Chronic Heart Failure
Evidence-based Pharmacotherapy

R. Todd Burkhardt, Pharm.D.
Cardiovascular Research Fellow
University of Minnesota
College of Pharmacy

Objectives

- Review basic pathophysiology
- ACC/AHA 2001 Heart Failure Practice Guidelines
- Evaluate Landmark Heart Failure Trials
  - Study Design / Main Results
  - Guideline Interpretation
  - Clinical Recommendations
- Apply HF Knowledge Base
  - Establish a Goal of Therapy
  - Therapeutic drug selection
  - Monitor efficacy and safety

Heart Failure Statistics

- 22% male and 46% female post-MI have CHF (6yr)
- Increasing hospitalizations (~$5,500 per admission)
  - 377,000(‘79) to 872,000(‘95) to 995,000(‘01)
- High mortality
  - Sudden Cardiac Death occurs 6-9 times more than general population

Heart Failure Statistics

- 22% male and 46% female post-MI have CHF (6yr)
- Increasing hospitalizations (~$5,500 per admission)
  - 377,000('79) to 872,000('95) to 995,000('01)
- High mortality
  - Sudden Cardiac Death occurs 6-9 times more than general population

Chronic HF Characteristics

<table>
<thead>
<tr>
<th>Systolic Dysfunction</th>
<th>Diastolic Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired ejection (LV dilated)</td>
<td>Impaired filling (LV hypertrophy)</td>
</tr>
<tr>
<td>EF ≤40%</td>
<td>EF &gt;40%</td>
</tr>
<tr>
<td>Men 50-70 years</td>
<td>Elderly female</td>
</tr>
<tr>
<td>Congestion and Cardiomegaly</td>
<td>Congestion ± Cardiomegaly</td>
</tr>
<tr>
<td>Strong clinical data to manage HF</td>
<td>Lack of clinical data to manage HF</td>
</tr>
</tbody>
</table>


ACC/AHA Stage A

- Description
  - High risk for HF
  - No structural heart disease and asymptomatic
- Patient examples
  - CAD (HF risk > for men)
  - HTN, DM, Dyslipidemia, Obesity (HF risk > for women)
- Therapy
  - JNC 7 Report and compelling indications
  - ATP III therapeutic recommendations
  - HOPE, ALLHAT, UKPDS 38
  - Recommend Smoking cessation
  - Encourage regular exercise

AHA/ACC HF Guidelines, 2001

Systolic and diastolic LV dysfunction compared with normal LV function. Solid lines indicate the extent of ventricular contraction during systole. Reference: Noble: Textbook of Primary Care Medicine, 3rd Edition. 2001
ACC/AHA Stage B
• Description
  – Structural heart disease and asymptomatic
• Patient examples
  – LVSD (EF ≤ 40%), Valvular (mitral) Disease, Previous MI
  – NYHA I
• Therapy
  – All measures under Stage A
  – ACEI in selected patients
  – Beta-blockers in selected patients

ACC/AHA Stage C
• Description
  – Structural heart disease and previous or current HF symptoms
• Patient examples
  – SOB, fatigue, reduced exercise tolerance
  – NYHA I,II,III, IV
• Therapy
  – All measures under Stage A
  – Drugs: ACEI, Beta-blockers, Diuretics, Digoxin, ±Aldosterone antagonists
  – Dietary sodium restriction (<2 grams/day)

ACC/AHA Stage D
• Description
  – Refractory HF requiring specialized interventions
• Patient examples
  – Symptoms at rest, Recurrently hospitalized
  – NYHA IV
• Therapy
  – All measures under Stage A, B, and C
  – Continuous IV inotropic infusions
  – Mechanical Assist Devices
  – Heart transplantation

Stages for Systolic HF

Key Evidence-Based HF Trials

SOLVD-Treatment (Studies of Left Ventricular Dysfunction)
• Design: P, R, DB, PC, MC trial
• Purpose: Evaluate all-cause mortality of pts with LVD and HF symptoms using Enalapril
• Population: 2,569 NYHA II-III, 21-80yo, EF ≤ 35%
• Treatment: 5-10mg/day Enalapril vs. placebo, avg. follow-up 41 months
• Concurrent Tx: Digoxin, diuretics, vasodilators

ACEI
β-blockers
Diuretics
Digoxin
ARBs
Vasodilators
CCB

SOLVD
MERIT-HF, COPERNICUS, COMET
RALES, EPHESUS
DIG
CHARM, Val-HeFT
V-HeFT I
PRAISE

AHA/ACC HF Guidelines, 2001
AHA/ACC HF Guidelines, 2001
AHA/ACC HF Guidelines, 2001
NEJM 1991; 325:293-302
**SOLVD-Treatment Results**

(Studies of Left Ventricular Dysfunction)

