Optimizing Heart Failure

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Outline

• Definitions and scope of problem

• Diagnosing and classifying heart failure

• Approach to management of CHF
  – Oral drug therapy (ACE-I, ARB, betablockers, aldosterone blockade, digoxin)
  – Device therapy

• Future directions and exciting developments
A Historical Perspective

• Ebers Papyrus
  – Dated circa 1550 BC
  – Early description of the heart and circulatory system
  – Passages describe heart failure
    “His heart is flooded. This is the liquid of the mouth. His body parts are all together weak”
  – Remedy is one which will “cause an emptying”
**Congestive Heart Failure**

- **Heart (or cardiac) failure** is the state in which the heart is unable to pump blood at a rate commensurate with the requirements of the tissues or can do so only from high pressures.

Types of Heart Failure

- Systolic (or squeezing) heart failure
  - Decreased pumping function of the heart, which results in fluid back up in the lungs and heart failure

- Diastolic (or relaxation) heart failure
  - Involves a thickened and stiff heart muscle
  - As a result, the heart does not fill with blood properly
  - This results in fluid backup in the lungs and heart failure
Risk Factors for Heart Failure

- Coronary artery disease
- Hypertension (LVH)
- Valvular heart disease
- Alcoholism
- Infection (viral)

- Diabetes
- Congenital heart defects
- Other:
  - Obesity
  - Age
  - Smoking
  - High or low hematocrit level
  - Obstructive Sleep Apnea
Epidemiology of Heart Failure in the US

- More deaths from heart failure than from all forms of cancer combined
- 550,000 new cases/year
- 4.7 million symptomatic patients; estimated 10 million in 2037

Congestive Heart Failure

• Symptoms:
  – Shortness of breath
  – Leg swelling (edema)
  – Breathing worsens with lying flat (orthopnea)
  – Fatigue
  – Decrease Exercise Tolerance
Chronic Congestive Heart Failure
Evolution of Clinical Stages

NORMAL

Asymptomatic LV Dysfunction
No symptoms
Normal exercise
Normal LV fxn

Compensated CHF
No symptoms
Normal exercise
Abnormal LV fxn

Decompensated CHF
No symptoms
Exercise
Abnormal LV fxn

Symptoms
Exercise
Abnormal LV fxn

Refractory CHF
Symptoms not controlled with treatment
Classifying Heart Failure: Terminology and Staging
A Key Indicator for Diagnosing Heart Failure

Ejection Fraction (EF)

- Ejection Fraction (EF) is the percentage of blood that is pumped out of your heart during each beat.
Echocardiographic Evaluation of CHF

- LV function (EF), chamber size, wall motion
- Segmental dysfunction - coronary disease
- MS-severity, valve area
- AS - valve gradient, valve area
- AR/MR severity
- TR - RV systolic pressure = PA pressure
- RV function
- R/O IHSS, HCM
- R/O Pericardial Disease
- R/O rare causes e.g. myxoma, infiltrative disorders - restrictive cardiomyopathy
- Diastolic function
- Hyperdynamic states
### Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Functional Class

<table>
<thead>
<tr>
<th>ACC/AHA HF Stage¹</th>
<th>NYHA Functional Class²</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for heart failure but without structural heart disease or symptoms of heart failure (eg, patients with hypertension or coronary artery disease)</td>
<td>None</td>
</tr>
<tr>
<td>B Structural heart disease but without symptoms of heart failure</td>
<td>I Asymptomatic</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current symptoms of heart failure</td>
<td>II Symptomatic with moderate exertion</td>
</tr>
<tr>
<td>D Refractory heart failure requiring specialized interventions</td>
<td>III Symptomatic with minimal exertion</td>
</tr>
<tr>
<td></td>
<td>IV Symptomatic at rest</td>
</tr>
</tbody>
</table>


BNP Diagnostic Cut Points for CHF

BNP > 400 pg/L – acute CHF present
BNP 100 pg/L – 400 pg/L
• Diagnostic of CHF with
  – Sensitivity 90%
  – Specificity 76%
  – Predictive accuracy 83%
  – R/O pulmonary embolism, LV dysfunction without acute CHF or cor pulmonale
BNP < 100 pg/L – 98% negative predictive accuracy
Pathophysiology
Pathologic Progression of CV Disease

- Coronary artery disease
- Hypertension
- Diabetes
- Cardiomyopathy
- Valvular disease

Myocardial injury → Pathologic remodeling → Low ejection fraction → Death

- Neurohormonal stimulation
- Myocardial toxicity

Symptoms: Dyspnea, Fatigue, Edema

Chronic heart failure

Sudden Death → Pump failure → Death
Compensatory Mechanisms: Renin-Angiotensin-Aldosterone System

