Congestive Heart Failure 2015

JP Mehegan / Mercy Cardiology

Definition
- Cardiac failure; Congestive heart failure; Chronic heart failure (synonyms)
- When the heart is unable to pump sufficiently and at the appropriate pressure to meet the body's needs
- Symptoms: dyspnea, edema, fatigue; activity intolerance
- STARTING POINT

Types of Heart Failure
- Systolic: heart failure with abnormal LV function; ejection fraction < 40%
- Diastolic: heart failure with normal LV systolic function and abnormal cardiac relaxation (diastolic function); 50%
- Other: valvular, ischemia, MI, constriction / pericardial disease

The Problem (USA)
- 5,000,000 patients
- 6,500,000 hospital days/year
- 300,000 deaths/year
- More than half of those diagnosed will be dead in 5 years
- 6% of health care budget (38 billion)
- Incidence doubling in last ten years

Heart Failure Costs
- 60% Inpatient care $23.1 billion
- 39% Outpatient care $14.7 billion
- 1% Transplants $270 million
Total = $38.1 billion (5.4% of total healthcare costs)


Stages in the evolution of Heart Failure
- A. HF risk factors; no documented heart disease or symptoms
- B. Heart disease; no symptoms. Asymptomatic LV dysfunction
- C. Prior or current symptomatic CHF
- D. Refractory HF symptoms

AHA / ACC HF guidelines 2005
Stages in Prevention and Treatment of Heart Failure

A. Treat risk factors, avoid toxins. ACE-I
B. ACE-I, Beta blockers
C. ACE-I, Beta blockers, diuretics, aldosterone antagonists, ARB, resynchronization (Bi-V pacing), new therapies
D. Ultrafiltration, inotrope therapy, VADs and transplant

Classification of Functional Status; NYHA

1. No physical limitations
2. Symptoms with moderate activity, exercise.
3. Symptoms with mild activity; activities of daily living
4. Symptoms at rest

Initial / Ongoing Evaluation

H&P
Assess functional capacity (NYHA, 6 min walk)
Assess volume status: (edema, rales, jugular, hepatomegaly, body weight)
Lab assessment: routine: electrolytes, renal function, ECHO, X ray, TSH, EKG
BNP

Causes of Cardiomyopathy/CHF

135 Causes of cardiomyopathy
CAD; prior MI, diffuse ischemia (70%)
Hypertension
Endocrine; diabetes, thyroid
Drugs/Toxins; ETOH, cocaine, chemo
Afib/Flutter; rate related
Infection, familial, nutritional, idiopathic

B type natriuretic peptide
BNP

Role in the emergency room
70 yo with PND, orthopnea, edema and vascular congestion on CXR
70 yo with COPD, wheezing, rales and edema, clear CXR
Role in the clinic

Treatment Objectives

Increase Survival
Improve LV function
Improve symptoms/Quality of Life
Improve exercise capacity
Block neurohormonal changes and prevent progressive HF
CHF Trials App ($2.99)
Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

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

ACE-I. Clinical Effects

- Improve symptoms
- Reduce remodeling / progression
- Reduce hospitalization
- Improve survival

ACE-I Practical Use

- Start with low dose
- Increase dose as tolerated
- Renal function & serum K⁺ after 1-2 weeks
- Dose NOT determined by symptoms
- Target randomized trial doses
- Reduce diuretics if possible

Mortality Reduction with ACE-I

<table>
<thead>
<tr>
<th>Study</th>
<th>ACE-I</th>
<th>Clinical Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS (1987)</td>
<td>Enalapril</td>
<td>CHF</td>
</tr>
<tr>
<td>SOLVD treatment</td>
<td>Enalapril</td>
<td>CHF</td>
</tr>
<tr>
<td>AIRE</td>
<td>Ramipril</td>
<td>CHF</td>
</tr>
<tr>
<td>Vheft-II</td>
<td>Enalapril</td>
<td>CHF</td>
</tr>
<tr>
<td>TRACE</td>
<td>Trandolapril</td>
<td>CHF</td>
</tr>
<tr>
<td>SAVE</td>
<td>Captopril</td>
<td>LVD/MI</td>
</tr>
<tr>
<td>SMILE</td>
<td>Zofenapril</td>
<td>High risk</td>
</tr>
<tr>
<td>HOPE (2000)</td>
<td>Ramipril</td>
<td>High risk</td>
</tr>
</tbody>
</table>

ACE-I Dose (mg)

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 / 8h</td>
<td>50 / 8h</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 / 12h</td>
<td>10 to 20 / 12h</td>
</tr>
<tr>
<td>Fesinopril</td>
<td>5 to 10 / day</td>
<td>40 / day</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5.0 / day</td>
<td>20 to 40 / day</td>
</tr>
<tr>
<td>Quinapril</td>
<td>10 / 12 h</td>
<td>40 / 12 h</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 to 2.5 / day</td>
<td>10 / day</td>
</tr>
</tbody>
</table>

