Chronic Heart Failure
Pathophysiology & Pharmacotherapy

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Objectives
- Describe basic pathophysiology of CHF
- Explain terminology related to CHF
- Describe signs & symptoms of CHF
- Outline therapeutic goals of treating CHF
- Describe the major objectives, general study design, therapies evaluated, significance and conclusions of major trials evaluating drug therapy of CHF

Heart Failure: An Increasing Burden
- 4.7 million Americans have HF
- ≈ 550,000 new cases each year in the U.S.
- 75% of HF cases have prior hypertension
- 5-year mortality rate for HF = 50%
- Hospital discharges ↑ 159.4% (1979 - 1998)


Heart Failure ~An Early Definition~
Chronic Heart Failure is a pathophysiologic state in which the heart is unable to pump blood at a rate sufficient to meet the metabolic needs of the body

Brunwald, Heart Disease 1985

Heart Failure Definition
Heart failure is a clinical syndrome in which heart disease:
✓ Reduces cardiac output
✓ Increases venous pressure
✓ Is accompanied by molecular abnormalities that cause progressive deterioration of the failing heart & premature myocardial cell death

Katz AM, Heart Failure, 2000

The Heart as a Target Organ

Coronary Artery Disease
Hypertension
Heart Failure
Arrhythmia
Valvular Heart Disease
Cardiomyopathy
Pathophysiology

Cardiac Failure

- Venous Pressure
- Cardiac Output
- Sympathetic Tone
- BP
- Renal Blood Flow
- Renin, Angiotensin II
- Aldosterone
- Capillary Filtration
- Na\(^+\) & H\(_2\)O Retention

EDEMA

Sympathetic Activation in Heart Failure

- CNS sympathetic outflow
- Cardiac sympathetic activity
- Sympathetic activity to kidneys and blood vessels
- Activation of RAS
- Myocyte death
- Increased arrhythmias
- Disease progression
- Sodium retention

Chronic Heart Failure

- Systolic Dysfunction
  - Impaired Ejection
  - Decreased Contractility
- Diastolic Dysfunction
  - Impaired Filling
  - Depressed Relaxation
  - Clinical trials lack this group of patients

NEW YORK HEART ASSOCIATION CLASSIFICATION OF HF PATIENTS

Based on the degree of effort needed to elicit symptoms:

**CLASS I**
- Pts. with documented heart disease of any type who are symptom free except with more than normal activity

**CLASS II**
- Slight limitation of physical activity because symptoms (shortness of breath, chest pain) occur only with ordinary physical activity

**CLASS III**
- Marked limitation of physical activity because symptoms occur even with less than ordinary physical activity (eg. eating meals)

**CLASS IV**
- Severe limitation of physical activity because symptoms occur even at rest (eg. in a sitting or lying position)

ACC/AHA Staging of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Patients at high risk of developing HF because of the presence of conditions strongly associated with HF but who have NO identified structural or functional abnormalities of the myocardium, pericardium, or cardiac valves and have never shown signs or symptoms of HF.</td>
<td>Systemic hypertension; coronary artery disease; diabetes mellitus; history of cardiotoxic drug therapy or alcohol abuse; personal or family history of cardiomyopathy.</td>
</tr>
<tr>
<td>B</td>
<td>Patients who have developed structural heart disease that is strongly associated with the development of HF but have never shown signs or symptoms of HF.</td>
<td>Left ventricular hypertrophy; dilated, fibrotic, or restrictive cardiomyopathy; asymptomatic valvular heart disease; previous myocardial infarction.</td>
</tr>
<tr>
<td>C</td>
<td>Patients who have current or prior symptoms of HF associated with underlying structural heart disease.</td>
<td>Dyspnea or fatigue due to LV systolic dysfunction, asymptomatic patients who are undergoing treatment for prior symptoms of HF.</td>
</tr>
<tr>
<td>D</td>
<td>Patients with advanced structural heart disease and marked symptoms of HF even despite maximal medical therapy and life support interventions.</td>
<td>Patients who are frequently hospitalized for HF and cannot be safely discharged from the hospital without in the hospital, requiring heart transplantation, support at home receiving home parenteral nutrition, support at home requiring continuous respiratory support or being supported with a mechanical or extracorporeal assist device; patients in a long-term setting for the management of HF.</td>
</tr>
</tbody>
</table>

