULTS Of 2 736 000 patients with HFrEF patients in the United States, 2 287 296 (84%) were projected to be candidates for ARNI therapy. Optimal implementation of ARNI therapy was empirically estimated to prevent 28 484 deaths a year (range, 18 230-41 017 deaths per year).
Points to remember about ARNI

• Use increases BNP levels but not NT-proBNP levels
• When changing from ACE inhibitor must have 36 hour “washout”
• Keep cost of therapy to patient in mind
Patient Case

• 63 year old Hispanic woman with Type 2 DM, HTN, dyslipidemia
• Remote anterior MI with LAD stent (single vessel CAD)
• Hospitalized for HF 3 months ago; now with NYHA class II-III fatigue > dyspnea; no angina
• MEDS:
  - furosemide 60 mg bid
  - metoprolol succinate 50 mg daily
  - spironolactone 50 mg daily
  - sacubitril / valsartan 97/103 mg bid
  - ASA 81 mg daily
  - atorvastatin 80 mg q day
Patient Case (cont)

- BP 96/68, P 85
- JVP 5 cm H2O, lungs clear, regular rhythm, II/VI HSM at apex, +S3 gallop, no edema
- Creatinine 1.7, K 4.5, proBNP 987
- Echo - LVEF 20%, mod LVE with anteroapical akinesis, mod MR, mild TR, RVSP 50
What therapy would you now consider/recommend?

A. Decrease sacubitril / valsartan to 49/51 mg bid
B. Increase metoprolol succinate to 100 mg daily
C. Add isosorbide dinitrate / hydralazine 20/37.5 mg tid
D. Add ivabradine 5 mg bid with meals
E. No change in medications
Ivabradine

- Selective $I_f$ current of the sinoatrial node providing HR reduction
ivabradine

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>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 (37-40).</td>
</tr>
</tbody>
</table>
Ivabradine (Corlanor)

- Has been shown to reduce HF hospitalizations compared to placebo
- BUT did not show reduction in all cause mortality
Patient with symptomatic HFrEF

Therapy with ACE-I\(^c\) and beta-blocker (Up-titrate to maximum tolerated evidence-based doses)

- Still symptomatic and LVEF ≤35%
  - No
  - Yes

Add MR antagonist\(^{d,e}\) (up-titrate to maximum tolerated evidence-based dose)

- Still symptomatic and LVEF ≤35%
  - No
  - Yes

Diuretics to relieve symptoms and signs of congestion

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

Able to tolerate ACEI (or ARB)\(^g\)

- ARNI to replace ACE-I

- Evaluate need for CRT\(^h\)

Sinus rhythm, QRS duration ≥130 msec

- Sinus rhythm, HR ≥70 bpm

- Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

- Yes
  - Consider digoxin or H-ISDN or LVAD, or heart transplantation

- No
  - No further action required

Consider reducing diuretic dose
Ivabradine Contraindications

- Acute decompensated heart failure
- Blood pressure < 90/50 mmHg
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present
- Resting heart rate < 60 bpm prior to treatment
- Severe hepatic impairment
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker)
- Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors
- Pregnancy and lactation
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators*

www.thelancet.com  Vol 376  September 11, 2010
Primary composite endpoint (CV death or hospital admission for worsening HF)

- Placebo (937 events)
- Ivabradine (793 events)

HR 0.82 (95% CI 0.75-0.90), p<0.0001

18% reduction
Hospitalization for HF

Placebo (672 events)
Ivabradine (514 events)

HR 0.74 (95% CI 0.66–0.83), p<0.0001

26% reduction
1st HF admissions on GDMT in SHIFT
Effect of Resting HR

Randomized, double-blind, placebo-controlled, multinational study in 6,505 patients with symptomatic HF on standard of care including beta blockers and LVEF ≤ 35% and in sinus rhythm with heart rates of ≥ 70 bpm
Incidence of selected adverse events (n = 6492) in SHIFT trial

<table>
<thead>
<tr>
<th>Patients with an event</th>
<th>Ivabradine</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All serious adverse events</strong></td>
<td>N=3232, n (%)</td>
<td>N=3260, n (%)</td>
<td></td>
</tr>
<tr>
<td>All serious adverse events</td>
<td>1450 (45%)</td>
<td>1553 (48%)</td>
<td>0.025</td>
</tr>
<tr>
<td>All adverse events</td>
<td>2439 (75%)</td>
<td>2423 (74%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5%)</td>
<td>32 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6%)</td>
<td>48 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>306 (9%)</td>
<td>251 (8%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>89 (3%)</td>
<td>17 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>17 (1%)</td>
<td>7 (&lt;1%)</td>
<td>0.042</td>
</tr>
</tbody>
</table>
Maximizing Medical Therapy

- Beta-blockers consistently shown to reduce morbidity and mortality from HFrEF
- New agent approved to target further HR lowering in patients on “maximally tolerated B-blocker dose”
FIGURE 1  Percentage of Target β-Blocker Dose Achieved in Major Clinical Trials and Registries

