Heart Failure: Diagnosis and Therapy

David T. Cragun, MD
Cardiologist, Central Utah Clinic

Objectives:
• Identify how to differentiate heart failure from other common cardiac and non-cardiac conditions
• Summarize the causes and treatment of both systolic heart failure and HF with normal EF
• State how to monitor for complications, and know when specialty consultation is appropriate
CHF Management: Time for a new PARADIGM?

david cragun, m.d., FACC

26 September 2014
Disclosures

- No relevant financial disclosures

- Note: I will borrow heavily from and highlight findings found in the 2013 American College of Cardiology Guidelines for the Management of Heart Failure
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Heart Failure Management: Time for a new PARADIGM?
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Stages, Phenotypes and Treatment of HF

**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
  - 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

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

- e.g., Patients with:
  - Previous MI
  - LV remodeling including LHV and low EF
  - Asymptomatic valvular disease

**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

**STAGE C**
Structural heart disease with prior or current symptoms of HF

- e.g., Patients with:
  - Known structural heart disease and HF signs and symptoms

**THERAPY**
- Goals
  - Control symptoms
  - Patient education
  - Prevent hospitalization
  - Prevent mortality
- Drugs for routine use
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Drugs for use in selected patients
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxin
- In selected patients
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

**STAGE D**
Refractory HF

- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**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

**Heart Failure**

- Development of symptoms of HF

- HFrEF

- HFpEF

- Refractory symptoms of HF at rest, despite GDMT
Classifications of Heart Failure

- **HF\(r\)EF**: Heart failure with *reduced* EF
  - Usually EF ≤ 35% but now ≤ 40%
  - Virtually all have components of diastolic dysfunction
  - Not everyone with reduced EF has the syndrome of heart failure

- **HF\(p\)EF**: Heart failure with *preserved* EF
  - Usually defined as EF > 40%
  - Often normal ejection fraction but they have the clinical syndrome of heart failure
How to diagnose heart failure?

- 3+ pedal edema or worse?
- BNP 348?
- Can’t walk ½ block without stopping to catch breath?
- Severe orthopnea?
- Frequent paroxysmal nocturnal dyspnea?
- JVD 12 cm H₂O?

It’s a syndrome, not a single finding on exam or labs
HF $\rho$EF

- In Framingham heart study, annual mortality was about half of HF $\tau$EF
  - 8.7% vs. 15.4%
- In Mayo Clinic inpatient study from 1987 – 2001 of patients admitted with HF, one year mortality was 29% vs. 32% ($p$ vs. $r$)
- Most measures of morbidity are similar between $p$ and $r$
  - Hospitalization rates, QoL scores, 6MWT, $O_2$ consumption
Prognosis of Heart Failure

- **HF rEF**
  - Framingham study 1990–1999
    - 1 year mortality 28%♂, 24%♀
    - 5 year mortality 59%♂, 45%♀
  - Medicare data 2001–2005
    - 2.5 million Medicare beneficiaries hospitalized with HF
    - 37% one–year mortality
<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At high risk for HF but without structural heart disease or symptoms of HF.</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but without signs or symptoms of HF.</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms of HF.</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions.</td>
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</table>
# Classifications of Heart Failure

<table>
<thead>
<tr>
<th>NYHA Functional Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
<tr>
<td>ACCF/AHA Stages of HF</td>
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</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>A At high risk for HF but without structural heart disease or symptoms of HF.</td>
<td>None</td>
</tr>
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Diagnosis

- Thorough history and physical
  - Identify cardiac and non-cardiac comorbidities
  - Symptoms: dyspnea, orthopnea, PND, angina, exercise intolerance
  - Jugular venous distention
  - Chest exam for rales, effusions
  - Peripheral edema / chronic venous stasis changes
  - Cardiac impulse, murmurs, rhythm
  - ECG
Diagnosis

- Labs
  - CBC
  - Urinalysis
  - CMP
  - Magnesium
  - Lipids
  - TSH
  - Maybe BNP or NT–proBNP
BNP

- Normal 0–100 in young, healthy patients
- Increases with age, atrial fibrillation
- Lessened by obesity
- Sensitivity 90%, specificity 74%, accuracy 83%
- Half-life 20 minutes
NT-proBNP