**Heart Failure Classifications**

<table>
<thead>
<tr>
<th>ACC-AHA Stage</th>
<th>NYHA Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic with moderate exertion</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic at rest</td>
</tr>
</tbody>
</table>

**Evolution of Clinical Stages**

- **NORMAL**
  - No symptoms
  - Normal LV function

- **Compensated CHF**
  - No symptoms
  - Normal LV function

- ** Decompensated CHF**
  - No symptoms
  - Abnormal LV function

- **Refractory CHF**
  - Symptoms not controlled with treatment

**Neurohormonal Responses to Impaired Cardiac Performance**

<table>
<thead>
<tr>
<th>Response</th>
<th>Short-term Effect</th>
<th>Long-term Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt and water retention</td>
<td>Augments preload</td>
<td>Pulmonary congestion, edema</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>Maintains blood pressure for perfusion of vital organs (brain, heart)</td>
<td>Exacerbates pump dysfunction (excessive afterload); increases cardiac energy expenditure</td>
</tr>
<tr>
<td>Sympathetic stimulation</td>
<td>Increases heart rate and ejection fraction</td>
<td>Increases energy expenditure, contributes to remodeling</td>
</tr>
</tbody>
</table>

**Management of Heart Failure**

**Correct Underlying Causes:** Hypertension

**Restrict Fluid Intake:**
- 1.5-2 liters is advised
- Mod. alcohol intake is permitted

**Restrict Sodium Intake:**
- Intake should be limited to 2 grams/day (1 tsp table salt)

**Drug Therapy:**
- Vasodilators (ACE-Inh, ARBs)
- Beta-blockers
- Diuretics
- Digoxin
- Spironolactone

**Treatment Guidelines**

<table>
<thead>
<tr>
<th>NYHA Classification</th>
<th>For Symptoms</th>
<th>For Survival/Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Reduce/stop diuretic</td>
<td>Continue ACE Inhibitor if asymptomatic; add beta-blocker if post MI</td>
</tr>
<tr>
<td>II</td>
<td>diuretic depending on fluid retention</td>
<td>ACE Inhibitor is first-line treatment; add beta-blocker if patient remains symptomatic</td>
</tr>
<tr>
<td>III</td>
<td>diuretics + digital if still symptomatic + nitrates/hydralazine if tolerated</td>
<td>ACE Inhibitor and beta-blockade; add spironolactone</td>
</tr>
<tr>
<td>IV</td>
<td>diuretics + digital + temporary isotropic support</td>
<td>ACE Inhibitor + beta-blockade; add spironolactone</td>
</tr>
</tbody>
</table>

ACE Inhibitors
SOLVD (Studies of Left Ventricular Dysfunction)

- Enalapril (titrated to 10mg BID) vs placebo in 6,794 patients
- Ejection fraction \( \leq 35\% \)
- End points include:
  - Delaying the progression of heart failure
  - Improving signs and symptoms
  - Reducing mortality
- Treatment arm - 2,568 symptomatic class II-III patients most on digitalis and diuretics
- Prevention arm - 4,226 asymptomatic class I-II patients, most on no concomitant therapy

**NEJM 1991:325:293-302**

SOLVD Prevention- Enalapril
Asymptomatic HF Patients w/ LVD (EF \( \leq 35\% \))
(NYHA Class I-II)

- 32% Fewer First Hospitalizations
  - Placebo (n=2,177)
  - Enalapril (n=2,111)

Number of First Hospitalizations for Heart Failure


SOLVD Prevention Trial
Morbidity and Combined Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo %</th>
<th>Enalapril %</th>
<th>RR %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of CHF</td>
<td>30.2</td>
<td>20.7</td>
<td>37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Development of CHF and anti-CHF Rx</td>
<td>22.5</td>
<td>13.9</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First Hospitalization for CHF</td>
<td>12.9</td>
<td>8.7</td>
<td>36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple Hospitalization for CHF</td>
<td>4.8</td>
<td>2.7</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death or Development of CHF</td>
<td>38.6</td>
<td>29.8</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death or Hospitalization for CHF</td>
<td>24.5</td>
<td>20.6</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**The SOLVD Investigators, N Engl J Med, 1992.**