Mean Daily Dose as Percent of Target Dose (%)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Bisoprolol</th>
<th>Carvedilol</th>
<th>Metoprolol Succinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS-II (1999)</td>
<td>60%</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>SHIFT (2010)</td>
<td>70%</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>CIBIS-ELD (2011)</td>
<td>60%</td>
<td>60%</td>
<td>70%</td>
</tr>
<tr>
<td>USCS (1996)</td>
<td>90%</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>COPERNICUS (2001)</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>COMET (2003)</td>
<td>70%</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>HF-ACTION (2009)*</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>COHERE (2007)</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>SHIFT (2010)</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>CIBIS-ELD (2011)</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>OPTIMIZE-HF (2008)</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>MERIT-HF (1999)</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Legend:
- **Landmark B-Blocker Trials**
- **Registries/Newer Trials**
### Table 3. Drugs Commonly Used for HFrEF (Stage C HF)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Doses(s)</th>
<th>Mean Doses Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg QD</td>
<td>10 mg QD</td>
<td>8.6 mg QD</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg BID</td>
<td>50 mg BID</td>
<td>37 mg QD</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg QD</td>
<td>80 mg QD</td>
<td>N/A</td>
</tr>
<tr>
<td>Metoprolol succinate extended release (metoprolol CR/XL)</td>
<td>12.5–25 mg QD</td>
<td>200 mg QD</td>
<td>159 mg QD</td>
</tr>
</tbody>
</table>
Why don’t we obtain target B blocker dose?

- “Intolerance”
  - Trials were selective
  - Provider aversion “too many meds”
  - Therapeutic inertia
  - Real or perceived undesired side effects
  - Clinically significant adverse effects

- Leads to:
  - Reluctance to initiate
  - Slowed or early-terminated uptitration
  - Down-titration
  - Discontinuation
B Blocker Intolerance

- Worsening HF symptoms
- Bradycardia
- Hypotension/orthostasis
- Fatigue
CENTRAL ILLUSTRATION: Clinical Algorithm for Up-Titration of β-Blockers

Patient with HF and left ventricular ejection fraction (LVEF) < 40%

Does patient have contradictions to β-blockers?
(Cardiogenic shock, symptomatic bradycardia, 2nd degree/3rd degree heart block)

Initiate and uptitrate β-blocker
(Double dose no more frequently than every 2 weeks; use specialized nurse facilitators)

- Metoprolol XL
  - Initial dose: 12.5-25 mg daily
  - Target dose: 200 mg daily
- Carvedilol
  - Initial: 6.25-12.5 mg twice daily
  - Target: 25 mg twice daily
- Bisoprolol
  - Initial: 1.25 mg daily
  - Target: 10 mg daily

Is patient intolerant of increased dose?
(Worsening HF, bradycardia, hypotension, fatigue)

Achieve a maximally tolerated dose

- Does patient have LVEF ≤ 35%, sinus rhythm and heart rate ≥ 70 bpm?
  - Y: Consider initiation of ivabradine

Strategies to increase tolerance:
- Decrease diuretic dose if volume depleted
- In-class switching
- Minimize other AVN blockers
- Reduce calcium channel blocker dose

β-blocker therapy not appropriate until conditions no longer persist

Regularly assess patient eligibility

Barriers to Medication Optimization

• 20-30% of prescriptions are never filled
• 50% of meds for chronic disease are not taken as prescribed

• Not “natural”
• Reminds patients they are “sick”
• Don’t feel any different when they stop taking their medicine

• Cost
  - Copays/out of pocket
Barriers to Medication Titration

- Abnormal renal function
- Hyperkalemia
- Fatigue
- “low” blood pressure

- Keep in mind that some side effects can be difficult to distinguish from HF symptoms
  - In beta blocker trials, fatigue was reported in 23% of pts on beta blockers and 22% of pts taking placebo
Patient Case

• 25 yo black man with niCMP seen in office.
  - SOB with less than one flight of stairs
  - MEDS
    ▪ Carvedilol 25 mg bid
    ▪ Lisinopril 40mg bid
    ▪ Furosemide 80mg bid
    ▪ Spironolactone 25mg daily
  - BP 150/100 (home SBP 145-160 mmHg), HR 78, JVP ~8 cm H2O, LEs warm with no edema
Which of the following is the most appropriate in his care?

