Chronic Heart Failure
Pathophysiology & Pharmacotherapy

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Objectives

• Describe the evidence based literature which supports the role of key therapeutic agents for the management of patients with HF

Trials to Know!

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<td>Role of ARBs in addition to standard therapy</td>
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<td>RALES, EPHESUS</td>
<td>Role of spironolactone in heart failure</td>
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Key Evidence-Based HF Trials

• ACEI SOLVD (Prev. vs. Treatment)
• β-blockers MERIT-HF, COPERNICUS, COMET
• Diuretics RALES, EPHESUS (Post-MI)
• Digoxin DIG
• ARBs CHARM, Val-HeFT
• Vasodilators V-HeFT I
• CCB PRAISE

SOLVD
(Studies of Left Ventricular Dysfunction)

• Enalapril (titrated to 10mg BID) vs placebo in 6,794 patients
• Ejection fraction ≤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 digitals and diuretics. Followed an average of 41 months.
• Prevention arm - 4,226 asymptomatic class I-II patients, most on no concomitant therapy. Followed an average of 37 months.

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

32% Fewer First Hospitalizations p<0.001

The SOLVD Investigators, N Engl J Med. 199

NEJM 1991;325:293-302
SOLVD Prevention Trial
Morbidity and Combined Outcomes


<table>
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<tr>
<th>Endpoint</th>
<th>Placebo %</th>
<th>Enalapril %</th>
<th>RR%</th>
<th>P value</th>
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<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>
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</table>


- 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

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

CONSENSUS Study Group
NEJM 1987

Cumulative Probability of Death in the Placebo and Enalapril Groups

CONSENSUS Study Group, NEJM 1987

- 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

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

JAMA 2000;283:1295-1302
**MERIT-HF**

Metoprolol XL Randomised Intervention Trial in Congestive Heart Failure (NYHA Class III/IV, n=795)

<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>
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P<0.01 for each endpoint

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**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

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**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 BR, HR, clinical status (congestion, mental status)
- Use caution when starting in an unstable NYHA III or IV patient
- Avoid in patients with reactive airway disease, symptomatic bradycardia, or advanced heart block

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**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
### 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

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### 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

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### 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

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### 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

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### 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**
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

*NEJM 1997;336:525-533*

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**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


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**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); 1578 losartan (50mg QD), 1574 captopril (50mg TID) followed for an avg 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


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**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 fxn
- Little evidence to support monitoring levels in chronic heart failure
- Monitor: HR, GI, Neuro
- Withdrawal of digoxin is NOT recommended

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**ELITE II: Endpoint Results**

![Graph showing results of ELITE II endpoint](https://example.com/graph.png)
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)

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: Effect of Valsartan on the Combined Endpoint*

*All-cause mortality, sudden death with resuscitation, hospitalization for worsening HF, or administration of IV inotropic or vasodilator drugs for 4 hours or more without hospitalization

Val-HeFT: Heart Failure Hospitalizations*

*First hospitalization

Cohn, et al NEJM 2001;345:1667-75
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Val-HeFT

Combined Morbidity / Mortality in subgroups

% Patients  Favors Valsartan  Favors Placebo

All Patients 100  0.3  0.4  0.5  0.6  0.7  0.8  0.9  1.0  1.1  1.2  1.3
< 65  47  
> 65  53  
Male  80  
Female  20  
EF ≤ 37  50  
EF > 37  50  
ACEI (yes)  93  
ACEI (no)  7  
BB (yes)  35  
BB (no)  65  
IHD (yes)  87  
IHD (no)  43  

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.

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)

CHARM Programme

3 component trials comparing candesartan to placebo in patients with symptomatic heart failure

CHARM Alternative
- n=2028
- LVEF ≤ 40%
- ACE inhibitor intolerant

CHARM Added
- n=2548
- LVEF ≤ 40%
- ACE inhibitor treated

CHARM Preserved
- n=3025
- LVEF > 40%
- ACE inhibitor treated/not treated

Primary outcome for each trial: CV death or CHF hospitalisation
Primary outcome for Overall Programme: All-cause death

CHARM-Alternative: Primary outcome CV death or CHF hospitalisation

Placebo 406 (40.0%)  Candesartan 334 (33.0%)

Lancet. 362:772-6, 2003

CHARM-Added

Patient disposition

2548 patients randomised
NYHA II-IV, LVEF ≤ 40%
ACE inhibitor treated

Candesartan n=1276
- Lost to follow-up n=3
- Completed Study n=1273

Placebo n=1272
- Lost to follow-up n=1
- Completed Study n=1271

Median follow-up of 41 months

What does the data mean?

- Addition of a ARB prevents
  - 1 death per 63 treated patients
  - 1 CHF hospitalization per 23 treated patients
  - ARBs should be prescribed, in addition to ACEIs, β blockers and/or spironolactone in patients with EF < 40% (Harvey White, Lancet 362: 754, 2003)
  - ARBs may have value in diastolic dysfunction (CHARM preserve) above and beyond ACE’s β blockers dig etc.

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