SOLVD-Treatment
Symptomatic HF patients with EF \( \leq 35\% \)

- **Placebo**
- **Enalapril**

% of Patients

- Death
- CV Death
- Died or hospitalized for HF after 1 year

**p < 0.01**

**The SOLVD Investigators, NEJM, 1991.**

Cooperative North Scandinavian Enalapril Survival Study
(CONSENSUS)

- Multicenter, randomized, double-blind, placebo-controlled trial
- 253 patients; 126 placebo, 127 enalapril (titrated to 10-20mg BID) followed for an average of 188 days
- Patient History:
  - Class IV CHF patients
  - Conventional treatment for heart failure was continued in both groups

**CONSENSUS Study Group**

**NEJM 1987.**

CONSENSUS
Cumulative Probability of Death in the Placebo and Enalapril Groups

**CONSENSUS Study Group**

**NEJM 1987.**
ATLAS
Assessment of Treatment with Lisinopril & Survival

- Multicenter, randomized, double-blind
- 3164 patients (40-80 years old), 1596 low dose (2.5-5mg/day), 1568 high dose (32.5-35mg/day) followed for 39-58 months
- NYHA Class II-IV (EF < 30%)
- Results:
  - Insignificant lower risk of total mortality (42.5% vs 44.9%)
  - Significantly fewer hospitalizations (3819 vs 4397, p=0.021)
  - During follow up 18% of low dose and 17% of high dose patients had to stop the study drug due to adverse effects

ACE Inhibitors in Heart Failure

- Start low and wait at least two weeks before increasing dose
- Dose titration is based on target dose rather than symptomatic improvement
  - Consider dividing the dose if necessary
- Monitor: BP, renal function, potassium
- Correction to notes on page 139 – maintenance dose of lisinopril should be 20-40mg QD

Beta-Blockers

MERIT-HF
Metoprolol XL Randomised Intervention Trial in Congestive Heart Failure

- Multicenter, randomized, double-blind, placebo-controlled trial
- 3991 patients (40-80 years old), 1990 metoprolol XL target dose 200mg/day, 2001 placebo followed for an average of one year
- Patient History:
  - NYHA Class II-IV (LVEF < 40%)
  - Conventional treatment for heart failure was continued in both groups
  - Exclusion criteria included: HR<68bpm, use of amiodarone 6 months prior to enrollment, use of calcium antagonists

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Metoprolol (N)</th>
<th>Placebo (N)</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>45</td>
<td>72</td>
<td>39%</td>
<td>0.0086</td>
</tr>
<tr>
<td>CV mortality</td>
<td>40</td>
<td>70</td>
<td>44%</td>
<td>0.0028</td>
</tr>
<tr>
<td>Sudden death</td>
<td>22</td>
<td>39</td>
<td>45%</td>
<td>0.024</td>
</tr>
<tr>
<td>Death from worsening HF</td>
<td>13</td>
<td>28</td>
<td>55%</td>
<td>0.015</td>
</tr>
<tr>
<td>Total hospitalizations</td>
<td>273</td>
<td>363</td>
<td>27%</td>
<td>0.0037</td>
</tr>
<tr>
<td>Total hospitalizations due to worsening HF</td>
<td>105</td>
<td>187</td>
<td>45%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


COPERNICUS
Carvedilol Prospective Randomized Cumulative Survival Study

- Multicenter, randomized, double-blind, placebo-controlled trial
- 2289 patients; 1133 placebo, 1156 carvedilol (titrated to 25mg BID) followed for an average of 10.4 months
- Patient History:
  - Severe heart failure
  - Symptoms at rest or minimal exertion for at least 2 months
  - LV ejection fraction < 25% despite conventional therapy
  - Conventional treatment for heart failure was continued in both groups