- **Design**: P, R, DB, PC, MC study
- **Purpose**: Evaluate all-cause mortality of pts with LVD and without HF symptoms using Enalapril
- **Population**: 4,228 NYHA I-II, 21-80yo, EF ≤ 35%
- **Treatment**: 2.5-20mg/day Enalapril vs. placebo, avg. follow-up 37 months
- **Concurrent Tx**: Digoxin (AF), diuretics (HTN)

**Endpoint Placebo% Enalapril% RR% P value**

- Development of CHF 30.2 20.7 37 <0.001
- Development of CHF and anti-CHF Rx 22.5 13.9 43 <0.001
- First Hospitalization for CHF 12.9 8.7 36 <0.001
- Multiple Hospitalization for CHF 4.8 2.7 44 <0.001
- Death or Development of CHF 38.6 29.8 29 <0.001
- Death or Hospitalization for CHF 24.5 20.6 20 <0.001

**ACC/AHA Guidelines HF (ACEI)**

- **Stage A**
  - Class I
    - Control SBP and DBP per recommended guidelines
    - Pts Hx of AVD, DM, HTN, and CV risk factors
- **Stage B**
  - Class I
    - Pts recent/remote Hx MI regardless of EF
    - Pts ↓ EF, whether or not experienced MI
- **Stage C**
  - Class I
    - All pts, unless contraindicated

AHA/ACC HF Guidelines, 2001

**ACEI Recommendations**

- **Selection of Agent**
  - captopril, enalapril, lisinopril, other agents?
- **Target Dose**: not for symptomatic improvement
  - Initial low dose to assess tolerability, titrate 1-2 wks
  - Max. effect at 3 mo. with additional benefit to 5 yr.
- **Monitor Safety**
  - Blood pressure
  - Renal function (serum creatinine)
  - Electrolytes (serum potassium)
  - Cough (rule out worsening HF)

**MERIT-HF**

(Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure)

- **Design**: P, R, DB, PC, MC trial
- **Purpose**: Evaluate all-cause mortality of pts with LVD and HF symptoms using metoprolol succinate daily
- **Population**: 3991 NYHA II-IV, 40-80yo, EF ≤ 40%
- **Treatment**: 200mg/day (target dose) vs. placebo, avg. follow-up 12 months (stopped early)
- **Concurrent Tx**: ACEI, Diuretics, Digoxin, ARBS, Hydralazine, or LA nitrate (ACEI not tolerated)

Lancet 1999; 353:2001-7
MERIT-HF

Results

Lancet 1999; 353:2001-7

RR = 34%

RR = 38%

RR = 41%

RR = 49%

P < 0.0001

P < 0.0001

P < 0.0001

P < 0.0001

Deaths

CV Deaths

Sudden Death

Death from worsening HF

Percent (%)

Placebo

Metoprolol CR/XL

COPERNICUS

(Carvedilol Prospective Randomized Cumulative Survival Study)

• Design: P, R, DB, PC, MC trial

• Purpose: Evaluate all-cause mortality of pts with LVD and severe HF symptoms using carvedilol

• Population: 2289 NYHA IV, EF \(\leq 25\%\)

• Treatment: 25mg BID (target dose) vs. placebo, avg. follow-up 10.4 months

• Concurrent: Diuretics, ACEI, ARB (ACEI not tolerated); required medications

NEJM 2001;344:1651-58

COPERNICUS

Results

NEJM 2001;344:1651-58

METOPROLOL XR Randomised Intervention Trial in Congestive Heart Failure, post-hoc analysis of patients with NYHA III-IV and EF < 25%

Endpoints

Metoprolol

Placebo

RR

P value

Total mortality

45

72

39%

0.0086

CV mortality

40

70

44%

0.0028

Sudden death

22

39

45%

0.024

Death from worsening HF

13

28

55%

0.015

Total hospitalizations

273

363

27%

0.0037

Total hospitalizations due to worsening HF

105

187

45%

<0.0001


COMET

(Carvedilol OR Metoprolol European Trial)

• Design: P, R, DB, PC, MC trial

• Purpose: Evaluate all-cause mortality of pts with HF comparing metoprolol tartrate and carvedilol

• Population: 3029 NYHA II-IV, EF < 35%

• Treatment: carvedilol 25mg bid (target dose) vs. metoprolol tartrate 50 mg bid (target dose) avg. follow-up 58 months

• Concurrent Tx: ACEI, loop diuretics. Digoxin, ARB, and vasodilators could be used.

Lancet 2003; 362:7-13

COMET: All-cause mortality

Lancet 2003; 362:7-13
**COMET**

Heart Rate on each visit

![Heart Rate Chart](Lancet 2003; 362:7-13)

Error bars are 1SE. *p=0.0022 †p=0.0034 ‡p=0.0040. No statistical difference after 16 months.

