Contemporary Management of Heart Failure

Greg Lewis, MD
Section Head, Heart Failure
Medical Director, Cardiac Transplantation
Director, Cardiopulmonary Exercise Testing Laboratory
glewis@partners.org
2017 Heart Failure Epidemiology

- At age 40, lifetime risk of developing HF is 20%, >900,000 new cases per year

- >1 million annual hospitalizations
  - Case fatality following HF hospitalization
    - 10% at 30 days
    - 22% at 1 year

- >1.7 million office visits
  - (1.7:1 ratio vs. 7:1 ratio for CHD)

- Cost: 2012: $21 billion
  2030: $70 billion ($244/US citizen)

American Heart Association 2017 Heart and Stroke Statistical Update
Mozaffarian et al, Circulation 2017
Heart Failure Prevalence

- 300 Million US Population
  - HF = 2.6% Population* or 7 Million Total

- 45-50% Preserved Systolic Function 3.0-3.5 M
- 50-55% Systolic HF 3.0-3.5 Million

- Class III B 100-150,000
- Class IV 75-150,000
- Class III B+IV < 75 yrs 150-250,000 Pts

- 35% Class I
- 35% Class II
- 25% Class III (5-10% III B)
- 2-5% Class IV
ACC/AHA Staging of Heart Failure Patients

**At Risk for Heart Failure**

**Stage A**
At high risk for HF, but without structural heart disease or symptoms of HF

**Stage B**
Structural heart disease, but without signs or symptoms of HF

**Stage C**
Development of symptoms of HF

**Stage D**
Refractory HF requiring specialized interventions

**Patients with:**
- HTN
- Atherosclerotic disease
- DM
- Obesity
- Metabolic syndrome
- Or
- Patients using cardiotoxins with FHx CM

**NYHA I**

**Patients with:**
- previous MI
- LV remodeling, including LVH and low EF
- asymptomatic valvular disease

**NYHA II-III**

**Patients with:**
- known structural heart disease and
- shortness of breath and fatigue, reduced exercise tolerance

**NYHA IV**

DM=diabetes mellitus; HTN=hypertension; LV=left ventricular; FHx= family history; CM=cardiomyopathy

### Does My Patient Have Heart Failure?

**Definition of Heart Failure**

- Heart Failure Definition: **Clinical syndrome** that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
  - Framingham Criteria: 2 MAJOR or 1 MAJOR + 2 MINOR

<table>
<thead>
<tr>
<th>MAJOR CRITERIA</th>
<th>MINOR CRITERIA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>Bilateral ankle edema</td>
</tr>
<tr>
<td>Radiographic cardiomegaly</td>
<td>Heart rate &gt; 120</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Weight loss &gt; 4.5kg in 5 days with Rx</td>
<td>Nocturnal cough</td>
</tr>
<tr>
<td>Neck vein distention</td>
<td>Dyspnea on ordinary exertion</td>
</tr>
<tr>
<td>Rales</td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>S3 Gallup</td>
<td>Reduced vital capacity by 1/3</td>
</tr>
<tr>
<td>Increased CVP (&gt;16)</td>
<td></td>
</tr>
<tr>
<td>Hepatojugular reflux</td>
<td>* Minor criteria only acceptable if not attributable to another medical condition</td>
</tr>
</tbody>
</table>

- HF is not a numeric value retrievable in EPIC
- HF patients are cared for by a wide variety of providers
Bedside Evaluation: Physical Exam Signs of Heart Failure and Heart Failure Severity

2. ADHERE Registry, 2005

S3: relation to ↑ LVEDP, ↓ EF
-40% sensitive
-90% specific

JVD: manipulate bed angle

Rales: Only present in 2/3 HF presentations

Proportional Pulse Pressure
SBP-DBP/SBP < 25% → CI < 2.2 L·min⁻¹·m²

Warm vs. cool and wet
“cold” patients, 2x mortality

Lewis GD. 2006

Heart Failure Characteristic Patient Course

Adapted From Gheorghiade M  Am Journal of Cardiology 2005
# Identify the “Trigger”/Precipitant for ADHF