Packer, et al. NEJM 2001; 344:1851-59
Beta-blockers in Heart Failure

- Patient should be on background ACE inhibition
- Start at a low dose
- Wait at least two weeks before increasing dose
- Monitor BP, HR, clinical status (congestion, mental status)
- Use caution when starting in an unstable NYHA III or IV patient

COPERNICUS
Carvedilol Prospective Randomized Cumulative Survival Study

![Graph showing the effect of carvedilol vs placebo on death from any cause and death or hospitalization.](Image)


Spironolactone

RALES
Randomized Aldactone Evaluation Study Investigators

- Multicenter, randomized, double-blind, placebo-controlled
- Purpose: Determine if spironolactone would decrease the risk of death in patients with severe heart failure
- 1663 patients (EF ≤ 35%) randomized and followed for an average of 24 months
- Spironolactone 25mg QD vs. Placebo
- Patient History:
  - NYHA Class III-IV
  - Patients were on ACE inhibitors & loop diuretics
  - Digoxin and vasodilators were allowed
  - K⁺ sparing diuretics were not allowed

![Graph showing the results of the RALES study.](Image)

RALES
Randomized Aldactone Evaluation Study Investigators

- Results:
  - Statistically significant reductions in:
    - Mortality (35% vs 46%, p<0.001)
    - 30% reduction in risk of hospitalization for cardiac causes
  - Side Effects:
    - Hyperkalemia (2% spironolactone vs 1% placebo, NS)
    - Gynecomastia (10% vs 1%, p<0.001)
  - Conclusion:
    - Spironolactone in addition to standard therapy may reduce morbidity and mortality in patients with severe heart failure

Spironolactone in Heart Failure

- Consider using in patients who remain symptomatic (NYHA III) despite the use of an ACE inhibitor, β-blocker, digoxin and diuretics
- Monitor potassium, blood pressure
Diuretics

• Consider for all patients predisposed to fluid retention
• Loops are considered the drug of choice
• Metolazone may be used in addition to a loop in cases of severe volume overload
• Do not use alone!!
• Monitor: daily weight, potassium, renal function, blood pressure

Diuretics in Heart Failure

• Have the potential to alter the efficacy and toxicity of agents used to treat heart failure
  – Underdosing may lead to fluid retention and ↓ the response to ACE inhibitors and ↑ risk of treating with beta-blockers
  – Overdosing may lead to volume depletion and increase the risk of renal insufficiency with ACE inhibitors & ARBs

Digoxin

DIG Digitalis Investigation Group

• Multicenter, randomized, double-blind, placebo-controlled
• Purpose: Assess the effects of digoxin on morbidity & mortality in patients with HF and normal sinus rhythm
• 6800 patients (EF ≤ 45%) randomized and followed for an average of 37 months
• Median daily dose 0.25mg/day (mean level 0.88ng/mL)
• Patient History:
  – NYHA Class II-III
  – ACE Inhibitors encouraged. If patients remained symptomatic despite optimization of other therapies, open-label digoxin was allowed and study drug was discontinued.

DIG Data from Digitalis Investigation Group

• Results:
  • No significant difference in mortality (34.8% D vs 35.1% PL, p<0.8)
  • Hospitalization rates were significantly lower in digoxin group:
    • Cardiovascular reasons (49.4% vs 54.4%, p<0.001)
    • Worsening heart failure (26.8% vs 34.7%, p<0.001)
    • All cause (64.3% vs 67.1%, p=0.006)

• Conclusions:
  • Digoxin therapy was associated with lower rates hospitalization
  • Digoxin therapy did not reduce overall mortality
**Digoxin in Heart Failure**

- Use in patients who remain symptomatic despite use of an ACE inhibitor & β-blocker
- No need to load for chronic heart failure
- Use low dose (0.125mg QD or QOD) if patient is >70 y.o. or has impaired renal function
- Little evidence to support monitoring levels in chronic heart failure
- Monitor: HR, GI, Neuro
- Withdrawal of digoxin is NOT recommended