AHA / ACC HF guidelines 2005
ACE-i Adverse Effects

- Hypotension
- Worsening renal function
- Hyperkalemia
- Cough 5-10% (iron pill may prevent)
- Angioedema (1/1000)
- Rash, ageusia, neutropenia (1-2%)
- ACE intolerant use ARB

Angiotensin Receptor Blockers (ARBs)

- As added therapy
- As alternative therapy (ACEi intolerant)
- FDA approved: Valsartan 40 mg BID start, 160 mg BID target
- Candesartan; 4 mg QD start, 32 mg QD target
- Most commonly used (not approved and underdosed), Losartan, target 150 mg QD

Val-HeFT

5010 patients ≥18 years; EF <40%; NYHA II-IV; LVIDd >2.9 cm/m²

Receiving background therapy

ACE inhibitors, diuretics, digoxin, β-blockers

Randomized to

Valsartan 40 mg bid titrated to 160 mg bid

Placebo


Effect of Valsartan on Combined Morbidity/Mortality Endpoint*

<table>
<thead>
<tr>
<th>Months</th>
<th>Probability of Event-Free Survival</th>
<th>Valsartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>65</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>80</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*All-cause mortality, sudden death with resuscitation, hospitalization for worsening heart failure, or therapy with IV inotropes or vasodilators.


CHARM

7,601 patients with heart failure

3 individual component randomized trials with the ARB candesartan (4 or 8 mg/day, titrated to target dose of 32 mg) or placebo

CHARM Added
- Patients with LVEF ≤40% and treated with an ACE-inhibitor

CHARM Alternative
- Patients with LVEF ≤40% and ACE-Inhibitor intolerant

CHARM Preserved
- Patients with LVEF >40% with or without ACE-inhibitor

Endpoints (follow-up minimum 2 years):
- Primary – Component trials: cardiovascular mortality or HF hospitalization
- Primary – Overall trial results: All-cause mortality

**Primary Outcome**

CV Death or CHF Hospitalization

**CHARM Added**

<table>
<thead>
<tr>
<th>Time, yr</th>
<th>Placebo</th>
<th>Candesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1272</td>
<td>1276</td>
</tr>
<tr>
<td>1</td>
<td>1017</td>
<td>1074</td>
</tr>
<tr>
<td>2</td>
<td>652</td>
<td>914</td>
</tr>
<tr>
<td>3</td>
<td>736</td>
<td>793</td>
</tr>
<tr>
<td>3.5</td>
<td>338</td>
<td>395</td>
</tr>
</tbody>
</table>

HR 0.85 (95% CI: 0.75, 0.96), \( p = 0.011 \)

Adjusted HR = 0.85, \( p = 0.010 \)

NNT = 23

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**β-Adrenergic Blockers**

**Mechanism of action**

- Inhibit cardiotoxicity of catecholamines
- Block Neurohormonal activation
- HR
- Antiischemic
- Antihypertensive
- Antiarrhythmic
- Antioxidant, Antiproliferative

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**β-Adrenergic Blockers**

**Clinical Effects**

- Improve symptoms (only long term)
- Reduce remodeling / progression
- Improve LV systolic function
- Reduce hospitalization
- Reduce sudden death
- Improve survival

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**β-Adrenergic Blockers**

**When to start**

- Patient stable
- Not volume overloaded
- No need for i.v. inotropic drugs
- Stable dose of ACEi / Diuretic / Dig

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**β-Adrenergic Blockers**

**Contraindications**

- Asthma (not COPD)
- AV block
- Symptomatic hypotension / Bradycardia
- PVD and Diabetes are NOT contraindications

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**β-Adrenergic Blockers**

**Adverse Effects**

- Hypotension
- Fluid retention / worsening heart failure
- Fatigue
- Bradycardia / heart block
- Reduce dose
- Consider cardiac pacing
- DON’T GIVE UP
**β-Adrenergic Blockers**

**Dose (mg)**

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 / 24h</td>
<td>10 / 24h</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 / 12h</td>
<td>25 / 12h</td>
</tr>
<tr>
<td>Carvedilol XL</td>
<td>10 / 24h</td>
<td>80 / 24h</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5-25 / 24h</td>
<td>200 / 24h</td>
</tr>
</tbody>
</table>

*Start Low, Increase Slowly*

*Increase the dose every 2 - 4 weeks*

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**Carvedilol Effect on Survival**

- 35% Reduction In death

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**What is Target Dose?**

**Effect of Carvedilol on Left Ventricular Ejection Fraction**

- Placebo
- 2.5 mg bid
- 5 mg bid
- 10 mg bid

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**What is Target Dose**

**Carvedilol Dose-Response Trial (MOCHA™): Effect on Mortality and Morbidity**

- Mortality
- Cardiovascular Hospitalizations

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**Which Agent Should We Use?**

- Substantial differences in Beta–Blocking Agents
- Beta-1 Selectivity
- Alpha-1 blockade
- Ancillary Properties
- Antioxidant
- Endothelin regulation