**ACC/AHA Guidelines HF**

(Beta-Blockers)

- **Stage A**
  - Class I
    - Control SBP and DBP per recommended guidelines

- **Stage B**
  - Class I
    - Recent MI regardless of EF
    - ↓ EF regardless of MI Hx

- **Stage C**
  - Class I
    - All euvoeemic stable pts, unless contraindicated

AHA/ACC HF Guidelines, 2001

**β-blocker Recommendations**

- **Selection of Agent**
  - metoprolol XL (metoprolol succinate), carvedilol

- **Caution:** unstable NYHA III-IV pt., resting HR <60, SPB <85mmHg, reactive airway disease, heart block without pacer, unstable DM

- **Target Dose,** not for symptomatic improvement
  - Initial low dose to assess tolerability, titrate q2 wks
  - Max. effect at 3 mo. with additional benefit to 1 yr.

- **Monitor Safety**
  - Blood pressure, Heart Rate, Fluid overload

**RALES**

(Randomized Aldactone Evaluation Study)

- **Design:** P, R, DB, PC, MC trial
- **Purpose:** Evaluate all-cause mortality of pts with severe HF symptoms using spironolactone
- **Population:** 1663 NYHA III-IV,
  - EF < 35%
- **Treatment:** 25 mg/day vs. placebo,
  - avg. follow-up 24 months (stopped early)
- **Concurrent:** ACEI, Diuretics (no K+ sparing),
  - Digoxin, Vasodilators (allowed)

NEJM 1999; 341:709-717

**RALES Results**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR = 30%</td>
<td>RR = 31%</td>
</tr>
<tr>
<td>46</td>
<td>35</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

**EPHESUS**

(Eplerenone Post-Acute Myocardial Infarction Heart Failure Survival Study)

- **Design:** P, R, DB, PC, MC trial
- **Purpose:** Evaluate all-cause mortality of pts with AMI complicated by LVD and HF symptoms using eplerenone
- **Population:** 6642, 3-14 days after AMI, EF ≤ 40%
- **Treatment:** 25 mg/day up to 50mg/day vs. placebo,
  - avg. follow-up 16 months
- **Concurrent:** ACEI, ARBs, Diuretics (no K+ sparing),
  - β-blockers

NEJM 2003; 348:1309-1321
Diuretic Recommendations

- Selection of Agent
  - Loops, metolazone (with loop), spironolactone
- Spironolacton Dose
  - Initial 25mg dose, assess tolerability in 8 wks
  - Max. effect at 2-3 mo. with additional benefit to 2yr.
- Monitor Safety
  - Blood pressure
  - Weight
  - Renal function (serum creatinine)
  - Electrolytes (serum potassium)

Therapeutic Context

- ACEI with mild-to-moderate HF
  - Prevent ~20-40 deaths per 1000 pts in 1 year
- B-blocker in mild-to-moderate HF
  - Prevent ~20-40 deaths per 1000 pts in 1 year
- Carvedilol with severe HF
  - Prevent ~70 deaths per 1000 pts in 1 year
- Spironolactone with severe HF
  - Prevent ~50 deaths per 1000 pts in 1 year

DIG

(Digoxin Investigation Group)

- Design: P, R, DB, PC, MC trial
- Purpose: Evaluate all-cause mortality and hospitalization of pts with normal sinus rhythm and HF symptoms using digoxin
- Population: 6800 had HF: NYHA III (30.6%) IV (2%), EF ≤ 45%
- Treatment: 0.25 mg/day vs. placebo, avg. follow-up 37 months
- Concurrent: ACEI, Diuretics

DIG Results

[Graph showing results]

NEJM 1997; 336:525-533
ACC/AHA Guidelines HF (Digoxin)

- Stage B
  - Class III
  - Pts with LVD in sinus rhythm
- Stage C
  - Class I
  - Symptoms of HF, unless contraindicate

Digoxin Recommendations

- Contraindication
  - Significant sinus or atrioventricular block
- Digoxin Dose
  - Initial 0.25mg dose every day
  - Symptoms can improve in 1-3 mo. benefit to 3 yr.
- Monitor Safety
  - Heart Rate
  - Electrolytes (serum potassium)
  - Renal Function (serum creatinine)
  - Therapeutic Drug Monitoring (0.7-2 ng/mL)

CHARM
Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity

- Overall
  - Combined Added, Alternative and Preserved
- Added
  - Confirm Val-HeFT results
- Alternative
  - Intolerant to ACEI (cough, hypotension, renal dysfunction, angioedema/anaphylaxis)
- Preserved
  - Patients with EF >40% and NYHA class II-IV

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%)
  - 334 (33.0%)
- Candesartan
  - Adjusted HR 0.70, p=0.0001

Number at risk
Candesartan
  - 1013
  - 929
  - 831
  - 434
  - 122
Placebo
  - 1015
  - 887
  - 798
  - 427
  - 126