**Angiotensin Receptor Blockers**

**The Renin-Angiotensin System**

**Major Angiotensin II Receptor Subtypes**

- **AT₁**
  - Vasoconstriction
  - Aldosterone release
  - Cell proliferation, hypertrophy, matrix deposition
  - Bradykinin, NO, and cGMP release
  - Antiproliferation
  - Apoptosis

- **AT₂**
  - Vasodilation

Adapted with permission from Siragy HM. Angiotensin Receptor Blockers: Evidence for Preserving Target Organs. 1999:1.1

**ELITE Evaluation of Losartan in the Elderly**

- Multicenter, randomized, double-blind
- Purpose: Compare the efficacy & safety of losartan and captopril in the treatment of elderly patients with HF
- 772 patients (>65 years old); 352 losartan (50mg QD), 370 captopril(50mg TID) followed for an average of 48 weeks
- Patient History:
  - NYHA Class II-IV
  - LV ejection fraction ≤40%
  - No prior ACE inhibitor therapy
  - Conventional treatment for heart failure (except open-label ACE inhibitors) was permitted
  - No difference in hospital admission for HF (5.7% each group)

**Results:**

- Persisting ≥SCr (≥0.3mg/dL) occurred in 10.5% in each group
- Fewer losartan patients discontinued treatment due to adverse effects (12.2% vs 20.8%)
- Cough present only in captopril group (12 patients, 3.2%)
- Decrease in all cause mortality in losartan group (4.8% vs 8.7%, p=0.035)
ELITE II
Evaluation of Losartan in the Elderly II

- Multicenter, randomized, double-blind
- Purpose: Verify whether losartan is better than captopril in reducing mortality in patients with heart failure
- 3152 patients (>60 years old); 352 losartan (50mg QD), 370 captopril (50mg TID) followed for an average of 1.5 years
- Patient History:
  - NYHA Class II-IV
  - LV ejection fraction ≤ 40%
  - No ACE inhibitor or ARB therapy (or were exposed ≤ 7 days)
  - Conventional treatment for heart failure (except open-label ACE inhibitors) was permitted

ELITE II: Endpoint Results

Val-HeFT
Randomized Trial of Valsartan in Heart Failure

- Multicenter, randomized, double-blind, placebo-controlled
- Purpose: To determine if Valsartan can further reduce morbidity & mortality in patients receiving pharmacologic therapy considered optimal by their physicians
- 5010 patients (>18 years old); 2511 valsartan (160mg BID), 2499 placebo followed for an average of 23 months
- Patient History:
  - NYHA Class II-IV
  - LV ejection fraction ≤40%
  - Receiving a fixed-dose drug regimen for 2 weeks prior to the study that could include ACE inhibitors, diuretics, beta-blockers, digoxin

Val-HeFT Overview

5010 patients
>18 years; EF ≤ 40%; NYHA II-IV
Receiving background therapy
ACE inhibitors (n=4644), diuretics (n=4300)
digoxin (n=3374), β-blockers (n=1784)
Valsartan 40mg bid titrated to 160mg bid
Randomized to
Placebo

Val-HeFT Primary Efficacy Endpoints

- All cause mortality (time to death)
- Combined all cause mortality and morbidity (time to event)
  - All cause mortality
  - Sudden death with resuscitation
  - Hospitalization for HF
  - Need for therapeutic doses of IV inotropic or vasodilating agent for at least 4 hrs

Val-HeFT Randomized Trial of Valsartan in Heart Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Events</th>
<th>OR (95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>n = 2511</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>n = 2499</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>495 (19.7 %)</td>
<td>484 (19.4 %)</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>0.90,1.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined All Cause Mortality</td>
<td>723 (28.8 %)</td>
<td>801 (32.1 %)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>0.79,0.98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Morbidity end points: cardiac arrest with resuscitation, hospitalization for HF, or administration of IV inotropic or vasodilators for 4 hours or more without hospitalization
Val-HeFT: Effect of Valsartan on the Combined Endpoint*

![Graph showing event-free probability over months for Val-HeFT study.](image)

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


Val-HeFT: Heart Failure Hospitalizations*

![Graph showing event-free probability over months for Val-HeFT study.](image)