A. Add candesartan 4 mg daily
B. Add isosorbide dinitrate 20mg/hydralazine 37.5 mg tid
C. Change lisinopril to sacubatril/valsartan 24/26 mg bid
D. Start clonidine 0.1 mg bid
E. Start diltiazem sustained release 120mg daily
Indications for nitrates and hydralazine in chronic systolic HF

2013 ACC/AHA HF Guidelines

Hydralazine and isosorbide dinitrate

The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III–IV HF/EF on GDMT

A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF/EF who cannot be given ACE inhibitors or ARBs
Figure 2. Treatment of HFrEF Stage C and D

Step 1: Establish Dx of HFrEF, NYHA class II–IV, provided est. CrCl > 30 mL/min & K+ < 5.0 mEq/L

- NYHA class II–III, LVEF ≤ 35%; (caveat: > 1 y survival, > 40 d post MI)
  - HFrEF NYHA class I–II (Stage C)
  - ACEI or ARB AN GDMT beta blockers as needed (COR I)

- NYHA class II–IV, LVEF ≤ 35%, NSR & QRS ≥ 150 ms with LBBB pattern
  - Palliative care‡ (COR I)
  - Transplant‡ (COR I)

- NYHA class II–III, NSR heart rate ≥ 70 bpm on maximally tolerated dose beta blocker
  - Refractory NYHA class III–IV (Stage D)
  - Symptoms improved
  - LVAD‡ (COR IIa)

- Investigational studies§

Continue GDMT with serial reassessment & optimized dosing/adherence
Decision Making in Advanced Heart Failure

A Scientific Statement From the American Heart Association

Circulation  April 17, 2012

Transition to Advanced Heart Failure:
- Oral therapies failing
- A time for many major decisions
- Consider MCS and/or transplantation, if eligible
- Consider inversion of care plan to one dominated by a palliative approach, which may involve formal hospice
How do I tell if my patient has Advanced HF?

Table 24. Clinical Events and Findings Useful for Identifying Patients With Advanced HF

- Repeated (≥2) hospitalizations or ED visits for HF in the past year
- Progressive deterioration in renal function (eg, rise in BUN and creatinine)
- Weight loss without other cause (eg, cardiac cachexia)
- Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
- Intolerance to beta blockers due to worsening HF or hypotension
- Frequent systolic blood pressure <90 mm Hg
- Persistent dyspnea with dressing or bathing requiring rest
- Inability to walk 1 block on the level ground due to dyspnea or fatigue
- Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d and/or use of supplemental metolazone therapy
- Progressive decline in serum sodium, usually to <133 mEq/L
- Frequent ICD shocks

ACE indicates angiotensin-converting enzyme; BUN, blood urea nitrogen; ED, emergency department; HF, heart failure; and ICD, implantable cardioverter-defibrillator.
What does a LVAD patient look like?

- Couldn’t walk 5 feet before stopping
- Implant Date: 11/15/2013
LVAD Patient

Multiple hospital admissions

Very poor hemodynamics

Could do ADLs but unable to do much more without severe fatigue
2 months after implant
What does a heart transplant patient look like?
### 7.3.3. Pharmacological Treatment for Stage C HFpEF: Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Stage C HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COR</strong></td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>IIa</td>
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<tr>
<td>IIa</td>
</tr>
<tr>
<td>IIa</td>
</tr>
<tr>
<td>IIb</td>
</tr>
</tbody>
</table>

See Online Data Supplement C.
What about that other type of HF?

• HFpEF (preserved EF HF)
  - Control BP
  - Diuretics for volume overload
  - Treat ischemia
  - Treat atrial fibrillation

In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations (83, 166, 167).

NEW: Current recommendation reflects new RCT data.

Mechanistic studies have suggested that mineralocorticoid receptor antagonists can improve measures of diastolic function in patients with HFpEF, possibly by a similar effect on remodeling (83, 168).

The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial (166) investigated the effects of spironolactone on a combined endpoint of death, aborted cardiac death, and HF hospitalization in patients with HFpEF. A small reduction (HR=0.89) in this composite endpoint did not reach statistical significance, although HF hospitalization was reduced (HR=0.83); known side effects of hyperkalemia and rising creatinine were seen more commonly in the treatment group (166). An unusual amount of regional variation was seen in this trial, prompting a post-hoc analysis (167) that showed that rates of the primary endpoint were 4-fold lower in Russia/Georgia than in North America and South America (the Americas). Rates in the Americas were comparable to those in other HFpEF trials (169, 170). The post-hoc analysis showed efficacy in the Americas (HR=0.83) but not in Russia/Georgia (HR=1.10). Moreover, a sample of the Russia/Georgia population, despite having been in the active treatment arm, had nondetectable levels of the metabolite of spironolactone. These post-hoc analyses have significant limitations, but they suggest that in appropriately selected patients with symptomatic HFpEF (with ejection fraction [EF] ≥45%, elevated BNP level or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min creatinine <2.5 mg/dL, and potassium <5.0 mEq/L), particularly in those with elevated BNP levels, use of spironolactone might be considered with close monitoring of potassium and renal function. Confirmatory studies are required.
Conclusions

• HF is not going anywhere
• Care of the HF patient is becoming more complex with more options available for individualizing
• Medications can make huge impact on patient outcomes
• New medications are being explored and other advancements may be available to help your patients “Turn Heart Failure into Heart Success”
Thank You/Questions