Beta Stimulation
- CO
- Na⁺

Renin + Angiotensinogen → Angiotensin I → Angiotensin II

- Peripheral Vasoconstriction → ↑ Afterload → ↓ Cardiac Output
- Heart Failure

- Aldosterone Secretion
- Salt & Water Retention → ↑ Plasma Volume → ↑ Preload → ↑ Cardiac Workload
- Kaliuresis

- Fibrosis → Edema

ACE
Drug Therapy
Rational for Medications

- **Improve Symptoms**
  - Diuretics (water pills)
  - digoxin

- **Improve Survival**
  - Betablockers
  - ACE-inhibitors
  - Aldosterone blockers
  - Angiotensin receptor blockers (ARB’s)
DIET Approach to the Patient With Heart Failure

- **D**iagnose
  - Etiology
  - Severity (LV dysfunction)
- **I**nitiate
  - Diuretic/ACE inhibitor
  - β-blocker
  - Spirololactone
  - Digoxin
- **E**ducate
  - Diet
  - Exercise
  - Lifestyle
  - CV Risk
- **T**itrate
  - Optimize ACE inhibitor
  - Optimize β-blocker
General Rx Strategies in HF

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Mild/Mod</th>
<th>Severe</th>
<th>Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct Cause:</td>
<td></td>
<td>Inotropes, mitral repair, VAD, Tx</td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure Load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tailored Rx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics (Spironolactone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol/ β-Blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin Converting Enzyme Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Added Salt</td>
<td></td>
<td>2 gm Na</td>
<td></td>
</tr>
<tr>
<td>Activity as Tolerated</td>
<td></td>
<td>Customized Ex Training</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Warner-Stevenson, ACC HF Summit
# ACE Inhibitors in CHF

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Males</th>
<th>Age</th>
<th>EF%</th>
<th>Class</th>
<th>Drug</th>
<th>F/U</th>
<th>Mortality Reduction %</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-HeFT</td>
<td>642</td>
<td>100%</td>
<td>58</td>
<td>30</td>
<td>II,III</td>
<td>HDZN/ISDN</td>
<td>2.3 yrs.</td>
<td>11</td>
</tr>
<tr>
<td>CONCENSUS</td>
<td>253</td>
<td>70%</td>
<td>70</td>
<td>NA</td>
<td>IV</td>
<td>Enalapril</td>
<td>188 Days</td>
<td>27</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>804</td>
<td>100%</td>
<td>61</td>
<td>29</td>
<td>II,III</td>
<td>Enalapril</td>
<td>2.5 yrs.</td>
<td>14</td>
</tr>
<tr>
<td>SOLVD Treatment</td>
<td>2569</td>
<td>80%</td>
<td>61</td>
<td>25</td>
<td>II,III</td>
<td>Enalapril</td>
<td>41.4 mo.</td>
<td>16</td>
</tr>
<tr>
<td>SOLVD Prevention</td>
<td>4228</td>
<td>89%</td>
<td>59</td>
<td>28</td>
<td>I,II</td>
<td>Enalapril</td>
<td>37.4 mo.</td>
<td>8</td>
</tr>
</tbody>
</table>
Optimal Dosing of ACE Inhibitors

- General Guideline:
- Start low and titrate to the target dose used in the clinical trials or the MAXIMUM TOLERATED DOSE (ATLAS trial)

- Captopril 6.25-12.5 mg ⇒ 50 mg BID-TID (SAVE)

- Enalapril 2.5 mg BID ⇒ 20 mg BID (SOLVD/X)

- Ramipril 2.5 mg BID ⇒ 5 mg BID (AIRE/EX)

- Lisinopril 10 mg OD ⇒ 30-40 mg OD (GISSI 3)

- Trandolapril 1mg ⇒ 4 mg (TRACE)
# Summary – ARBs in CHF

<table>
<thead>
<tr>
<th>ELITE II</th>
<th>Val-HeFT</th>
<th>VALIANT</th>
<th>CHARM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB vs ACEI</td>
<td>ARB vs placebo (± ACEI ±BB)</td>
<td>Captopril, Valsartan or Combination</td>
<td>ARB vs placebo (± ACEI)</td>
</tr>
<tr>
<td># pts.</td>
<td>3,152</td>
<td>5,010</td>
<td>4909/4909/4885</td>
</tr>
<tr>
<td>Population</td>
<td>Heart failure</td>
<td>Heart failure</td>
<td>Post MI with clinical or radiologic HF</td>
</tr>
<tr>
<td>End-points</td>
<td>1(^o) All-cause mortality, sudden death or resuscitated cardiac arrest: NS</td>
<td>1(^o) All-cause mortality: NS 1(^o) Combined M/M: ACEI+ARB = -13.2% ACEE intolerant: -33% all cause mortality</td>
<td>1(^o) All-cause mortality: NS 2(^o) CV Death, MI, or HF:NS</td>
</tr>
</tbody>
</table>
# Evidence for Various ARBs