- Longer half-life 25–70 minutes
- Improved accuracy
- Cutoff varies with age
  - Age <50, cutoff < 450 pg/mL
  - Age 50–75, cutoff < 900 pg/mL
  - Age >75, cutoff < 1800 pg/mL
- Across all ages, value < 300 pg/mL had 98% specificity
## Causes for Elevated Natriuretic Peptide Levels

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<tr>
<th>Cardiac</th>
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<td>• Pulmonary causes: obstructive sleep apnea, severe pneumonia, pulmonary hypertension</td>
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<td>• Critical illness</td>
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<td>• Bacterial sepsis</td>
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<td>• Myocarditis</td>
<td>• Severe burns</td>
</tr>
<tr>
<td>• Cardiac surgery</td>
<td>• Toxic-metabolic insults, including cancer chemotherapy and envenomation</td>
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Imaging for HF

- Chest x-ray
- Echocardiogram
  - At onset
  - With significant change in status, i.e., exacerbations
  - To guide need for device placement
- Imaging stress test
  - New HF if candidates for revascularization
- Angiography
  - If new, unexplained LVEF < 40%, may be appropriate to proceed to angiography
Medical management

STAGE A
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e.g., Patients with:
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- Atherosclerotic disease
- DM
- Obesity
- Metabolic syndrome or
- Patients
  - Using cardiotoxins
  - With family history of cardiomyopathy

THERAPY

Goals
- Heart healthy lifestyle
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Drugs
- ACEI or ARB in appropriate patients for vascular disease or DM
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2013 ACC HF Guidelines
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In selected patients
- ICD
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2013 ACC HF Guidelines
THERAPY

Goals
- Control symptoms
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- Prevent mortality

Drugs for routine use
- Diuretics for fluid retention
- ACEI or ARB
- Beta blockers
- Aldosterone antagonists

Drugs for use in selected patients
- Hydralazine/isosorbide dinitrate
- ACEI and ARB
- Digoxin

In selected patients
- CRT
- ICD
- Revascularization or valvular surgery as appropriate
Medications for HF/EF

- ACEI or ARB
- Beta blockers
- Aldosterone antagonists
  - Post–MI if EF < 40%
  - HF NYHA II–IV and EF < 35%
- Loop diuretics
- Selected patients
  - Hydralazine / isosorbide dinitrate
  - Digoxin
- Avoid calcium antagonists (especially non–dihydropyridine)
Heart Failure Medications Proven to Reduce Mortality in HFrEF

Drugs that inhibit the renin-angiotensin system have modest effects on survival.

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Courtesy of the Paradigm HF Investigators
## Medical Therapy for Stage C HF\(r\)EF: Magnitude of Benefit Demonstrated in RCTs

<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>
<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
</tr>
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2013 ACC HF Guidelines
# 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>
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</thead>
<tbody>
<tr>
<td><strong>Beta Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once</td>
<td>10 mg once</td>
<td>8.6 mg/d (118)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice</td>
<td>50 mg twice</td>
<td>37 mg/d (446)</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg once</td>
<td>80 mg once</td>
<td>[]</td>
</tr>
<tr>
<td>Metoprolol succinate extended release (metoprolol CR/XL)</td>
<td>12.5 to 25 mg once</td>
<td>200 mg once</td>
<td>159 mg/d (447)</td>
</tr>
<tr>
<td><strong>Hydralazine &amp; Isosorbide Dinitrate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed dose combination (423)</td>
<td>37.5 mg hydralazine/20 mg isosorbide dinitrate 3 times daily</td>
<td>75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily</td>
<td>~175 mg hydralazine/90 mg isosorbide dinitrate daily</td>
</tr>
<tr>
<td>Hydralazine and isosorbide dinitrate (448)</td>
<td>Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg 3 or 4 times daily</td>
<td>Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses</td>
<td>[]</td>
</tr>
</tbody>
</table>