<table>
<thead>
<tr>
<th>Precipitating Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence to care</strong></td>
</tr>
<tr>
<td>-Dietary indiscretion</td>
</tr>
<tr>
<td>-Nonadherence to medications</td>
</tr>
<tr>
<td><strong>Drug Exposures</strong></td>
</tr>
<tr>
<td>-βB, CCB, NSAIDs, TZDs</td>
</tr>
<tr>
<td>-chemo (anthracyclines, trastuzumab)</td>
</tr>
<tr>
<td><strong>Direct cardiac insults</strong></td>
</tr>
<tr>
<td>-Ischemia</td>
</tr>
<tr>
<td>-Valve disease (i.e. rupture chordae)</td>
</tr>
<tr>
<td>-Arrhythmia</td>
</tr>
<tr>
<td>-Takatsubo CM</td>
</tr>
<tr>
<td>-Cardiotoxins (EtOH)</td>
</tr>
<tr>
<td>-RV pacing</td>
</tr>
<tr>
<td><strong>Extra-cardiac insults</strong></td>
</tr>
<tr>
<td>-Hypertension (RAS, OSA)</td>
</tr>
<tr>
<td>-Renal failure (AKI, CKD progression)</td>
</tr>
<tr>
<td>-Anemia</td>
</tr>
<tr>
<td>-Thyroid dysfunction</td>
</tr>
<tr>
<td>-Systemic Infection</td>
</tr>
<tr>
<td>-Extreme emotional distress</td>
</tr>
</tbody>
</table>
Predictors of Survival with ADHF and Clues to the Presence of Impending Cardiogenic Shock

N=1960 ADHF PROTECT Trial

**Skin**
- Cool
- ± Mottled
- ± Cyanotic

**Kidney**
- Urine < 0.5ml/kg/hr

**Brain**
- Confused
- Obtundated

Myocardial Substrate Considerations

Reversibility tends to be inversely related to
- Chronicity
- LV size (much more important than LVEF!)

Chronicity

Non-compaction DCM (familial)↑↑LVEDD (>7cm)

Old remodeled MI Infiltration Anthracycline CM

Myocarditis Tachy-myopathy Stress CM (Tako-tsubo) Acute Ischemia/ACS DCM (EtOH)
# Newly Diagnosed Heart Failure: Specific Etiologic Considerations that Impact Management

<table>
<thead>
<tr>
<th>Etiology</th>
<th>ECG Pattern</th>
<th>Imaging Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia/Infarction</td>
<td>Qw, ST segment deviation</td>
<td>TTE: regional WMA, ± thinning/aneurysm, infarct Cor angio/CTA: obstructive CAD MRI: subendocardial or transmural LGE</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Low limb lead voltage, heart block, pseudoMI</td>
<td>TTE: LVH, “starry sky,” ↑ biatrial size → amyloid MRI: Inapprop nulling of myocardium + diffuse LGE → amyloid; patchy LV + RV LGE → sarcoidosis; ↓ T2 star → iron overload</td>
</tr>
<tr>
<td>Idiopathic DCM</td>
<td>Low limb lead volts, precordial LVH, BBB</td>
<td>TTE: 4 chamber dilation, diffuse hypokinesis MRI: mid-myocardial LGE</td>
</tr>
<tr>
<td>Tachy-myopathy</td>
<td>Persistent SVT</td>
<td>TTE: diffuse hypokinesis MRI: absent LGE in early stage</td>
</tr>
<tr>
<td>Myo(peri)-carditis</td>
<td>Pseudo-ischemia/MI Pericard: diffuse concave STE w/ ST:T ratio &gt;0.24 in V6</td>
<td>TTE: typically global HK MRI: mid-myocardial + epicardial LGE, ↑ T2 (edema)</td>
</tr>
<tr>
<td>LV non-compaction</td>
<td>Non-specific</td>
<td>TTE: heavily trabeculated LV MRI: &gt;2:1 non-compacted/compacted</td>
</tr>
</tbody>
</table>
APPROACH TO CHRONIC MANAGEMENT OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION
Post-Acute Decompensation Management

Focus on
- Decongestion
- Afterload reduction (ACE/ARNI alternative until decongested, stable Cr)
- Beta-blockade only after assurance of normalized end-organ perfusion

Adapted From Gheorghiade M. Am Journal of Cardiology 2005
2 Year Mortality in Systolic Heart Failure Trials

NYHA CLASS

II/III

III/IV

ACC/AHA 2005

C

ACE I + Bblock + A_LRB + ARB

ICD

CRT

Bblock

A_LRB

Control

Neurohormonal block

Device Therapy

V-HeFT II
SOLVD-Rx
CIBIS II
MERIT
EPHESUS
CHARM Added
PARADIGM
MADIT II
SCD-HeFT
CARE-HF
COMPANION
COPERNICUS
RALES
CONSENSUS
REMATCH
HRTMATE2

DT LVAD
Beta Blockers with Proven Mortality Benefit in HF

CIBIS = Cardiac Insufficiency Bisoprolol Study; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Trial.

