Advances in Heart Failure: The “New” Guidelines

John R. Teerlink, M.D., FACC, FAHA, FESC, FRCP(UK)
Director, Heart Failure Program
Director, Echocardiography
San Francisco Veterans Affairs Medical Center;
Professor of Clinical Medicine,
University of California San Francisco
California, USA


Presenter Disclosure Information:
UCSF Advances in Internal Medicine 2015

- Financial Disclosure
  - J.R. Teerlink has received research grants and/or consulting fees from Amgen, Cytokinetics, Janssen, Medtronic, Novartis, St. Jude, Takeda, and Trevena.
- Unlabeled/unapproved uses disclosure
  - I will be discussing investigational therapies that are not approved by the FDA.
Mr. “HCE” (Here Comes Everybody): Question #1

- Intake sheet reports: 76 yo man with h/o diabetes mellitus (oral agents), hypertension, COPD, and obesity

According to the ACC/AHA 2013 Heart Failure Guidelines, does Mr. HCE have heart failure?

A. Yes
B. No
C. Maybe; Need more information

Advances in Heart Failure

- Definition, Nomenclature, Epidemiology
- Evaluation and Diagnosis
- Treatment of Stages of Heart Failure
- Co-morbidities
- Future directions
Heart Failure

• HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.

• No single diagnostic test for HF; a clinical diagnosis based on careful history and physical examination, supplemented by diagnostic studies.

• May result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels or from certain metabolic abnormalities, but most patients with HF have symptoms due to impaired left ventricular (LV) myocardial function.

• Heart failure (not Congestive Heart Failure)
Heart Failure with Reduced/Preserved Ejection Fraction (HFrEF and HFpEF)


<table>
<thead>
<tr>
<th>Classification</th>
<th>EF (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Heart failure with reduced ejection fraction (HFrEF)</td>
<td>≤40</td>
<td>Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>II. Heart failure with preserved ejection fraction (HFpEF)</td>
<td>≥50</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFpEF, borderline</td>
<td>41 to 49</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.</td>
</tr>
<tr>
<td>b. HFpEF, improved</td>
<td>&gt;40</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>

Heart Failure: Here Comes Everybody

- Lifetime risk of developing HF is 20% for Americans 40 years of age
- >650,000 new HF cases diagnosed annually
- Approximately 5.1 million persons in the US have clinically manifest HF
- Blacks have the highest risk for HF and a greater 5-year mortality rate than whites
- Absolute mortality rates for HF remain approximately 50% within 5 years of diagnosis
2013 ACC/AHA Heart Failure Guidelines

Advances in Heart Failure

• Definition, Nomenclature, Epidemiology
• Evaluation and Diagnosis
Diagnosis of Heart Failure

• Symptoms
  – Dyspnea (Exertional, PND, Orthopnea)
  – Cough
  – Fatigue
  – Abd discomfort (bloating, anorexia)
  – Sleep disturbances

• Physical Exam
  – Edema (Legs, Abd, Sacral)
  – Rales, Effusion
  – JVP, HJR/AJR
  – Weight
  – Cool extremities
  – MR murmur
  – S3 (S4)
  – Blood/ pulse pressure
  – Pulsus alternans

“First, strike for the jugular and let the rest go”

-Oliver Wendell Holmes, Jr.
Potential Limitations to BNP in the Evaluation of Heart Failure

Teerlink JR. Acute Heart Failure. Braunwald’s Heart Disease. 2008

<table>
<thead>
<tr>
<th>TABLE 24–6</th>
<th>Conditions that Influence B-Type Natriuretic Peptide (BNP) Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased BNP concentrations may be found in:</td>
<td></td>
</tr>
<tr>
<td>Age (older)</td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (black)</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction/acute coronary syndromes</td>
<td></td>
</tr>
<tr>
<td>Right-sided heart failure (cor pulmonale, acute pulmonary embolus)</td>
<td></td>
</tr>
<tr>
<td>High output failure (cirrhosis, septic shock)</td>
<td></td>
</tr>
<tr>
<td>Decreased BNP concentrations may be found in:</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Early acute heart failure (less than 1 hr)</td>
<td></td>
</tr>
<tr>
<td>Acute mitral regurgitation</td>
<td></td>
</tr>
<tr>
<td>Mitral stenosis (in the absence of right ventricular failure)</td>
<td></td>
</tr>
<tr>
<td>Stable NYHA Class I patients with decreased LV ejection fraction</td>
<td></td>
</tr>
</tbody>
</table>


Practical Diagnostics in the Evaluation of Heart Failure

- History
  - Etiology: CAD, HTN, Familial, Toxins (EtOH, drugs, chemo, alternative rx, etc.)
  - Symptoms, exercise tolerance (specific personal markers)
- Physical exam: Diagnosis and Monitoring
- Labs include Chem-7, HgbA1c, Ca, Mg, CBC, ferritin/TIBC, TSH, U/A, Lipid profile, LFT
- CXR, ECG
- Echocardiogram: probably single most useful; RVG/MUGA useful at some centers
- Cardiac catheterization: right and left heart
- Other: HIV, sleep disordered breathing, disease specific tests, BNP/ NT-pro-BNP (diagnosis/ risk stratification/?Guide therapy)
Advances in Heart Failure

- Definition, Nomenclature, Epidemiology
- Evaluation and Diagnosis
- Treatment of Stages of Heart Failure

Stages of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>At Risk for Heart Failure</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>High risk for HF but without structural heart disease or symptoms of HF</td>
<td>Refractory HF</td>
</tr>
<tr>
<td>Stage B</td>
<td>Structural heart disease but without signs or symptoms of HF</td>
<td>HFpEF</td>
</tr>
<tr>
<td>Stage C</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
<td>HFpEF</td>
</tr>
<tr>
<td>Stage D</td>
<td>Refractory HF</td>
<td>Refractory symptoms despite optimal therapy</td>
</tr>
</tbody>
</table>