2013 ACC HF Guidelines
# Drugs Commonly Used for HFrEF (Stage C HF)

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<th>Maximum Doses(s)</th>
<th>Mean Doses Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3 times</td>
<td>50 mg 3 times</td>
<td>122.7 mg/d (421)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice</td>
<td>10 to 20 mg twice</td>
<td>16.6 mg/d (412)</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5 to 10 mg once</td>
<td>40 mg once</td>
<td>---------</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5 mg once</td>
<td>20 to 40 mg once</td>
<td>32.5 to 35.0 mg/d (444)</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg once</td>
<td>8 to 16 mg once</td>
<td>---------</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg twice</td>
<td>20 mg twice</td>
<td>---------</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 to 2.5 mg once</td>
<td>10 mg once</td>
<td>---------</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg once</td>
<td>4 mg once</td>
<td>---------</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 to 8 mg once</td>
<td>32 mg once</td>
<td>24 mg/d (419)</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 to 50 mg once</td>
<td>50 to 150 mg once</td>
<td>129 mg/d (420)</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20 to 40 mg twice</td>
<td>160 mg twice</td>
<td>254 mg/d (109)</td>
</tr>
<tr>
<td><strong>Aldosterone Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25 mg once</td>
<td>25 mg once or twice</td>
<td>26 mg/d (424)</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once</td>
<td>50 mg once</td>
<td>42.6 mg/d (445)</td>
</tr>
</tbody>
</table>
Regarding B–blockers in HFrEF

- Use of 1 of the 3 beta blockers proven to reduce mortality (i.e., **bisoprolol, carvedilol, and sustained–release metoprolol succinate**) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality

2013 ACC HF Guidelines
Drugs proven to reduce hospitalizations, death, or serious morbidity:
Medications for HFrEF

TOPCAT Trial
NEJM 2014 370:1388

Figure 1. Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.

The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. The inset shows the same data on an expanded y axis.
Medications for HFpEF

Hazard ratio, 0.83 (95% CI, 0.69–0.99)
P=0.04 by log-rank test

TOPCAT Trial
NEJM 2014 370:1388

Figure 2. Kaplan–Meier Plots of Two Components of the Primary Outcome.
Panel A shows the time to confirmed death from cardiovascular causes, and Panel B the time to the first confirmed hospitalization for heart failure. The insets show the same data on an expanded y axis.

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spironolactone</td>
</tr>
<tr>
<td>0</td>
<td>1722</td>
</tr>
<tr>
<td>12</td>
<td>1502</td>
</tr>
<tr>
<td>24</td>
<td>1167</td>
</tr>
<tr>
<td>36</td>
<td>869</td>
</tr>
<tr>
<td>48</td>
<td>613</td>
</tr>
<tr>
<td>60</td>
<td>330</td>
</tr>
<tr>
<td>72</td>
<td>53</td>
</tr>
</tbody>
</table>
Medications for HFpEF

- Reasonable to use for HTN or other compelling reasons
  - ACEI or ARB
  - Beta-blockers
  - Aldosterone antagonists

- Loop diuretics
  - For symptomatic improvement

- Retrospective trials suggest some benefit from statins
HF: Which loop diuretic?

- Three sulfa based:
  - Furosemide/Lasix (85–90% penetrance)
  - bumetanide/Bumex (10–12% penetrance)
  - Torsemide/Demadex (0–3% penetrance)

- One non-sulfa based
  - ethacrynic acid (Edecrin)
### Which loop diuretic for HF?

- **Three sulfa based:**

<table>
<thead>
<tr>
<th></th>
<th>Furosemide</th>
<th>Bumetanide</th>
<th>Torsemide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose equivalent</strong></td>
<td>40mg</td>
<td>1 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>t$_{1/2}$</strong></td>
<td>1–2h</td>
<td>&lt;1 h</td>
<td>3.5h</td>
</tr>
<tr>
<td><strong>Available</strong></td>
<td>IV / PO</td>
<td>IV / PO</td>
<td>IV / PO</td>
</tr>
<tr>
<td><strong>PO bioavailability</strong></td>
<td>&lt;50%</td>
<td>&gt;80%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td><strong>IV:PO</strong></td>
<td>1:2</td>
<td>About 1:1</td>
<td>About 1:1</td>
</tr>
<tr>
<td><strong>Kaliuresis</strong></td>
<td>++++</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Cost (30 days)</strong></td>
<td>$11</td>
<td>$23</td>
<td>$34</td>
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### Which loop diuretic for HF?