<table>
<thead>
<tr>
<th></th>
<th>Diovan (valsartan)</th>
<th>Avapro (irbesartan)</th>
<th>Cozaar (losartan)</th>
<th>Atacand (candesartan cilexetil)</th>
<th>Micardis (telmisartan)</th>
<th>Teveten (eprosartan)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction in microalbuminuria with starting dose</strong></td>
<td>-45%</td>
<td>-6%</td>
<td>-35%</td>
<td>-30%</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td><strong>Heart failure hospitalizations</strong></td>
<td>-27.5% (ValHeFT)</td>
<td>N/a</td>
<td>-8.1% (ELITE II)</td>
<td>-17% (CHARM)</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td><strong>CV outcome in CHF-treated patients</strong></td>
<td>-13.3% (ValHeFT)</td>
<td>N/a</td>
<td>+7% (ELITE II)</td>
<td>-15% (CHARM)</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td><strong>Positive CV outcomes in CHF</strong></td>
<td>Yes</td>
<td>N/a</td>
<td>No</td>
<td>Yes</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td><strong>Equivalent Efficacy to ACEi post MI</strong></td>
<td>Yes</td>
<td>N/a</td>
<td>No</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
</tr>
</tbody>
</table>
# HF Trials Modulating $\beta$ receptors

<table>
<thead>
<tr>
<th>Trial</th>
<th>HF Pts</th>
<th>N</th>
<th>Rx</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol</td>
<td>II-III</td>
<td>1,094</td>
<td>Carvedilol</td>
<td>0.35</td>
</tr>
<tr>
<td>Aus-NZ</td>
<td>II</td>
<td>415</td>
<td>Carvedilol</td>
<td>0.74</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>EF&lt;35%</td>
<td>2,647</td>
<td>Bisoprolol</td>
<td>0.66</td>
</tr>
<tr>
<td>MERIT</td>
<td>EF&lt;40%</td>
<td>3,991</td>
<td>Metoprol-CR</td>
<td>0.66</td>
</tr>
<tr>
<td>CO PERNICUS</td>
<td>EF&lt;25%</td>
<td>2,289</td>
<td>Carvedilol</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**Background Rx** = ACEi + Diuretics +/- Digoxin
## Number Need to Rx in HF

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Therapy</th>
<th>Annual Mortality - Placebo</th>
<th>Annual Mortality - Treatment</th>
<th>Absolute Risk Reduc’n</th>
<th>NNRx/year to Save One Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD</td>
<td>Enalapril vs. Plac</td>
<td>12.5%</td>
<td>11.2%</td>
<td>1.3%</td>
<td>77</td>
</tr>
<tr>
<td>MERIT</td>
<td>Metoprolol vs. Plac</td>
<td>11.0%</td>
<td>7.2%</td>
<td>3.8%</td>
<td>26</td>
</tr>
<tr>
<td>CIBIS-2</td>
<td>Bisoprolol vs. Plac</td>
<td>13.2%</td>
<td>8.8%</td>
<td>4.4%</td>
<td>23</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol vs. Plac</td>
<td>18.5%</td>
<td>11.4%</td>
<td>7.1%</td>
<td>14</td>
</tr>
<tr>
<td>RALES</td>
<td>Spiro vs. Placebo</td>
<td>22.5%</td>
<td>15.8%</td>
<td>6.7%</td>
<td>15</td>
</tr>
</tbody>
</table>

Lee, Liu, Packer
**β-adrenergic Blocking Agents**

- Titrate to target dose
  - Bisoprolol 1.25 - 10 mg OD
  - Carvedilol 3.125 - 25 mg BID
  - Metoprolol 12.5 - 50 to 75 mg /BID
- If unable to tolerate high dose β-blocker maintain highest tolerated dose
- Continue indefinitely
Patient Selection for Successful β - Blocker Initiation

- Stable symptoms
- Stable background heart failure medications
- No recent CV hospitalization
- Stable CV status (no hypotension or bradycardia)
- Euvolemic status
- Start low and titrate slowly
Patients With Heart Failure Who Should **Not** Be Started on β-blockers

- **General Contraindications**
  - Bronchospastic pulmonary disease
  - Severe bradycardia, high degree AV block, sick sinus syndrome