Evidence based use of Beta-blockers

Dose Escalation Strategy

<table>
<thead>
<tr>
<th>Beta-blocker</th>
<th>Starting Dose</th>
<th>Target Dose</th>
<th>Reference Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol XL</td>
<td>12.5mg qd</td>
<td>200mg qd</td>
<td>MERIT-HF 1999, Class II-III</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25mg qd</td>
<td>10mg qd</td>
<td>CIBIS II 1999, Class II-III</td>
</tr>
</tbody>
</table>

Comparative Studies: Coreg > Metoprolol Tartrate (COMET)  
Coreg vs. Toprol XL unknown
Evidence based use of Beta Blockers Based on ACC/AHA Classification

ACC/AHA Guidelines All stable patients with current or previous symptoms of HF and reduced LVEF Class I, Evidence A

Coreg > Metoprolol Tartrate (COMET)
Coreg vs. Toprol XL unknown
  - Significant blood pressure rese → coreg
  - Marginal blood pressure, concern about non-selective bblck → metoprolol xl
# Evidence Based use of ACE I Dose titration strategy

<table>
<thead>
<tr>
<th>ACE I</th>
<th>Initial Dose</th>
<th>Target Dose</th>
<th>Reference Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25mg tid</td>
<td>50mg tid</td>
<td>SAVE</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5mg bid</td>
<td>10mg bid</td>
<td>CONSENSUS V-HeFT II</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5mg qd</td>
<td>20-40mg qd</td>
<td>ATLAS</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5mg qd</td>
<td>10mg qd</td>
<td>AIRE</td>
</tr>
</tbody>
</table>
Bradykinin-mediated ACE I Intolerance

No ACE I intolerance

Evidence Based Use of ARBs Based on ACC/AHA Classification

Val-HEFT

CHARM
Alternative

CHARM
Added

Persistent NYHA 2-4 on Conventional therapy
Monitor electrolytes/renal function

TRANSCEND → trend only

ONTARGET → neutral
Telmisartan = Ramipril

Bradykinin-mediated ACE I Intolerance

No ACE I intolerance
## Angiotensin Receptor Blockers

<table>
<thead>
<tr>
<th>DRUG</th>
<th>BIOAVAILABILITY</th>
<th>HALF LIFE</th>
<th>DAILY DOSE Goal (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>33%</td>
<td>6-9 hours</td>
<td>50-100</td>
</tr>
<tr>
<td>Candesartan</td>
<td>15%</td>
<td>9 hours</td>
<td>16-24</td>
</tr>
<tr>
<td>Valsartan</td>
<td>25%</td>
<td>6 hours</td>
<td>160-320</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>50%</td>
<td>24 hours</td>
<td>40-80</td>
</tr>
</tbody>
</table>
Angiotensin Receptor Blockers in the Treatment of Heart Failure

- ARBs are better tolerated than ACE inhibitors

- ARBs are comparable to ACE I for first line therapy in HF (ELITE I, II)

- ARBs should be substituted for ACE I in bradykinin-mediated ACE I intolerance (CHARM Alternative)
Evidence for use of Angiotensin Receptor-Nephrilysin Inhibition in Systolic HF
Neprilysin Inhibition: Potentiates Actions of Endogenous Vasoactive Peptides that Counter Maladaptive Mechanisms in HF

Endogenous vasoactive peptides
(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin inhibition

Inactive metabolites

Neprilysin

Neurohormonal activation
Vascular tone
Cardiac fibrosis, hypertrophy
Sodium retention
LCZ 696 (Sacubitril/Valsartan) vs. Enalapril: PARADIGM Trial

NYHA class II-IV heart failure

- LV ejection fraction ≤ 40% changed to < 35%
- BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
- Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m² and serum K ≤ 5.4 mEq/L at randomization
<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td>NYHA functional class II / III (%)</td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>N-terminal pro-BNP (pg/ml)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td>ICD and/or CRT</td>
<td>16.5%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>
LCZ 696 (Sacubitril/Valsartan) vs. Enalapril: PARADIGM Trial