Therapy

- Stage A
  - Goal: Prevent HF symptoms
  - Therapy: ACEi or ARB as appropriate, beta blockers as appropriate, ICD, Resynchronization or cardiac resynchronization, CRT-D

- Stage B
  - Goal: Prevent further cardiac remodeling
  - Therapy: ACEi or ARB as appropriate, beta blockers as appropriate, ICD

- Stage C
  - Goal: Identify and relieve symptoms of congestion
  - Therapy: ACEi or ARB, Beta blockers, Aldosterone antagonists, Diuretics

- Stage D
  - Goal: Refractory symptoms at rest
  - Therapy: Advanced care strategies, Pacing, Circulatory support, Cardiac transplantation, VAD, Biventricular support, Optimal medical therapy, Cardiac surgery, Palliative care and hospice, ICD deactivation
Prognostic Significance of the Stages of Heart Failure


ACCF/AHA Stages Compared to NYHA Functional Class


ACCF/AHA Stages of HF (38) NYHA Functional Classification (48)

<table>
<thead>
<tr>
<th>A</th>
<th>At high risk for HF but without structural heart disease or symptoms of HF</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Structural heart disease but without signs or symptoms of HF</td>
<td>I</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
<td>II</td>
</tr>
<tr>
<td>II</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
<td>IV</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
<td>V</td>
</tr>
</tbody>
</table>

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.
Stages of Heart Failure

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

e.g., Patients with:
- HTN
- Atherosclerotic disease
- DM
- Obesity
- Metabolic syndrome

or

Patients
- Using cardiotoxins
- With family history of cardiomyopathy

**THERAPY**

Goals
- Heart healthy lifestyle
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

Drugs
- ACEI or ARB in appropriate patients for vascular disease or DM
- Statins as appropriate

“**When you’re a Hammer, Everything looks like a Nail!”**

... AND THEN I HEARD A LOUD BANG AND WHEN I TURNED BACK HE WAS GONE
Mr. “HCE” (Here Comes Everybody)
Question #1: Discussion

• 76 yo man with h/o diabetes mellitus (oral agents), hypertension, COPD, and obesity

• Does Mr. HCE have heart failure?
  A. Yes
  B. No
  C. Maybe; Need more information

Risk Factor Modification in HF

• Weight loss
• Smoking cessation
• Hypertension therapies
• Diabetes management
• Lipid control
• Sleep apnea
• Exercise
Lifetime Risk of Heart Failure According to Number of Healthy Lifestyle Factors


- Physicians Health Study cohort (20,900 men)
- Six modifiable risk factors:
  - Maintained Body weight
  - No Smoking
  - Exercise
  - Less Alcohol intake
  - Eats breakfast cereals
  - Eats fruits and vegetables

Essential Topics in Patient Education


<table>
<thead>
<tr>
<th>Educational topics</th>
<th>Skills and self-care behaviours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition and aetiology of heart failure</td>
<td>Understand the cause of heart failure and why symptoms occur</td>
</tr>
<tr>
<td>Symptoms and signs of heart failure</td>
<td>Monitor and recognize signs and symptoms</td>
</tr>
<tr>
<td></td>
<td>Record daily weight and recognize rapid weight gain</td>
</tr>
<tr>
<td></td>
<td>Know how and when to notify healthcare provider</td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td>Use flexible diuretic therapy if appropriate and recommended</td>
</tr>
<tr>
<td>Risk factor modification</td>
<td>Understand indications, dosing, and effects of drugs</td>
</tr>
<tr>
<td>Diet recommendation</td>
<td>Recognize the common side-effects of each drug prescribed</td>
</tr>
<tr>
<td>Exercise recommendations</td>
<td>Understand the importance of smoking cessation</td>
</tr>
<tr>
<td></td>
<td>Monitor blood pressure if hypertensive</td>
</tr>
<tr>
<td></td>
<td>Maintain good glucose control if diabetic</td>
</tr>
<tr>
<td></td>
<td>Avoid obesity</td>
</tr>
<tr>
<td></td>
<td>Sodium restriction if prescribed</td>
</tr>
<tr>
<td></td>
<td>Avoid excessive fluid intake</td>
</tr>
<tr>
<td></td>
<td>Modest intake of alcohol</td>
</tr>
<tr>
<td></td>
<td>Monitor and prevent malnutrition</td>
</tr>
<tr>
<td></td>
<td>Be reassured and comfortable about physical activity</td>
</tr>
<tr>
<td></td>
<td>Understand the benefits of exercise</td>
</tr>
<tr>
<td></td>
<td>Perform exercise training regularly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Educational topics</th>
<th>Skills and self-care behaviours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual activity</td>
<td>Be reassured about engaging in sex and discuss problems with healthcare professionals</td>
</tr>
<tr>
<td>Immunization</td>
<td>Understand specific sexual problems and various coping strategies</td>
</tr>
<tr>
<td>Sleep and breathing disorders</td>
<td>Receive immunization against infections such as influenza and pneumococcal disease</td>
</tr>
<tr>
<td>Adherence</td>
<td>Recognize preventative behaviour such as reducing weight of obese, smoking cessation, and abstinence from alcohol</td>
</tr>
<tr>
<td></td>
<td>Learn about treatment options if appropriate</td>
</tr>
<tr>
<td>Psychosocial aspects</td>
<td>Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure and the importance of social support</td>
</tr>
<tr>
<td></td>
<td>Learn about treatment options if appropriate</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Understand important prognostic factors and make realistic decisions</td>
</tr>
<tr>
<td></td>
<td>Seek psychosocial support if appropriate</td>
</tr>
</tbody>
</table>
Stages of Heart Failure

**STAGE A**
- At risk for HF but without structural heart disease or symptoms of HF

**STAGE B**
- Structural heart disease but without signs or symptoms of HF
  - e.g., Patients with:
    - Previous MI
    - LV remodeling including LVH and low EF
    - Asymptomatic valvular disease