Median follow-up of 41 months

CHARM-Added
Patient disposition

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

Candesartan
  - n=1276
  - Complete study: n=1273
  - Lost to follow-up: n=3

Placebo
  - n=1272
  - Complete study: n=1271
  - Lost to follow-up: n=1

Lancet. 362:759-81, 2003
Lancet. 362:772-6, 2003
**What does the data mean?**

- Addition of an 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*

---

**Val-HeFT**

(Randomized Trial of Valsartan in Heart Failure)

- **Design:** P, R, DB, PC, MC trial
- **Purpose:** Evaluate all-cause mortality of pts with HF symptoms using valsartan
- **Population:** 5010 NYHA II-IV, ≥18 yo, EF ≤ 40%
- **Treatment:** 160 mg BID (target dose) vs. placebo, avg. follow-up 23 months
- **Concurrent:** ACEI, Diuretics, β-blockers, Digoxin

*NEJM 2001;345:1667-75*

---

**Val-HeFT: Overall Mortality**

- **Design:** P, R, DB, PC, MC trial
- **Purpose:** Evaluate all-cause mortality of pts with HF symptoms using valsartan
- **Population:** 5010 NYHA II-IV, ≥18 yo, EF ≤ 40%
- **Treatment:** 160 mg BID (target dose) vs. placebo, avg. follow-up 23 months
- **Concurrent:** ACEI, Diuretics, β-blockers, Digoxin

*Cohn JN, et al. NEJM 2001*
Val-HeFT: Effect of Valsartan on the Combined Endpoint*

- Valsartan
- Placebo

13.2% Risk Reduction
P = .009

Val-HeFT: Heart Failure Hospitalizations*

- Valsartan
- Placebo

27.5% Risk Reduction
P < .001

Val-HeFT ACE Inhibitor/Beta Blocker Subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined end point</td>
<td>ACE inhibitor + beta-blocker</td>
<td>300</td>
</tr>
<tr>
<td>Death</td>
<td>ACE inhibitor + beta-blocker</td>
<td>180</td>
</tr>
<tr>
<td>ACE inhibitor + beta-blocker</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor + beta-blocker</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor + beta-blocker</td>
<td>140</td>
<td></td>
</tr>
</tbody>
</table>

Val-HeFT ACE Inhibitor/Beta Blocker Subgroups

ACC/AHA Guidelines HF (ARBs)

- Stage A
  - Class I
    - Control SBP and DBP per recommended guidelines
- Stage C
  - Class Iia
    - Cannot have ACEI due to cough or angioedema, but on digoxin, diuretic, β-blocker
  - Class Iib
    - Add ARB to ACEI therapy
- Class III
  - Add ARB, no ACEI trial

ACC/AHA Guidelines HF (Vasodilators/Calcium Channel Blocker)

- Stage B
  - Class Iib (vasodilators)
    - Long-term treatment with severe aortic regurgitation
- Stage C
  - Class Iia
    - Combination hydralazine and LA nitrate on digoxin, diuretic, β-blocker. Cannot have ACEI due to cough or angioedema
  - Class III
    - Treatment with Calcium Channel Blocker

ARB Recommendations

- Selection of Agent
  - candesartan, valsartan
- ACEI induced angioedema
- Target Dose, not for symptomatic improvement
  - Initial low dose to assess tolerability
  - Better tolerated
- Monitor Safety
  - Blood Pressure
  - Renal function (serum creatinine)
  - Electrolytes (serum potassium)

Abbreviations

ACC: American College of Cardiology
ACEI: Angiotensin Converting-Enzyme Inhibitors
AMI: Acute Myocardial Infarction
AF: Atrial Fibrillation
AHA: American Heart Association
ARBs: Angiotensin II Receptor Blockers
AVD: Atherosclerotic Vascular Disease
Avg.: average
BID: Twice a day
CAD: Coronary Artery Disease
CCB: Calcium Channel Blockers
CHF: Chronic Heart Failure
CV: Cardiovascular
DB: Double-Bled
DBP: Diastolic Blood Pressure
DM: Diabetes Mellitus
EF: Ejection Fraction
HF: Heart Failure
Hosp.: Hospitalizations
HTN: Hypertension

Abbreviations continued

Hx: History
LVD: Left Ventricular Dysfunction
LVSD: Left Ventricular Systolic Dysfunction
MI: Myocardial Infarction
NEJM: New England Journal of Medicine
NYHA: New York Heart Association
P: Prospective
PC: Placebo-Controlled
Pts.: Patients
P value: Probability
qd: daily
R: Randomized
RR: Risk Reduction
SBP: Systolic Blood Pressure
SOB: Shortness of Breath
TID: Three times a day
wks: weeks
VAD: Ventricular Assistant Device
yo: years old