Enalapril
(n=4212)

LCZ696
(n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Patients at Risk

<table>
<thead>
<tr>
<th>LCZ696</th>
<th>4187</th>
<th>3922</th>
<th>3663</th>
<th>3018</th>
<th>2257</th>
<th>1544</th>
<th>896</th>
<th>249</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>4212</td>
<td>3883</td>
<td>3579</td>
<td>2922</td>
<td>2123</td>
<td>1488</td>
<td>853</td>
<td>236</td>
</tr>
</tbody>
</table>
Patient Population
Tolerated run-in Phase (12\% dropout)
Enalapril $\geq 10$mg
**LCZ 696 (Sacubitril/Valsartan) vs. Enalapril: PARADIGM Trial**

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with systolic blood pressure &lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Elevated serum creatinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Elevated serum potassium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Angioedema†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P = 0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P = 0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P = 0.56).

† Angioedema was adjudicated in a blinded fashion by an expert committee.
LCZ 696 (Sacubitril/Valsartan) vs. Enalapril: PARADIGM Trial

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
Class I: In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.

- A 36 hour ACE I washout is required
- Avoid in patients with a history of angioedema
- Start slowly (24/26mg combination bid for enalapril or lisinopril <10 mg/d)
- Not yet studied in hospitalized HF patients
  - PIONEER Trial (enrolling)
  - Not yet studied in NYHA Class IIIb and IV Patients
    - LIFE Trial (enrolling)
- Obtain prior authorization prior to cessation of ACE/ARB

Aldo-Receptor Blocker Trials

**RALES**
- 1663 pts, NYHA III-IV, LVEF < 35%
- Rx with loop diuretics (100%) with omission of KCl unless K<3.5
- Average dose: **26 mg/d**

**Exclusion Criteria:**
- Cr > 2.5, K > 5.0
- Use of K-sparing diuretics

**EPHESUS**
- 6634 pts, 3-14 days post-MI, Evident HF, LVEF < 40%
- 16 month follow-up
- Target dose: **50 mg/d**

-15% reduction in all-cause mortality (p=0.008);
-13% reduction in combined end-point of CV death or hospitalization (p=0.002)

**Trial Designs:**
- Frequent electrolyte monitoring

Aldo-Receptor Blocker Trials

**EMPHASIS**
2737 pts, NYHA II, LVEF < 35%
Rx with ACE/ARB, BBBlock, Hosp within 6mo
Excl: K>5.0, GFR<30
Average dose: **40 mg/d**

Placebo-corrected fall in SBP: 2mmHg
K>5.5 in 11.8% vs. 7.2%

**Take home points**
- Potent anti-remodeling and ↓ mortality at a minimal blood pressure cost
- With use in NYHA II patients who are not on loop diuretics monitor K levels very closely
## SHIFT: Heart Rate Modulation Ivabradine

Selective inhibitor of Na/K channel in the sinus node  
N=6505, LVEF<0.35, HR>70, HF hospitalization in last yr

<table>
<thead>
<tr>
<th>Outcomes in SHIFT</th>
<th>Ivabradine, n=3241</th>
<th>Placebo, n=3264</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or HF hospitalization</td>
<td>24</td>
<td>29</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>3</td>
<td>5</td>
<td>0.74 (0.58-0.94)</td>
<td>0.014</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>16</td>
<td>21</td>
<td>0.74 (0.66-0.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death, HF hospitalization, or admission for nonfatal MI</td>
<td>25</td>
<td>30</td>
<td>0.82 (0.74-0.89)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

90% block use, comparable to Registry use but < clinical trial goals  
Greatest benefit with highest HR.

Swedberg K, Lancet 2010
Class IIa: 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

Digoxin \( \leq 0.125\text{mg/d} \)

**Evidence:**

**DIG:** Neutral mortality, decreased HF hospitalizations, levels < 1 ng/ml preferable

**RADIANCE:** Withdrawal of digoxin \( \rightarrow \) 5X RR of HF hospitalization, decr LVEF

**Positives:**
- Adjunctive rate control in HF with AF
- Reduces HF hospitalizations
- Positive inotrope without harm

**Negatives:**
- Narrow therapeutic index
- Unknown outcomes with BBlck
- Polypharmacy w/o incr survival
Emerging Targets and Treatments: HFrEF
Isordil + Hydralazine: A fortuitous combination in HF

VHEFT 2, White vs. Black Patients

A

B
A-HeFT: Results Isosorbide/Hydralazine Confers a 43% Relative Risk Reduction for Mortality in NYHA III-IV patients self-identified as black.