**STAGE C**
- Heart failure exacerbation
  - E.g., Patients with:
    - Systolic LV dysfunction
    - Dyspnea
    - Lower extremity edema

**STAGE D**
- Refractory HF

**THERAPY**

**Goals**
- Prevent HF symptoms
- Prevent further cardiac remodeling

**Drugs**
- ACEI or ARB as appropriate
- Beta blockers as appropriate

**In selected patients**
- ICD
- Revascularization or valvular surgery as appropriate

Intake sheet reports: 76 yo man with h/o diabetes mellitus (oral agents), hypertension, COPD, and obesity

ECG: NSR @88bpm, LAE, LVH, possible inferior MI
Mr. “HCE” (Here Comes Everybody)

- 76 yo man with h/o diabetes mellitus (oral agents), hypertension, COPD, and obesity
- ECG: NSR @88bpm, LAE, LVH, possible inferior MI
- Reports early satiety, abdominal discomfort, mildly increasing abdominal girth, 5 kg weight gain
- HR 90 bpm, BP 134/76, RR 14, O2 sat 98%

Lungs: clear to A&P
CV: JVP~10 cm, -A(H)JR; S1,S2 +S4, no S3,
Abd: mild RUQ tenderness, abd distension;
?ascites
Extrem: No peripheral edema

Stages of Heart Failure
Mr. “HCE” (Here Comes Everybody)

- 76 yo man with h/o diabetes mellitus (oral agents), hypertension, COPD, and obesity
- ECG: NSR @88bpm, LAE, LVH, possible inferior MI
- Reports early satiety, abdominal discomfort, mildly increasing abdominal girth, 5 kg weight gain
- HR 90 bpm, BP 134/76, RR 14, O2 sat 98%
  Lungs: clear to A&P
  CV: JVP~10 cm, -A(H)JR; S1,S2 +S4, no S3,
  Abd: mild RUQ tenderness, abd distension; ?ascites
  Extrem: No peripheral edema
- Labs: Na 135, K 3.9, BUN 30, Cr 1.6
- Echo: moderate LAE, mild LVH, mild LVE, EF 30%, global hypokinesis

The optimal initial therapy for this patient is:

A. Furosemide 20 mg po qd
B. Lisinopril 10 mg po qd
C. Furosemide 20 mg po bid and Lisinopril 2.5 mg po qd
D. Metoprolol tartrate 25 mg po bid

Mr. “HCE”: Question #2

- 76 yo man with h/o diabetes mellitus (oral agents), hypertension, COPD, obesity
- ECG: NSR @88bpm, LAE, LVH, possible inferior MI
- Reports early satiety, abd discomfort, mildly increasing abd girth, 5 kg weight gain
- HR 90 bpm, BP 134/76, RR 14, O2 sat 98%; Lungs: clear to A&P
  CV: JVP~10 cm, -A(H)JR; S1,S2 +S4, no S3, Murmur;
  Abd: mild RUQ tenderness, abd distension, ?ascites;
  Extrem: No peripheral edema
- Labs: Na 135, K 3.9, BUN 30, Cr 1.6
- Echo: moderate LAE, mild LVH, mild LVE, EF 30%, global hypokinesis

The optimal initial therapy for this patient is:

A. Furosemide 20 mg po qd
B. Lisinopril 10 mg po qd
C. Furosemide 20 mg po bid and Lisinopril 2.5 mg po qd
D. Metoprolol tartrate 25 mg po bid
Mr. “HCE”: Question #2 Discussion

- 76 yo man with h/o diabetes mellitus (oral agents), hypertension, COPD, obesity
- ECG: NSR @88bpm, LAE, LVH, possible inferior MI
- Reports early satiety, abd discomfort, mildly increasing abd girth, 5 kg weight gain
- HR 90 bpm, BP 134/76, RR 14, O2 sat 98%; Lungs: clear to A&P
- CV: JVP~10 cm, -A(H)JR; S1,S2 +S4, no S3, Murmur; Abd: mild RUQ tenderness, abd distension, ?ascites; Extrem: No peripheral edema
- Labs: Na 135, K 3.9, BUN 30, Cr 1.6
- Echo: moderate LAE, mild LVH, mild LVE, EF 30%, global hypokinesis

The optimal initial therapy for this patient is:

A. Furosemide 20 mg po qd
B. Lisinopril 10 mg po qd
C. Furosemide 20 mg po bid and Lisinopril 2.5 mg po qd
D. Metoprolol tartrate 25 mg po bid

Stages of Heart Failure
Use of Diuretics in Heart Failure Patients

- **Self-titration:** need “dry” weight on patient’s scale
  - Daily weights (routine; daily log with symptoms, etc.)
  - If weight increased by >3-5 lbs, take double diuretic
  - If patient requires supplemental potassium, also double
  - If worsening at any time or no improvement after 2-3 days, call
- Some patients can be maintained on thiazides (i.e. HCTZ)
- Many patients will require loop diuretics; furosemide has short duration of action, should be dosed b.i.d. (AM and mid-afternoon/ early evening)
- Many patients may not require diuretics when ACE inhibitor, beta blocker, aldosterone antagonist, etc. are optimized; reassess diuretic requirements after time on stable regimen
Diuretics in Chronic Heart Failure


TORIC Study
- Open-label, non-randomized, post-marketing study
- 1377 patients; NYHA II-III
- 778 pts torsemide (10 mg/d)
- 527 pts furosemide (40 mg/d)
- 72 pts other diuretics
- 12 month follow-up

Incidence of Mortality (%)