- **Three sulfa based:**
  - Furosemide
  - Bumetanide
  - Torsemide

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<td><strong>Dose equivalent</strong></td>
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<td>20mg</td>
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<tr>
<td><strong>t₁/₂</strong></td>
<td>1-2h</td>
<td>&lt;1h</td>
<td>3.5h</td>
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<td>$34</td>
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<tr>
<td><strong>KCl 20 mEq</strong></td>
<td>$18</td>
<td>$18</td>
<td>$0</td>
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Why torsemide (not furosemide) for HF?

- Simpler
  - No potassium replacement, generally
- Better tolerated
  - Patients prefer it
  - Gentler onset and action
- Cheaper
- More predictable
- More effective in lowering NYHA class
- Mortality benefits
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  - Patients prefer it
  - Gentler onset and action

Eur Jnl Hrt Failure 2003; 5:793

Fig. 3. Mean number of mictions within 6 h after diuretic intake. ○ Torasemide, ▲ Furosemide. $P<0.000001$ (global value over 9 months).
Why torsemide (not furosemide) for HF?

- Better tolerated
  - Patients prefer it
  - Gentler onset and action

Eur Jrnl Hrt Failure 2003; 5:793

Fig. 4. Evolution of the restriction of daily life due to diuretic treatment over the trial period as rated by the patients (0: no, 1: little, 2: moderate, 3: severe restriction). ○ Torasemide, ▲ Furosemide. $P < 0.001$ (global value over 9 months).
Why torsemide (not furosemide) for HF?

- Simpler
  - No potassium replacement, generally
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  - Gentler onset and action
- Cheaper
- More predictable
- More effective in lowering NYHA class
- Mortality benefits
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Why torsemide (not furosemide) for HF?

- Mortality benefits

### Table

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Torsemide Events</th>
<th>Total</th>
<th>Furosemide Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random. 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Cosin 2002</td>
<td>17</td>
<td>778</td>
<td>27</td>
<td>527</td>
<td>38.4%</td>
<td>0.43 [0.23, 0.77]</td>
</tr>
<tr>
<td>Murray 2001</td>
<td>18</td>
<td>113</td>
<td>25</td>
<td>121</td>
<td>41.2%</td>
<td>0.77 [0.45, 1.33]</td>
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<tr>
<td>Müller 2003</td>
<td>8</td>
<td>122</td>
<td>6</td>
<td>115</td>
<td>20.4%</td>
<td>1.26 [0.45, 3.51]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1013</strong></td>
<td><strong>763</strong></td>
<td><strong>58</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td>0.68 [0.39, 1.18]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 3.87$, df = 4 ($P = 0.14$); $I^2 = 48%$

Test for overall effect: $Z = 1.38$ ($P = 0.17$)
5% of patients don’t tolerate it as well / prefer furosemide
Higher doses are a bit more expensive
  ◦ $34 for 20 mg (30 doses)
  ◦ $96 for 100mg (30 doses)
IV formulation not currently available
Data is admittedly weak but appears to show significant benefits
Patients generally prefer torsemide after being on both it and furosemide
Cheaper
Much less need for potassium replacement
Lifestyle interventions

- Exercise regimen
- Sodium restriction (2,000 mg / day)
- Regular weigh-ins, close fluid status monitoring
- CPAP for sleep apnea
ICD for HF

- Recommended for patients with HF–EF if
  - EF < 35%
  - More than 40 days since MI
  - Class II–III symptoms on GDMT
  - Life span expectation > 1 year

- Or
  - LVEF < 30% post-MI
  - 40 days post-MI
  - No HF symptoms
Cardiac Resynchronization Therapy (CRT) for HF

- Bi-ventricular pacemaker
Cardiac Resynchronization Therapy (CRT) for HF

- Bi-Ventricular pacemaker
- Indicated in HR EF
  - EF $\leq 35\%$
  - Sinus rhythm
  - LBBB (or IVCD) with QRS duration of at least 150 msec (some utility at 120–149 msec)
  - Class II–IV symptoms on GDMT
Other treatments for HF

- Stents
- Coronary artery bypass surgery
- Aortic valve replacement for AS
- Mitral valve surgery
- Rarely aneurysmectomy
Other treatments for HF