Fixed-dose I/H: 37.5 + 20mg TID

Hazard ratio = 0.57

$P = .01$

Taylor AL et al NEJM 2005
The Influence of Iron on Functional Capacity in Heart Failure

**Iron Deficiency**

- Erythropoietic Effects
  - ↓Hb
  - ↓RBC
- Extra-Erythropoietic Effects
  - ↓Aerobic Enzymes
  - ↓Myoglobin
  - ↓O₂ delivery
  - ↓O₂ utilization

**Gold Standard Objective Measurement of Functional Capacity**

\[ VO_2 = (CaO_2 - CvO_2) \times \text{Cardiac Output} \]
Background and Rationale: Prevalence of Iron Deficiency in HFrEF

Iron (Fe) Deficiency is common in HFrEF

Incidence
- 70%: ↓ bone marrow iron¹
- 35-61%: ↓ ferritin, T-sat ²,³
- 25-42%: without anemia³

International Pooled Analysis (Klip I et al, AHJ 2013)
1506 patients with LVSD (Ferritin < 100 ug/L or 100-299 ug/L with Tsat < 20%)
50% had iron deficiency
Fe deficiency (but not anemia) independently predicted mortality (HR=1.42 1.14-1.77, P=0.002)

-No consensus guidelines on when, how, and whether to treat Fe Def in HF
-Oral Fe is inexpensive and readily available without reliance on industry support
  - Oral iron repletion in HF has not been investigated

1. Nanas, JN  JACC 2006
2. Grzeslo, A  Eur Heart J 2007
3. Klip IT, AHJ 2013
4. Anker S, NEJM 2009
# IV Iron Repletion Trials in HFrEF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Authors/Journal</th>
<th>N</th>
<th>Subjects Studied</th>
<th>Fe-Def Definition</th>
<th>Time</th>
<th>Primary Endpoint</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Iron Sucrose</td>
<td>Tobilli JACC 2007</td>
<td>40</td>
<td>NYHA 3-4</td>
<td>Ferritin&lt;100 ng/ml and/or Tsat&lt;20%</td>
<td>5 wks</td>
<td>△ Global Assessment score</td>
<td>↑ PGAS, ↑ 6MWT, ↑ NT-BNP, ↑ LVEF</td>
</tr>
<tr>
<td>IV Iron Sucrose</td>
<td>Okonko JACC 2008</td>
<td>35</td>
<td>NYHA 2-3</td>
<td>Ferritin&lt;100 ng/ml or 100-300 with Tsat&lt;20%</td>
<td>16 wks</td>
<td>△ peak VO₂</td>
<td>↑ PGAS, ↑ NYHA, ↑ Peak VO2  α  △ Tsat</td>
</tr>
<tr>
<td>IV Iron Carboxy maltose</td>
<td>Anker NEJM 2009</td>
<td>459</td>
<td>NYHA 2-3</td>
<td>Ferritin&lt;100 ng/ml or 100-300 with Tsat&lt;20%</td>
<td>24 wks</td>
<td>△ Global Assessment Score</td>
<td>↑ PGAS, ↓ NYHA, ↑ 6MWD Similar benefit  Hb&lt;&gt;12</td>
</tr>
<tr>
<td>IV Iron Carboxy maltose</td>
<td>Ponikowski EHJ 2014</td>
<td>304</td>
<td>NYHA 2-3</td>
<td>Ferritin&lt;100 ng/ml or 100-300 with Tsat&lt;20%</td>
<td>52 wks</td>
<td>△ 6MWD</td>
<td>↑ PGAS, ↓ NYHA, Similar benefit  Hb&lt;&gt;12, ↓ HF hospitalizations</td>
</tr>
</tbody>
</table>