2013 ACC/ AHA Heart Failure Guidelines

Importance of Afterload Reduction

Effect of ACE Inhibitors on Mortality Reduction in Patients With Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>ACEI</th>
<th>Controls</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS I</td>
<td>39%</td>
<td>54%</td>
<td>0.56 (0.34–0.91)</td>
</tr>
<tr>
<td>SOLVD (Treatment)</td>
<td>35%</td>
<td>40%</td>
<td>0.82 (0.70–0.97)</td>
</tr>
<tr>
<td>SOLVD (Prevention)</td>
<td>15%</td>
<td>16%</td>
<td>0.92 (0.79–1.08)</td>
</tr>
<tr>
<td>Post MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td>20%</td>
<td>25%</td>
<td>0.81 (0.68–0.97)</td>
</tr>
<tr>
<td>AIRE</td>
<td>17%</td>
<td>23%</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>TRACE</td>
<td>35%</td>
<td>42%</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>SMILE</td>
<td>6.5%</td>
<td>8.3%</td>
<td>0.78 (0.52–1.12)</td>
</tr>
<tr>
<td>Average</td>
<td>21%</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

Use of ACE Inhibitors in Heart Failure Patients

- Indicated in potentially ALL pts with HF and EF ≤ 40%
- Some ACE Inhibitor is better than none
- Start low dose, up-titrate q2 wks or so; check labs within 1-2 weeks of dose adjustment, then about q4 months
- Asymptomatic low blood pressure: usually no change
- Symptomatic Hypotension: often improves with time (reassure); re-evaluate other meds (nitrates, diuretics, etc.)
- Cough: Other causes, rechallenge, consider ARB
- Worsening renal function: Smaller of an increase in creatinine up to 50% above baseline or 3 mg/dL or eGFR < 25 ml/min/1.73m² is acceptable; K<5.5
- ARBs may be INFERIOR to ACEi in CHF

Mr. “HCE”: Question #3

One week later, Mr. HCE presents to clinic with:
- Improvement in early satiety and abdominal bloating; 5 kg weight loss
- BP 128/76, HR 84, RR 14; JVP ~6 cm; abdomen soft, non-tender
- Labs: Na 136, K 3.8, BUN 24, Cr 1.8

An optimal next step would be to:
A. Add Carvedilol 3.125 mg po bid
B. Repeat echocardiogram to re-assess EF
C. Serially uptitrate Lisinopril to goal of 40 mg po qd with symptom, blood pressure, and lab monitoring
D. Add Spironolactone 25 mg po qd
Mr. “HCE”: Question #3 Discussion

One week later, Mr. HCE presents to clinic with:

- Improvement in early satiety and abdominal bloating; 5 kg weight loss
- BP 128/76, HR 84, RR 14; JVP ~6 cm; abdomen soft, non-tender
- Labs: Na 136, K 3.8, BUN 24, Cr 1.8

An optimal next step would be to:

A. Add Carvedilol 3.125 mg po bid
B. Repeat echocardiogram to re-assess EF
C. Serially uptitrate Lisinopril to goal of 40 mg po qd with symptom, blood pressure, and lab monitoring
D. Add Spironolactone 25 mg po qd

Assessment of Treatment with Lisinopril and Survival (ATLAS)

- Randomized, double-blind, placebo-controlled, multicenter
- Target 3000 pts with NYHA II-IV, LVEF≤ 30%
- 3164 pts randomized to Lisinopril:
  - Low Dose (2.5 or 5 mg): 1596
  - High Dose (32.5-35 mg): 1568
- Followed 39-58 months


- All cause Mortality: HR 0.92 (0.82–1.03), p=0.128
- All cause Mortality and Hospitalization: HR 0.88 (0.82–0.96); p=0.002

Low dose: 717 (44.9%)
High dose: 666 (42.5%)

Low Dose: 1338 (83.8%)
High Dose: 1250 (79.7%)
Carvedilol Or Metoprolol European Trial (COMET)


- Randomized, multicenter, double-blind, placebo-controlled,
- Target 3000 pts with NYHA II-IV, LVEF ≤ 35%; ≥1 CV hospitalization in last 2 years
- 3029 pts randomized to:
  - Metoprolol: 1518
  - Carvedilol: 1511
- Followed 58±6 months

Beta-Blockers in HF Effect on Mortality

Modified from: Teerlink JR, Massie BM. Am J Cardiol 1999; 84:94R-102R.
Magnitude of Benefit of Therapies for Heart Failure


<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality (%)</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34</td>
<td>9</td>
<td>41</td>
</tr>
</tbody>
</table>

Use of Beta blockers in Heart Failure Patients

- Indicated in potentially ALL pts with HF and EF≤40%
- Some beta blocker is better than none; Some beta blocker probably better than more ACE inhibitor
- Start low dose, up-titrate q2 wks or so; check labs within 1-2 weeks of dose adjustment, then about q4 months
- Severe asthma is a contraindication (NOT COPD)
- Asymptomatic low blood pressure: usually no change
- Symptomatic Hypotension: often improves with time (reassure); re-evaluate other meds (nitrates, diuretics, etc.)
- Worsening HF: Congestion, Increase diuretic; Fatigue, usually reassurance
- Low heart rate: if <55 bpm, halve dose
- Other beta blocker side effects minimal in HF patients
2013 ACC/AHA Heart Failure Guidelines


EMPHASIS-HF


- Randomized, double-blind, placebo-controlled, multicenter trial
- Target 3100 pts with NYHA II HF, LVEF ≤ 35%; HF hosp in 6 months or elevated BNP/NT-proBNP
- 2737 pts enrolled; stopped for mortality benefit of eplerenone
- Potassium monitored baseline, weeks 1 & 4, then q4 months
- Hyperkalemia: Eplerenone 109 (8.0%) vs. Placebo 50 (3.7%); p < 0.001.
Use of Mineralocorticoid Receptor Antagonists (MRAs) in HF Patients

- Indicated in potentially ALL NYHA II-IV pts with HF and EF≤35%
- Start low dose, up-titrate after q4-8 wks or so; check labs within 1 and 4, 8 and 12 weeks of dose adjustment, at 6,9,12 months, and then q4 months
- Avoid potassium repletion and K-containing salt substitutes
- Hyperkalemia: If K>5.5 or Cr ≥2.5 mg/dL, halve dose and f/u; if K>6.0 or Cr >3.5 mg/dL, d/c dose and f/u. Consider rechallenge if reversible cause identified.
- Gynecomastia in males: change to eplerenone