- **Heart Failure Considerations**
  - Congestive symptoms at rest (NYHA Class IV)
  - Patients who require intravenous therapy for HF
  - Unstable symptoms or recent changes in background medications
  - Hospitalized patients (especially for worsening HF)
Device Therapy: Biventricular Pacing
Cardiac Resynchronization Therapy (CRT)

- Atrial-biventricular stimulation
- Electrical synchronization → narrower QRS
- Mechanical synchronization → reverse remodeling
Cardiac Resynchronization Therapy

Key Points

• Indications
  – Moderate to severe CHF who have failed optimal medical therapy
  – EF<30%
  – Evidence of electrical conduction delay

• Timing of Referral Important
  – Patients often not on optimal Medical Rx
  – Patients referred too late- Not a Bail Out
Defibrillators (ICD’s)
Severity of Heart Failure
Modes of Death

**NYHA II**
- CHF: 64%
- Other: 24%
- Sudden Death: 12%
  - n = 103

**NYHA III**
- CHF: 59%
- Other: 15%
- Sudden Death: 26%
  - n = 103

**NYHA IV**
- CHF: 56%
- Other: 33%
- Sudden Death: 11%
  - n = 27

Therapies Provided by Today’s Dual-Chamber ICDs

Atrium
- AT/AF tachyarrhythmia detection
- Antitachycardia pacing
- Cardioversion

Ventricle
- VT/VF detection
- Antitachycardia pacing
- Cardioversion
- Defibrillation

Atrium & Ventricle
- Bradycardia sensing
- Bradycardia pacing
SCD-HeFT: Primary Conclusions

1. In class II or III CHF patients with EF $\leq$ 35% on good background drug therapy, the mortality rate for placebo-controlled patients is 7.2% per year over 5 years

2. Simple, single lead, shock-only ICDs decrease mortality by 23%

3. Amiodarone, when used as a primary preventative agent, does not improve survival
# Implantable Cardiac Defibrillators

<table>
<thead>
<tr>
<th>EBM Therapies</th>
<th>Relative Risk Reduction</th>
<th>Mortality 2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I</td>
<td>↓ 23%</td>
<td>27%</td>
</tr>
<tr>
<td>B-Blockers</td>
<td>↓ 35%</td>
<td>12%</td>
</tr>
<tr>
<td>Aldosterone Antagonists</td>
<td>↓ 30%</td>
<td>19%</td>
</tr>
<tr>
<td>ICD</td>
<td>↓ 31%</td>
<td>8.5%</td>
</tr>
</tbody>
</table>
Who should Consider an ICD?

• Patients with weakened heart, New York Heart Association (NYHA) Class II and III heart failure, and measured left ventricular ejection fraction (LVEF) ≤ 35%

• Patients who meet all current requirements for a cardiac resynchronization therapy (CRT) device and have NYHA Class IV heart failure;
Other Therapies
CardioMEMSTM HF System

PA Pressure Sensor on Catheter Delivery System

4.5cm
120cm

Patient Home Electronics Unit

PA Pressure

Physician Access Via Secure Website
Adult and Pediatric Heart Transplants
Number of Transplants by Year

JHLT. 2014 Oct; 33(10): 996-1008
Ventricular Assist Devices (VAD)

- The first VADs were developed in the 1960s.
- Successful use did not occur until 1980s, but their use has been limited to heart transplant centers
  - Durability measured in days to weeks
  - Large in size
  - Many moving parts
  - Exclusively bridge to transplant
- Widespread use in the HF population has not been seen until recently
HeartMate II

- FDA approved as a bridge to transplant 2008.
- FDA approved as destination therapy in 2010
- Appropriate for end-stage systolic heart failure patients
Total Artificial Heart

- Bridge to transplant
  - Biventricular failure
  - Refractory arrhythmias
  - Restrictive cardiomyopathy
- Longest “run” 46 months
- Pneumatic
- Patients can be outpatient
Final Frontier
Heart Recovery/Cure?

• VADs + aggressive neurohormonal blockade
  – Myocardial recovery and VAD explant

• Gene Therapy?

• Stem Cells?
What have we learned?
Goals & Outcomes

- Improve symptoms
- Improve quality of life
- Prevent progression of LV dysfunction
- Reduce hospitalization and morbidity
- Reduce mortality
  - Progression of HF
  - Sudden death
In Summary....

• Heart failure is common and has high mortality

• Drug therapy improves survival
  – Betablockers, ACE-I, aldosterone antagonists

• Newer device therapies are showing promise for symptom relief and improved survival
  – Biventricular pacing, ICD’s, LVADs
Summary

• Chronic disease management models of multidisciplinary teams and home monitoring will be a mainstay of therapy

• The standard of care ranges from medical therapy to surgical therapy

• Other therapies continue to be developed