*First hospitalization


Val-HeFT

Combined Morbidity / Mortality in subgroups

<table>
<thead>
<tr>
<th>% Patients</th>
<th>Favors Valsartan</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>&gt; 65</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>EF &lt; 27</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>EF &gt; 27</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>ACEI (yes)</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>ACEI (no)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>BB (yes)</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>BB (no)</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>HD (yes)</td>
<td>57</td>
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<tr>
<td>HD (no)</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

Val-HeFT ACE Inhibitor/Beta Blocker Subgroups

![Graph showing event-free probability over months for Val-HeFT study.](image)

CHARM

Candesartan in Heart Failure-Assessment of Reduction in Mortality & Morbidity

• Purpose: To determine if candesartan will reduce the combined endpoint of CV death or hospitalization for HF

• Patient Inclusion Criteria:
  - Age ≥ 18
  - NYHA class II-IV for ≥ 4 weeks before randomization
  - LV ejection fraction ≤ 40% (assessed within previous 6 months)

Swedberg, et al. 1999 J. of Cardiac Failure

Val-HeFT Summary of Results

- Valsartan exerted a neutral effect on mortality but significantly reduced the combined endpoint of mortality and morbidity by 13.3% in patients with heart failure
- Significantly reduced heart failure hospitalizations by 27.5%
- Results indicate that ARBs should NOT be added to a heart failure drug regimen that includes both an ACE Inhibitor & a Beta-blocker

Summary

• Purpose: To determine if candesartan will reduce the combined endpoint of CV death or hospitalization for HF

• Patient Inclusion Criteria:
  - Age ≥ 18
  - NYHA class II-IV for ≥ 4 weeks before randomization
  - LV ejection fraction ≤ 40% (assessed within previous 6 months)

Swedberg, et al. 1999 J. of Cardiac Failure
**CHARM Trial Overview**

Duration=42 mo

- CHF: NYHA class II - IV
  - EF < 40%
  - EF > 40% not on an ACEI (N = 3022)

Randomization

ACEI intolerant (N = 2028)

- ACEI treated (N = 2548)

- Placebo

Candesartan 4/8 mg

Primary endpoint = CV death and CHF hospitalization
Overall endpoint = all-cause mortality


**CHARM Baseline Medications**

<table>
<thead>
<tr>
<th></th>
<th>Alternative (ACE Intolerant)</th>
<th>Preserved (EF &gt;40%)</th>
<th>Added (+ ACE)</th>
<th>Val-HeFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers (%)</td>
<td>55</td>
<td>55</td>
<td>56</td>
<td>36</td>
</tr>
<tr>
<td>Spironolactone (%)</td>
<td>24</td>
<td>17</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>46</td>
<td>58</td>
<td>28</td>
<td>68</td>
</tr>
<tr>
<td>Loop Diuretic (%)</td>
<td>85</td>
<td>90</td>
<td>75</td>
<td>85</td>
</tr>
</tbody>
</table>


**Role of ARBs in the Guidelines**

- ACC/AHA
  - “Angiotensin receptor blockers should be considered instead of ACE inhibitors who are intolerant of ACE inhibitors because of angioedema or intractable cough”

- European Society of Cardiology
  - “ARBs could be considered in patients who do not tolerate ACE inhibitors for symptomatic treatment”

♥ If intolerant to ACE, consider ARB
♥ If beta-blocker intolerant, consider ARB + ACE

**Calcium Channel Antagonists in Heart Failure**

- European Society of Cardiology Guidelines 2001
  - Not recommended for treatment of heart failure due to systolic dysfunction
  - Data with felodipine & amlodipine indicate a neutral effect on survival and may be considered for concomitant arterial HTN or angina

**Antiarrhythmics**

- Class I
  - Patients with HF may be predisposed to the cardiodepressant and proarrhythmic effects
  - AVOID!

- Class III
  - Amiodarone is effective in maintaining normal sinus rhythm in some patients
  - Routine administration of Amiodarone is not justified
  - Use of other agents (sotalol, dofetilide) is associated with a worse prognosis when used in patients with AF and AF

**Trials to Know!**

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