2013 ACC/ AHA Heart Failure Guidelines

African-American Heart Failure Trial (A-HeFT)


A-HeFT
- Randomized, double-blind, placebo-controlled, multicenter
- 1050 self-identified black pts; NYHA III-IV, LVEF<35%
  (or LVEF <45% and dilated)
- 518 pts ISDN/Hydral
  (target 120/ 225mg/d)
- 532 pts placebo
- Mean follow-up 10 months
- Stopped early due to excess mortality in placebo group
- Decreased first HF hospitalization by 33%
- 48% headache, 29% dizziness

Hydralazine-Isosorbide Dinitrate Use in Eligible Patients


- Observational analysis
- 54,622 pts admitted with HFrEF and discharged home
- 207 Hospitals in GWTG-HF registry (April 2008- March 2012)
- 11,185 African-American pts eligible for H-ISDN therapy
- Only 2500 (22.4%) received H-ISDN therapy at discharge.
- Potential reasons:
  - Not in performance measures
  - Side effects: headache/dizziness, etc.
  - Low baseline blood pressure
  - Three times a day dosing
  - Concomitant therapies (e.g. PDE V inhibitors)

Hydralazine-isosorbide dinitrate (H-ISDN) use in African American patients in hospitals with ≥10 self-identified African American patients.
An Approach to Management of Patient with Stage C Symptomatic HF-REF

- Control volume overload with diuretics
- Initiate ACE inhibitor therapy (2.5-5 mg lisinopril); substitute with ARB only if absolutely necessary
- Initiate Beta blocker therapy (prefer Carvedilol 3.125 or 6.25 mg po bid) and up-titrate to max tolerated
- Initiate spironolactone (switch to eplerenone if needed)
- Maximize ACE inhibitor
- If after stable therapy and meets criteria, ICD/CRT
- If still symptomatic, consider ISDN/ Hydral or ARB
- If still symptomatic, initiate digoxin (earlier if AF)

---

Mr. “HCE”: Question #4

One year later, Mr. HCE presents to clinic with:

- Bendopnea; Early satiety and abdominal bloating; 5 kg wt gain
- Current meds: Furosemide 40 –>80 mg bid; Carvedilol 25 mg bid; Lisinopril 10 mg qd; Spironolactone 25 mg qd
- BP 128/76, HR 68, RR 18; JVP ~14 cm; abdomen distended, RUQ tenderness; o/w no change
- Labs: Na 134, K 4.2, BUN 48, Cr 2.8 (from 1.5)

An optimal diagnostic step would be to:

A. Order BNP (or NT-proBNP)
B. Repeat echocardiogram
C. Obtain Chest X-ray
D. None of the above
Question #4: Discussion

An optimal diagnostic step would be to:

A. Order BNP (or NT-proBNP)
B. Repeat echocardiogram
C. Obtain Chest X-ray
D. None of the above

Mr. “HCE”: Question #5

One year later, Mr. HCE presents to clinic with:

- Bendopnea; Early satiety and abdominal bloating; 8 kg wt gain
- Current meds: Furosemide 40 –>80 mg bid; Carvedilol 25 mg bid; Lisinopril 10 mg qd; Spironolactone 25 mg qd
- BP 128/76, HR 68, RR 18; JVP ~14 cm; abdomen distended, RUQ tenderness; o/w no change
- Labs: Na 134, K 4.2, BUN 48, Cr 2.8 (from 1.5)

An optimal therapeutic diuretic step would be to:

A. Increase Furosemide to 160 mg bid
B. Increase Spironolactone to 50 mg qd
C. Hold all diuretics
D. Discontinue Furosemide and start Bumetanide
E. Add Metolazone 5 mg qd
Question #5: Discussion

One year later, Mr. HCE presents to clinic with:

- Bendopnea; Early satiety and abdominal bloating; 8 kg wt gain
- Current meds: Furosemide 40 –>80 mg bid; Carvedilol 25 mg bid; Lisinopril 10 mg qd; Spironolactone 25 mg qd
- BP 128/76, HR 68, RR 18; JVP ~14 cm; abdomen distended, RUQ tenderness; o/w no change
- Labs: Na 134, K 4.2, BUN 48, Cr 2.8 (from 1.5)

An optimal therapeutic diuretic step would be to:

A. Increase Furosemide to 160 mg bid
B. Increase Spironolactone to 50 mg qd
C. Hold all diuretics
D. Discontinue Furosemide and start Bumetanide
E. Add Metolazone 5 mg qd

Use of Diuretics in Heart Failure Patients-Redux

- Often increasing creatinine can be evidence of worsening heart failure, elevated CVP and need for more diuretics
- Furosemide’s poor bioavailability is worse in the setting of abdominal edema/ congestion.
- Diuretic resistance may be treated with switch to bumetanide/ torsemide, metolazone, (or adding spironolactone).
- Sequential nephron blockade with loop diuretic and metolazone very effective for diuresis, but should be done VERY cautiously or by specialist
- Frequent monitoring of electrolytes is imperative; HYPOkalemia is as dangerous as HYPERkalemia (maintain K+ ≥4.0).
Mr. “HCE”: Question #6

One year later, Mr. HCE presents to clinic with:

- Bendopnea; Early satiety and abdominal bloating; 8 kg wt gain
- Current meds: Furosemide 40 →80 mg bid; Carvedilol 25 mg bid; Lisinopril 10 mg qd; Spironolactone 25 mg qd
- BP 128/76, HR 68, RR 18; JVP ~14 cm; abdomen distended, RUQ tenderness; o/w no change
- Labs: Na 134, K 4.2, BUN 48, Cr 2.8 (from 1.5)

Optimal management of concomitant medications includes:

A. Discontinue Carvedilol
B. Discontinue Lisinopril
C. Discontinue Spironolactone
D. Discontinue Carvedilol and Lisinopril
E. None of the above

Question #6: Discussion

One year later, Mr. HCE presents to clinic with:

- Bendopnea; Early satiety and abdominal bloating; 8 kg wt gain
- Current meds: Furosemide 40 →80 mg bid; Carvedilol 25 mg bid; Lisinopril 10 mg qd; Spironolactone 25 mg qd
- BP 128/76, HR 68, RR 18; JVP ~14 cm; abdomen distended, RUQ tenderness; o/w no change
- Labs: Na 134, K 4.2, BUN 48, Cr 2.8 (from 1.5)

Optimal management of concomitant medications includes:

A. Discontinue Carvedilol
B. Discontinue Lisinopril
C. Discontinue Spironolactone
D. Discontinue Carvedilol and Lisinopril
E. None of the above
Cardiac Resynchronization Therapy (CRT) in Heart Failure


Implantable Cardioverter Defibrillator (ICD) Device Therapy in Heart Failure

Surgical/ Percutaneous/ Transcatheter Interventions in Heart Failure


<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG or percutaneous intervention is indicated for HF patients on GDMT with angina and suitable coronary anatomy, especially significant left main stenosis or left main equivalent</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>CABG to improve survival is reasonable in patients with mild to moderate LV systolic dysfunction and significant multivessel CAD or proximal LAD stenosis when viable myocardium is present</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>CABG or medical therapy is reasonable to improve morbidity and mortality for patients with severe LV dysfunction (EF &lt;35%), HF, and significant CAD</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>Surgical aortic valve replacement is reasonable for patients with critical aortic stenosis and a predicted surgical mortality of no greater than 10%</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>Transcatheter aortic valve replacement is reasonable for patients with critical aortic stenosis who are deemed inoperable</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>CABG may be considered in patients with ischemic heart disease, severe LV systolic dysfunction, and operable coronary anatomy whether or not viable myocardium is present</td>
<td>IIB</td>
<td>B</td>
</tr>
<tr>
<td>Transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency is of uncertain benefit</td>
<td>IIB</td>
<td>B</td>
</tr>
<tr>
<td>Surgical reverse remodeling or LV aneurysmectomy may be considered in HF/EF for specific indications, including intractable HF and ventricular arrhythmias</td>
<td>IIB</td>
<td>B</td>
</tr>
</tbody>
</table>

Advances in Heart Failure

- Definition, Nomenclature, Epidemiology
- Evaluation and Diagnosis
- Treatment of Stages of Heart Failure
- Co-morbidities
Management of Co-morbidities in Patients with Stage C HF

- Hypertension
- Hyperlipidemia
- Obesity
- Coronary artery disease
- Peripheral vascular disease
- Diabetes mellitus
- Chronic obstructive pulmonary disease
- Sleep apnea/ Sleep disordered breathing
- Depression
- Atrial fibrillation

---

Maintenance of Sinus Rhythm in Heart Failure: AF-CHF


Enrollment Criteria:
- Age >18 years
- LVEF ≤35%
- Hosp with HF
- h/o HF NYHA II - IV
- h/o atrial fib episode >6h or with cardioversion

Study Groups: Unblinded
- Rhythm-control
- Rate-control

No differences for any other endpoint or subgroup

Cardiovascular Death:
- HR= 1.06 (0.86-1.30)
- p=0.59 by log-rank test

<table>
<thead>
<tr>
<th>Months of Follow-up</th>
<th>No. at Risk</th>
<th>Rate control</th>
<th>Rhythm control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>593</td>
<td>514</td>
<td>378</td>
</tr>
<tr>
<td>1</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>2</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>3</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>4</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>5</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>6</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>7</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>8</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>9</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>10</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>11</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>12</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>13</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>14</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>15</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>16</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>17</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>18</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>19</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>20</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>21</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>22</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>23</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>24</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>25</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>26</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>27</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>28</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>29</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>30</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>31</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>32</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>33</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>34</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>35</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>36</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>37</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>38</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>39</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>40</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>41</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>42</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>43</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>44</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>45</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>46</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>47</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>48</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>49</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>50</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>51</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>52</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>53</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>54</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>55</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>56</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>57</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>58</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>59</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
<tr>
<td>60</td>
<td>514</td>
<td>381</td>
<td>219</td>
</tr>
</tbody>
</table>

Survival Rate (%) vs Months of Follow-up

P=0.59
Maintenance of Sinus Rhythm in Heart Failure: AF-CHF

**A**
Cardiovascular Death

- Hazard ratio 0.998 (0.894-1.038)
- p=0.963

**B**
Total Mortality

- Hazard ratio 1.051 (0.967-1.274)
- p=0.615

Digoxin-Associated Mortality in Patients with Atrial Fibrillation or Heart Failure: A Meta-Analysis

### Atrial fibrillation
- 9 studies of only AF
- 3 studies of AF + HF
- Total 235,047 AFib pts

### Heart Failure
- 7 studies of only HF
- 3 studies of AF + HF
- Total 91,379 HF pts
Catheter Ablation of Atrial Fibrillation in Patients With Left Ventricular Systolic Dysfunction: A Meta-Analysis


Systematic review, 26 studies, 1838 pts with A fib, LV dysfxn
Mean LVEF 40% (95%CI 35-46)
Mean f/u 23 months
HF NYHA I/II/III or IV: 20/45/35%
Paroxysmal/ Persistent AF: 45/50%

Overall complication rate: 4.2% (3.6%–4.8%)
Efficacy in maintaining NSR at follow-up end: 60% (54%–67%)

Stages of Heart Failure

At Risk for Heart Failure

<table>
<thead>
<tr>
<th>STAGE A</th>
<th>STAGE B</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk for HF but without structural heart disease or symptoms</td>
<td>Structural heart disease but without signs or symptoms</td>
</tr>
<tr>
<td>e.g., Patients with: • NYHA class I/II • Recent MI • Pre-existing heart disease</td>
<td></td>
</tr>
</tbody>
</table>