- Vasopressor therapy
- Ultrafiltration (IIb)
- Temporary or semi-permanent mechanical support
  - Tandem Heart
  - Impella
  - ECMO
  - LVAD / RVAD
  - Artificial heart
- Heart transplant
Newest Drug for HF

- tolvaptan (Samsca)
  - Novel class of drugs called aquaretics
  - Vasopressin antagonist: blocks ADH receptors in distal tubules of the kidney
  - Prevents water resorption at the final step of nephron filtration
  - Particularly effective in hyponatremia, use generally with Na < 128
  - Costly, $300/tablet
  - Safety concerns
    - ? Liver toxicity
    - Closely monitor sodium levels
Heart Failure Medications Proven to Reduce Mortality in HFrEF

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Courtesy of the Paradigm HF Investigators
Heart Failure Medications Proven to Reduce Mortality in HFrEF

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Drugs that inhibit the renin-angiotensin system have modest effects on survival

% Decrease in Mortality

- 0%
- 10%
- 20%
- 30%
- 40%
Heart Failure Medications Proven to Reduce Mortality in HFrEF

- Angiotensin receptor blocker
- ACE inhibitor
- Beta blocker

Drugs that inhibit the renin-angiotensin system have modest effects on survival.

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Courtesy of the Paradigm HF Investigators
Neprilysin Inhibition Potentiates Endogenous Vasoactive Peptides

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

- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention

Courtesy of the Paradigm HF Investigators
Neprilysin Inhibition Potentiates Endogenous Vasoactive Peptides

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Neprilysin Inactive metabolites

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

Neprilysin

Inactive metabolites

Neprilysin inhibition

Neurohormonal activation
Vascular tone
Cardiac fibrosis, hypertrophy
Sodium retention

Courtesy of the Paradigm HF Investigators
LCZ697: Angiotension Receptor Neprilysin Inhibition

LCZ696

Angiotensin receptor blocker + Inhibitor of neprilysin

losartan + sacubitril

Courtesy of the Paradigm HF Investigators
Design of the PARADIGM–HF Trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

LCZ696 400 mg daily  ↔  Enalapril 20 mg daily

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE

Courtesy of the Paradigm HF Investigators
PARADIGM–HF Entry Criteria

- NYHA Class II–IV heart failure
- LVEF ≤40% initially; lowered to ≤35%
- Elevated BNP or N-terminal proBNP
- Any use of ACEI or ARB’s, but needed to able to tolerate a dose equivalent to at least enalapril 10 mg daily for 4 weeks
- GDMT including beta–blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥ 95, eGFR ≥ 30 mL/min, and serum K≤5.4 mEq/L at randomization

Courtesy of the Paradigm HF Investigators
PARADIGM–HF Endpoints

- Primary endpoint: composite of cardiovascular death or hospitalization for heart failure
- Pre-determined that the Data Monitoring Committee was allowed to stop the trial early only for a compelling effect on cardiovascular mortality
- A difference of at least 15% in cardiovascular mortality was prospectively identified as being important enough to stop the trial early.

Courtesy of the Paradigm HF Investigators
Heart Failure Medications Proven to Reduce Mortality in HFrEF

Drugs that inhibit the renin-angiotensin system have modest effects on survival.

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

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- Angiotensin receptor blocker
- ACE inhibitor
- Beta blocker
- Mineralocorticoid receptor antagonist

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Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Courtesy of the Paradigm HF Investigators
PARADIGM–HF: 8399 patients baseline characteristics

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<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
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<tbody>
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<td>Age (years)</td>
<td>63.8 ± 11.5</td>
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<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
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<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
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<tr>
<td>LV ejection fraction (%)</td>
<td>29.6 ± 8.1</td>
<td>29.4 ± 6.3</td>
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<td>71.6% / 23.1%</td>
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<td>122 ± 15</td>
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<td>72 ± 12</td>
<td>73 ± 12</td>
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<td>N-terminal pro-BNP (pg/ml)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
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<td>255 (155-474)</td>
<td>251 (153-465)</td>
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<td>History of diabetes</td>
<td>35%</td>
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<td>Digitalis</td>
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PARADIGM-HF: Primary Endpoint
Cardiovascular Death or Rehospitalization