**Challenges and Unanswered Questions:**
1. No consensus guidelines on when, whether, and how to treat Fe deficiency in HF
2. IV Fe is expensive ($4,000/dose) and requires repeated IV infusions (5+ in trials)
   -IV Rx studies: Blinded + unblinded study staff, 6% injection site reactions
3. The efficacy of oral iron repletion in HF is unknown despite its low cost and availability
High dose oral iron minimally repleted iron stores and did not improve peak VO$_2$ in patients with iron deficiency and HFrEF

Lewis GD, JAMA 2017
IIb Guideline:
In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and QoL.
NNT \times \text{years} = \frac{100}{(\% \text{Mortality in Control Group} - \% \text{Mortality in Treatment Group})}

<table>
<thead>
<tr>
<th>CRT</th>
<th>ICD</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>56</td>
</tr>
</tbody>
</table>

Years of tested treatment:
- CRT: 1 Yr
- CRT-D: 1 Yr
- MUSTT: 5 Yr
- MADIT: 2.4 Yr
- MADIT II: 3 Yr
- AVID: 3 Yr
- COPERNICUS: 0.8 Yr
- SAVE: 3.5 Yr
- CIBIS II: 1 Yr
- MERIT HF: 1 Yr
- CAPRICORN Amiodarone: 1.5 Yr
- HOPE: 2 Yr
- HOPE: 4 Yr
## Indications for ICD in HF in 2017

### Ischemic Cardiomyopathy

- LVEF < 30% (MADIT II)
- LVEF < 35% with NYHA Class II-III HF (SCD-HeFT)
- LVEF < 40% with +EPS MADIT I, MUST

### Non-ischemic Cardiomyopathy

- LVEF < 35% with Class II-III HF (SCD-HeFT, DEFINITE vs. DANISH)

- Excluding patients with Class D (NYHA IV) HF unless Bi-V PPM as well
- Excluding patients with concomitant diseases that will shorten life expectancy
- ≥40 days s/p myocardial infarction (DINAMIT)
- At least 3 months of standard HF pharmacotherapy with persistent LVSD
The Pulmonary Artery Pressure Measurement System*

Catheter-based delivery system

MEMS-based pressure sensor

Home electronics

PA Measurement database

*CardioMEMS Inc., Atlanta, Georgia, USA
Cumulative HF Hospitalizations Over Entire Randomized Follow-Up Period

- **Treatment**
  - At Risk: 270
  - Days: 0, 90, 180, 270, 360, 450, 540, 630, 720, 810, 900
- **Control**
  - At Risk: 280
  - Days: 0, 90, 180, 270, 360, 450, 540, 630, 720, 810, 900

- **p < 0.001, based on Negative Binomial Regression**

- **FDA Approval 2014**
- **MGH Launch: 2016**

Days from Implant:

- 0: Treatment 0, Control 0
- 90: Treatment 262, Control 267
- 180: Treatment 244, Control 252
- 270: Treatment 209, Control 215
- 360: Treatment 168, Control 179
- 450: Treatment 130, Control 138
- 540: Treatment 107, Control 105
- 630: Treatment 81, Control 67
- 720: Treatment 28, Control 25
- 810: Treatment 5, Control 10
- 900: Treatment 1, Control 0
Sick Enough or Too Sick to Consider a Left Ventricular Assist Device?

Technological advances
- Fully implantable VADs
- Partial support
Multimodality Rx
- Stem cell/gene therapy

Accurate Phenotyping + Risk Prediction

Time

Patient Profile at Time of Implant

Unspecified
1 Critical Cardiogenic Shock
2 Progressive Decline
3 Stable but Inotropic dependent
4 Resting Symptoms
5 Exertion intolerant
6 Exertion limited
7 Advanced NYHA Class 3

Heart Failure Clinical Stability
The Evidence: Survival in VAD Trials

HM2 LVAD: \( \sim 60\% \) 24 mo survival

vs

IV inotropes: \( \sim 50\% \) 6 mo survival

“The rise of the machines”

……J Fang, 2009
Approximately 40% of all cases of heart failure occur in patients with normal or near normal LVEF >45%.

Disease prevalence varies widely by age:
- <15% for middle-aged patients
- >50% for elderly patients

Annual mortality ranges from 1.3% to 17.5%; 2 largest retrospective series report rates of 8%-9%.