Heart Failure

<table>
<thead>
<tr>
<th>STAGE C</th>
<th>STAGE D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural heart disease with prior or current symptoms of HF</td>
<td>Refractory HF</td>
</tr>
<tr>
<td>e.g., Patients with: • Known structural heart disease and • HF signs and symptoms</td>
<td></td>
</tr>
</tbody>
</table>

Goals
- Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Prevent mortality

Strategies
- Identification of comorbidities

Treatment
- Diuresis to relieve symptoms of congestion
- Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT)

- Randomized, double-blind, placebo-controlled, multicenter trial.
- Target 3515 pts with ≥1 sign and ≥1 symptom of HF, LVEF ≥45%, SBP <140 mm Hg (or ≤160 mm Hg if ≥3 BP meds), serum K <5.0 mmol/L; either HF hosp ≤12 months or BNP ≥100 pg/mL or NTproBNP ≥360 pg/mL.
- 3445 pts randomized to Placebo or Spironolactone 15-45 mg qd.
- Potassium monitored baseline, weeks 1 & 4, then q4 months.
- Hyperkalemia: Spironolactone 18.7%, vs. 9.1% in Placebo group.
- Hypokalemia: Spironolactone 16.2%, vs. 22.9% in Placebo group.
- Worsening renal function: Spironolactone 10.2%, vs. 7.0% in Placebo group; p <0.001.

TOPCAT: Regional Outcomes

- ≈4-fold greater composite event rate in 1767 enrolled from the United States, Canada, Brazil, Argentina (Americas) compared to the 1678 patients randomized from Russia/Georgia.
- Significant differences in patient characteristics and outcomes.
Phenomapping of HFpEF

• 397 patients with HFpEF
• Detailed clinical, laboratory, ECG, echo phenotyping.
• Several statistical learning algorithms, including unbiased hierarchical cluster analysis of phenotypic data (67 continuous variables) and penalized model-based clustering,
• Define and characterize mutually exclusive groups making up a novel classification of HFpEF.
• Mean age was 65±12 years; 62% were female; 39% were black; and comorbidities were common

Pheno-Groups of HFpEF

1) Younger patients, moderate diastolic dysfunction who have relatively normal BNP;
2) Obese, diabetic patients with high prevalence of obstructive sleep apnea, worst LV relaxation;
3) Older patients with significant chronic kidney disease, electric and myocardial remodeling, pulmonary hypertension, and RV dysfunction.
Stages of 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**
- Structural heart disease with poor or recent symptoms of HF

**STAGE D**
- Refractory HF

**THERAPY**
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient's end-of-life goals

**Options**
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

**Examples**
- Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**THERAPY**
- Goals:
  - Present HF symptoms
  - Present further cardiac remodeling
  - Improve HRQOL
  - Present mortality

**Strategies**
- Identification of comorbidities
- Treatment

**Notes**
- Adjunctive care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation
Advances in Heart Failure

- Definition, Nomenclature, Epidemiology
- Evaluation and Diagnosis
- Treatment of Stages of Heart Failure
- Co-morbidities
- Future directions

Emerging Therapies for Chronic Heart Failure

- HCN Channel/ $I_f$ current blockers: Ivabradine
Ivabradine: Mechanism of Action


Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in sino-atrial node

---

Ivabradine in Stable Coronary Artery Disease and LV Systolic Dysfunction (BEAUTIFUL)


- Event-driven, multinational, randomized, double-blind, placebo-controlled, parallel-group trial
- Documented stable CAD, LVEF ≤40%, LVEDD >56 mm, NSR≥60 bpm
- 10,917 total randomized
  - 5479 Ivabradine
  - 5438 Placebo
- Median f/u 19 (IQR 16–24) months
- 1° endpoint (CV death/ MI/ HF hosp):
  - Ivabradine 844 (15.4%)
  - Placebo 832 (15.3%)
  - HR 1.00, 95% CI 0.91–1.10, p=0.94

---

All Patients

HR≥70 bpm

---
Ivabradine in Stable Coronary Artery Disease and LV Systolic Dysfunction (BEAUTIFUL)


<table>
<thead>
<tr>
<th>Prespecified subgroup with heart rate of 70 bpm or greater (N=5392)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Primary composite endpoint</td>
</tr>
<tr>
<td>Cardiovascular death* or admission to hospital for myocardial infarction or new-onset or worsening heart failure</td>
</tr>
<tr>
<td>Mortality endpoints</td>
</tr>
<tr>
<td>All-cause death</td>
</tr>
<tr>
<td>Cardiovascular death*</td>
</tr>
<tr>
<td>Cardiac death</td>
</tr>
<tr>
<td>Heart failure endpoints</td>
</tr>
<tr>
<td>Admission to hospital for heart failure†</td>
</tr>
<tr>
<td>Cardiovascular death* or admission to hospital for new-onset or worsening heart failure</td>
</tr>
<tr>
<td>Coronary endpoints</td>
</tr>
<tr>
<td>Admission to hospital for myocardial infarction†</td>
</tr>
<tr>
<td>Admission to hospital for myocardial infarction† or unstable angina</td>
</tr>
<tr>
<td>Coronary revascularisation</td>
</tr>
</tbody>
</table>

Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT)


- Event-driven, multinational, randomized, double-blind, placebo-controlled, parallel-group trial
- NYHA II-III, LVEF ≤35%, NSR>70 bpm, HF Hospitalization within 12 months
- 6558 total
  - 3268 Ivabradine
  - 3290 Placebo
- Median f/u 22±9 (IQR 18–28) months
- 1° endpoint (CV death/ HF hosp):
  - Ivabradine, 793 (24%)
  - Placebo 937 (29%)
  - HR 0.82, 95% CI 0.75–0.90, p<0.0001
Recurrent Heart Failure Hospitalizations in SHIFT


Adverse Events in SHIFT

Adverse Events in SHIFT


<table>
<thead>
<tr>
<th>Patients with an adverse event</th>
<th>Ivabradine group (n=3232)</th>
<th>Placebo group (n=3260)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2439 (75%)</td>
<td>2423 (74%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Heart failure</td>
<td>804 (25%)</td>
<td>937 (29%)</td>
<td>0.0005</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>

**Ivabradine Approvals**

Approved in the US in April 15, 2015.

- Indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
Ivabradine in heart failure—no paradigm SHIFT...yet


### Table: Baseline variables in selected contemporary β-blocker trials and SHIFT

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>HR (bpm)</th>
<th>LVEF (%)</th>
<th>All-cause mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEBIT-HF</td>
<td>3991</td>
<td>64</td>
<td>77</td>
<td>130</td>
<td>78</td>
<td>83</td>
<td>28</td>
</tr>
<tr>
<td>CIBIS-1</td>
<td>641</td>
<td>60</td>
<td>86</td>
<td>127</td>
<td>79</td>
<td>83</td>
<td>25</td>
</tr>
<tr>
<td>CIBIS-2</td>
<td>2647</td>
<td>61</td>
<td>80</td>
<td>130</td>
<td>80</td>
<td>80</td>
<td>28</td>
</tr>
<tr>
<td>AMI</td>
<td>415</td>
<td>67</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>28</td>
<td>17.3</td>
</tr>
<tr>
<td>US Carvedilol</td>
<td>1094</td>
<td>58</td>
<td>77</td>
<td>116</td>
<td>73</td>
<td>84</td>
<td>23</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2289</td>
<td>63</td>
<td>79</td>
<td>123</td>
<td>76</td>
<td>83</td>
<td>20</td>
</tr>
<tr>
<td>COMET</td>
<td>3029</td>
<td>62</td>
<td>80</td>
<td>126</td>
<td>77</td>
<td>81</td>
<td>26</td>
</tr>
<tr>
<td>SHIFT</td>
<td>6505</td>
<td>60</td>
<td>77</td>
<td>122</td>
<td>76</td>
<td>80</td>
<td>29</td>
</tr>
</tbody>
</table>

All-cause mortality assessed at different times between the trials. SBP=systolic blood pressure. DBP=diastolic blood pressure. HR=heart rate. bpm-beats per minute. LVEF=left ventricular ejection fraction. NS=not statistically significant. *s-metoprolol succinate. t=s-isoprenaline. l=s-carvedilol. m=s-metoprolol fumarate. f=i-vabradine.

**Ivabradine Approvals**

Approved in the US in April 15, 2015.

- Indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
Relative Contraindications to Beta-blockers in Heart Failure

- Heart rate <60 bpm
- Symptomatic hypotension
- Greater than minimal evidence of fluid retention
- Signs of peripheral hypoperfusion
- PR interval >0.24 sec
- Second- or third-degree atrioventricular block (without electronic pacemaker)
- History of asthma or reactive airways *(NOT COPD)*
- Peripheral artery disease with resting limb ischemia

Emerging Therapies for Chronic Heart Failure

- HCN Channel/ $I_f$ current blockers: Ivabradine
- Angiotensin Receptor Blocker/ Neprilysin inhibitor (ARNI): LCZ696
**LCZ696 – A First-in-Class Angiotensin Receptor Neprilysin Inhibitor (ARNI)**

**Natriuretic Peptide System**

- pro-BNP
- BNP
- NT-pro BNP
- Neprilysin
- Inactive fragments

- Vasodilation
  - ↓ blood pressure
  - ↓ sympathetic tone
  - ↓ aldosterone levels
  - ↓ fibrosis
  - ↓ hypertrophy
- Natriuresis/Diuresis

**Renin Angiotensin System**

- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II
- AT₁ receptor
- ANP
- BNP
- pro-BNP
- NT-pro BNP

- Vasodilation
  - ↑ blood pressure
  - ↑ sympathetic tone
  - ↑ aldosterone levels
  - ↑ fibrosis
  - ↑ hypertrophy

**PARADIGM-HF: Study design**


- CHF NYHA Class II-IV, LVEF ≤ 35%, Elevated BNP/NT-proBNP; on stable standard therapy
- Double-blind treatment period
- LCZ696 200 mg bid
- N = 8458 pts randomized
- Enalapril 10 mg bid
- On top of standard heart failure therapy (excluding ACEIs and ARBs)

- Single-blind run-in period
- Enalapril 10 mg bid
- LCZ696 100 mg bid
- LCZ696 200 mg bid
- 36-hour washout period
- Testing tolerability to target doses of Enalapril and LCZ696

- 2 weeks
- 1-2 weeks
- 2-4 weeks
- ~ 17 to 52 months (event-driven)

Primary outcome: CV death or HF hospitalization (event driven: 2,410 pts with primary events)
PARADIGM-HF: Main Results


PARADIGM-HF: Adverse Events


<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>Hypotension</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>Elevated serum creatinine</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>Elevated serum potassium</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>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema[†]</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>
PARADIGM-HF: Adverse Events


<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>Hypotension</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>Elevated serum creatinine</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>Elevated serum potassium</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>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema†</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>

PARADIGM-HF: Considerations

- Run-in period excluded many patients (~20%)
  - May limit generalizability
  - Markedly underestimates absolute adverse event rates and relative AE rate (Enalapril, then LCZ696)
- All patients required to tolerate ACEi
- Possible limited benefit in ACEi naïve patients
- Predominantly NYHA II patients (70%); 22% Female (1832 pts); 5% Black (428 pts); 15% ICD, 7% CRT; 7% North American
- Early stopping of the trial may have exaggerated the treatment effect
Advances in Heart Failure

• Definition, Nomenclature, Epidemiology
• Evaluation and Diagnosis
• Treatment of Stages of Heart Failure
• Co-morbidities
• Future directions

Thank you!

San Francisco Veterans Affairs Medical Center