Kaplan-Meier Estimate of Cumulative Rates (%)

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>900</td>
<td>1544</td>
<td>1488</td>
</tr>
<tr>
<td>1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>

HR = 0.80 (0.73-0.87)
P = 0.00000002
Number needed to treat = 21

Courtesy of the Paradigm HF Investigators
PARADIGM–HF: Cardiovascular Death

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

Enalapril  
(n=4212)  
693  
558

LCZ696  
(n=4187)  

Patients at Risk

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>0</td>
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<td>180</td>
<td>4056</td>
<td>4051</td>
</tr>
<tr>
<td>360</td>
<td>3891</td>
<td>3860</td>
</tr>
<tr>
<td>540</td>
<td>3282</td>
<td>3231</td>
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<tr>
<td>720</td>
<td>2478</td>
<td>2410</td>
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<tr>
<td>900</td>
<td>1716</td>
<td>1726</td>
</tr>
<tr>
<td>1080</td>
<td>1005</td>
<td>994</td>
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<tr>
<td>1260</td>
<td>280</td>
<td>279</td>
</tr>
</tbody>
</table>

Courtesy of the Paradigm HF Investigators
PARADIGM–HF: All–Cause Mortality

HR = 0.84 (0.76-0.93)  
P<0.0001

Enalapril  
(n=4212)

LCZ696  
(n=4187)

Patients at Risk

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<tr>
<td></td>
<td>4187</td>
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</tr>
<tr>
<td>1 year</td>
<td>4056</td>
<td>4051</td>
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<tr>
<td>2 years</td>
<td>3891</td>
<td>3860</td>
</tr>
<tr>
<td>3 years</td>
<td>3282</td>
<td>3231</td>
</tr>
<tr>
<td>4 years</td>
<td>2478</td>
<td>2410</td>
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<tr>
<td>5 years</td>
<td>1716</td>
<td>1726</td>
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<tr>
<td>6 years</td>
<td>1005</td>
<td>994</td>
</tr>
<tr>
<td>7 years</td>
<td>280</td>
<td>279</td>
</tr>
</tbody>
</table>

Courtesy of the Paradigm HF Investigators
PARADIGM–HF: What else?

- LCZ696 was also *more effective* than enalapril in
  - Reducing the risk of a HF hospitalization by an additional 21%
  - Incrementally improving symptoms and physical limitations of heart failure
- LCZ696 was *better tolerated* than enalapril
  - Less likely to cause cough, hyperkalemia, renal impairment, or to be discontinued for adverse event
  - More hypotension but this didn’t result in more discontinuations
  - No increased risk of serious angioedema (unlike omapatrilat)

Courtesy of the Paradigm HF Investigators
HFrEF drug effects:

- Angiotensin receptor blocker
- ACE inhibitor
- Beta blocker
- Mineralocorticoid receptor antagonist

% Decrease in Mortality:
- 0%
- 10%
- 20%
- 30%
- 40%

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Courtesy of the Paradigm HF Investigators
HFrEF: a new paradigm

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Courtesy of the Paradigm HF Investigators
Angiotensin–Neprilysin 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*
Authors argue for a ‘moral imperative’ or ‘ethical mandate’
Should replace the use of ACE inhibitors or ARB agents
Cost will be the biggest barrier to adoption
Not discussed

- In-hospital management of HF
- Transitioning from inpatient to outpatient management
- Idiopathic cardiomyopathies
- Rare syndromes / causes (i.e., Chagas)
Final thoughts

- We have made a lot of progress over the last 2 decades in the management of HF
- It remains a leading cause of American morbidity and mortality
- STEMI care prevents significant ischemic HF incidence
- Mortality rates have only dropped modestly
- Prognosis is still quite poor
Conclusions

- We need to follow the guidelines (GDMT)
- HFrEF
  - ACEI/ARB
  - Beta-blockers
  - Aldosterone blockade
  - Diuretic, preferably torsemide
  - Consider ICD / Bi-ventricular pacing
  - Treat underlying cause
  - Dietary / exercise / lifestyle changes
  - Neprilysin antagonist when available
- HFpEF
  - Manage co-morbidities including hypertension, CAD
  - Diuretics are the mainstay for symptom management
  - Role for aldosterone blockade?