Hogg et al, JACC 2004; Bursi et al, JAMA 2006; Owan et al, NEJM 2006; Bhatia et al, NEJM 2006; Klapholz et al JACC 2004
Current Pharmacologic Treatments for HPpEF that Improve 2 year Survival
HFpEF vs. HFrEF Comparative Results with Neurohormonal Blockade

Borlaug BA et al, Circulation, 2011
## Trials of Therapeutic Interventions that Improve 2-year Mortality in HFpEF

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>N</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP CHF</td>
<td>ACE I (Perindopril)</td>
<td>850</td>
<td>HR 0.92, p=0.55</td>
</tr>
<tr>
<td>SENIORS</td>
<td>Bblck (Nebivolol)</td>
<td>752</td>
<td>HR 0.71-1.08, all p=0.21</td>
</tr>
<tr>
<td>CHARM Added</td>
<td>ARB (candasartan)</td>
<td>700</td>
<td>HR 0.89, p=0.12</td>
</tr>
<tr>
<td>I-Preserve</td>
<td>ARB (irbesartan)</td>
<td>4128</td>
<td>HR 0.99</td>
</tr>
<tr>
<td>TOPCAT</td>
<td>MRA (spironolactone)</td>
<td>3450</td>
<td>HR 0.89, p=0.12</td>
</tr>
<tr>
<td>RELAX</td>
<td>PDE 5I (sildenafil)</td>
<td>220</td>
<td>pkVO2 -0.2ml/kg, p=0.9</td>
</tr>
<tr>
<td>NEAT</td>
<td>Nitrates (isosorbide)</td>
<td>100</td>
<td>↓ Actigraphy levels</td>
</tr>
<tr>
<td>PARAGON-HF</td>
<td>LCZ 696</td>
<td>4300</td>
<td>Enrollment→2019</td>
</tr>
</tbody>
</table>

Patients: Symptomatic, LVEF>0.45, ± structural hrt disease (LAE, LVH)
# Definition of HFpEF

<table>
<thead>
<tr>
<th>HFpEF Definitions</th>
<th>ACC/AHA</th>
<th>ESC</th>
<th>HFSA</th>
<th>TOPCAT</th>
<th>RELAX</th>
<th>PARAGON-HF</th>
<th>FHS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>x (for stage C)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>xx</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td>&gt;=50%</td>
<td>normal/mildly depressed</td>
<td>&gt;=50%</td>
<td>&gt;=45%</td>
<td>&gt;=50%</td>
<td>&gt;=45%</td>
<td>&gt;=50%</td>
</tr>
<tr>
<td><strong>structural heart disease</strong></td>
<td>LVH, LAE, or DD and not dilated</td>
<td>cLVH, LAE echo or cath evidence of DD</td>
<td></td>
<td></td>
<td></td>
<td>LAE or LVH</td>
<td></td>
</tr>
<tr>
<td><strong>HF admission</strong></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CV admission</strong></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclude</strong></td>
<td>noncardiac causes</td>
<td>nonmyocardial disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BNP/NT-proBNP</strong></td>
<td>alternative to echo: &gt;=100/ &gt;=300 (acute) or &gt;=35/ &gt;=125 (non-acute)</td>
<td>alternative to HF admission: &gt;=100/ &gt;=360</td>
<td>alternative to HF admission: &gt;=100/ &gt;=360</td>
<td>NT-proBNP &gt;=400 or elevated filling pressures at time of NT-proBNP&lt;400</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HFpEF Trials: TOPCAT

- **Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist**

- NHLBI sponsored trial; n=4500 patients randomized to an aldosterone antagonist versus placebo, LVEF > 45%; age > 50 years; controlled blood pressure; K⁺ < 5.0 mEq/L

- Endpoints: CV mortality, aborted sudden cardiac death, or hospitalization
Next Steps in HF Treatments

There is an unmet need to apply heart failure physiologic subphenotyping in order to improve targeted approaches to interventions.

Candidate Subphenotypes

* Obesity with normal cardiometabolic capacity
* Isolated/Predominant LV dysfunction
* Abnormal peripheral function: impaired oxygen utilization
* Chronotropic incompetence
* Right Ventricular - Pulmonary Vascular Dysfunction
## ACC/AHA Guidelines on Pharmacological Treatment of Diastolic Heart Failure

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat hypertension in a</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>in accordance with guidelines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control ventricular rate in atrial fibrillation</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Diuretics to control congestion</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Beta-blockers, ACE-I, ARBs or</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>calcium channel blockers may ↓Sx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis may reduce symptoms</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

THANK YOU

END