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**COMET**

**Carvedilol vs Metoprolol Tartrate**

- 5.7%mortality reduction
Digitalis. Clinical Effects
- Improve symptoms and measured exercise
- Reduction in hospitalization for CHF
- Does not improve survival

DIG trial

NYHA II-III

N=6800

[Graph showing data]

N Engl J Med 1997;336:525

Digitalis. Indications

In combination with ACE-i + diuretics
If persisting symptoms
AF, to slow AV conduction
Dose 0.125 to 0.250 mg / day

AHA / ACC Guidelines 2005

Diuretics. Indications

1: Symptomatic HF, with fluid retention
- Edema
- Dyspnea
- Lung Rales
- Jugular distension
- Hepatomegaly
- Pulmonary edema (Xray)

Diuretics. Dose (mg)

<table>
<thead>
<tr>
<th>Initial</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>0.5 to 1.0 / 12-24h</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20 to 40 / 12-24h</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 to 20 / 12-24h</td>
</tr>
</tbody>
</table>

Loop Diuretics / Thiazides. Practical Use
- Start with low dose. Titrate to achieve dry weight
- Monitor serum K+ / renal function at “frequent intervals”
- Reduce dose when fluid retention is controlled
- Teach the patient when, how to change dose
- Combine to overcome “resistance”
- Do not use alone
Thiazides, Loop Diuretics. Adverse Effects

- $\text{K}^+$, $\text{Mg}^+$ wasting (sudden death???)
- $\text{Na}^+$
- Stimulation of neurohormonal activity
- Hyperuricemia (15 - 40%)

Diuretic Resistance

- Neurohormonal activation
- Hypertrophy of distal nephron
- Reduced tubular secretion (renal failure, NSAIDs)
- Decreased renal perfusion (low output)
- Altered absorption of diuretic
- Noncompliance with drugs/ Dennys biscuits and gravy

Managing Resistance to Diuretics

- Restrict $\text{Na}^+/$H$_2$O intake (Monitor Sodium)
- Increase dose (individual dose, frequency, i.v.)
- Combine! furosemide + thiazide / spiro / metolazone
- Reduce dose of ACE-I
- Stop NSAIDS
- Dopamine (increase cardiac output)

Aldosterone in Heart Failure

- Levels up 20X from normal
- Produces adverse effects
  - Cardiac remodeling
  - $\text{Na}^+$ retention
  - Up SNS
  - Down arterial compliance

RALES Trial

- 1663 patients
- LVEF greater than or equal to 35
- NYHA III-IV
- Spironolactone or placebo in addition to standard therapy

RALES Trial; Mortality Data
**Adverse Effects of Spironolactone**

<table>
<thead>
<tr>
<th>Effect</th>
<th>RALES</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia</td>
<td>NA</td>
<td>34%</td>
</tr>
<tr>
<td>Mild</td>
<td>NA</td>
<td>34%</td>
</tr>
<tr>
<td>Severe</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>Azotemia</td>
<td>NA</td>
<td>12%</td>
</tr>
</tbody>
</table>

**EMPHASIS-HF**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eplerenone (%)</th>
<th>Placebo (%)</th>
<th>Adjusted hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death/heart-failure hospitalization</td>
<td>18.3</td>
<td>25.9</td>
<td>0.63 (0.54–0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>10.8</td>
<td>13.5</td>
<td>0.76 (0.61–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart-failure hospitalization</td>
<td>12.0</td>
<td>18.4</td>
<td>0.58 (0.47–0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization for hyperkalemia</td>
<td>0.3</td>
<td>0.2</td>
<td>1.15 (0.25–5.31)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

NYHA Class II HF (N=2737)
LV EF < 30%
Eplerenone 25-50mg QD vs. Placebo

**Aldosterone Antagonist Recommendations**
- Add to standard treatment if:
  - Advanced symptoms
  - No contraindications
  - Increased K+
  - Azotemia
- Follow K+ and BUN/Cr

**Aldosterone Antagonist Recommendations**
- Decrease KCL by 50%
- Lab Follow-up
  - Low risk
    - K+ and BUN/Cr level at week 1 & 4
  - High Risk
    - K+ and BUN/Cr level at day 3 and at week 1 & 4

**PARADIGM-HF**
- Entresto formerly LCZ696
- Approved July 2015
- ARB-Neprilysin inhibition vs enalapril 10 mg BID
- Valsartan-Sacubitril
- Starting dose 49/51 mg BID, target 97/103 BID

**Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure**

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

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

- Inactive metabolites

- Neprilysin
- Neprilysin inhibition
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588</td>
<td>388</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181</td>
<td>236</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139</td>
<td>188</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474</td>
<td>601</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>99</td>
<td>0.001</td>
</tr>
<tr>
<td>Angioedema (adjudicated)</td>
<td>16</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Medications, no hospitalization</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

ENTRESTO

- Entresto $400/month, $4800/year
- Enalapril $4/month, $48/year
Cardiac resynchronization