Guidelines for the Treatment of HEART FAILURE

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HEART FAILURE

Facts

- 5 million patients with CHF in U.S.
- 550,000 new cases/year
- 300,000 deaths/year
- 4 fold increase in risk mortality

End-Stage Congestive Heart Failure
Scope of Problem

- 2-3 million hospitalizations/year
- Average LOS=5.7 days
- Highest DRG volume Dx(days X # pts)
- Highest readmission rate
- Number 1 discharge Dx in pts >63 y.o.

HEART FAILURE
Estimated Prevalence by Age & Gender

Demographic Trends
Elderly U.S. population will double with graying of “baby boomer” generation
Symptomatic HEART FAILURE
Diastolic Dysfunction
Ejection Fraction

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>&lt;.30</td>
<td></td>
</tr>
</tbody>
</table>

Vasan et al, JACC '99;33(7):1948-55

Primary Diastolic Dysfunction
Incidence/Prevalence
Hypertension is the leading cause
Prevalence Increases in advancing age
Effects women > men
ECHO is the best way to make the diagnosis
Treatment is based on control of HR and BP
Beta Blockers, ARB, ACEI, CCB

Pathophysiology of CHF
Eras in Understanding

OLD → RECENT → NEATEST

- HEART IS PROBLEM
- Poor Pump Fx
- Frank Starling
- Contractile Proteins

- PERIPHERY/ COMP MECH's
- Neurohormones
- RAAS
- SNS

- Heart & Peripheral
- Heart – Endocrine Organ - NP's
- ADM, ET, AVP
- Alter Gene Express
- Remodeling
- Hyperplasia

Treatment of Heart Failure
Changing Goals for Therapy

<table>
<thead>
<tr>
<th>ERA</th>
<th>TARGET</th>
<th>THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>60’s</td>
<td>Symptoms</td>
<td>Diuretic/Digoxin</td>
</tr>
<tr>
<td>70’s</td>
<td>Hemodynamics</td>
<td>Inotropes/Vasodil.</td>
</tr>
<tr>
<td>80’s</td>
<td>Survival</td>
<td>ACEI/β-Blockers</td>
</tr>
<tr>
<td>90’s</td>
<td>Remodeling</td>
<td>ACEI/β-Blockers</td>
</tr>
<tr>
<td>2000</td>
<td>Prevention</td>
<td>Earlier Dx/Rx</td>
</tr>
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ACC/AHA Guidelines on Heart Failure
Definition

HF is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

No longer “Congestive” HF, because not all patients have volume overload, but low output

Pathophysiology of CHF

↓ contractility
↑ wall stress

- ADM
- ET-1
- NP’s
- RAAS
- SNS
- Cytokines
- VP

Altered Gene Expression
Remodeling
CHF Syndrome
ACC/AHA Guidelines on Heart Failure

**Drug Treatment**

- ACEI
- ARB
- Hydral/Nitr
- Beta Blocker
- Digoxin
- Diuretic

**Control of Risk**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage</th>
<th>Stage</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>High risk Asymptomatic w/o struct. dis</td>
<td>Struct. Dis Asymptomatic (eg. MI, MR)</td>
<td>Struct. Dis Symptoms</td>
<td>Advanced Symptoms</td>
</tr>
<tr>
<td>?Beta Blocker</td>
<td>ACE</td>
<td>Beta Blocker Diuretics Digitalis</td>
<td>HT. Tx VAD’s Inotropes Hospice</td>
</tr>
</tbody>
</table>

**Treatment of Chronic HF**

**Hydralazine/Nitrates**

- **Hydralazine:**
  - Target Dose: 75-100 mg QID
  - Side Effects: Lupus-like syndrome, tachy
- **Nitrates:**
  - Target Dose: 90 mg/day
  - Side Effects: Headache
Treatment of Heart Failure
HOPE - Secondary Endpoint Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Ramipril (Relative Risk Reduction)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Heart Failure</td>
<td>22% Risk Reduction p=0.005</td>
<td>9.4</td>
</tr>
<tr>
<td>Any Revascularization Procedure</td>
<td>19% Risk Reduction p=0.0013</td>
<td>16.4</td>
</tr>
<tr>
<td>New Onset of Diabetes Mellitus</td>
<td>31% Risk Reduction p&lt;0.01</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Effectiveness of Drug Therapy in Patients with CHF

- Receiving an ACEI: 40 – 50%
- Effective Dose: 20 – 25%
- Patient Compliance: 15%

Limitations of Medical Rx of HF
ACE Inhibitors

- Consistent Survival Benefit
  Relative Risk Reduction 15-20%
  Absolute Risk 3-4%
- 7-10% intolerance
- No significant change in E.F.
- May not be as effective in Afr.-Americans
- Genotype may influence response
- May be a dose maximum – alternative pathway

What is the Renin-Angiotensin System (RAS)?
Pathophysiology of CHF
Renin Angiotensin System
Alternate Pathway – ARB’s

<table>
<thead>
<tr>
<th>Angiotensinogen</th>
<th>Renin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACE(I)</td>
</tr>
<tr>
<td>Angiotensin I</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II</td>
<td></td>
</tr>
</tbody>
</table>

Caspace
Cathepsin

AT₁
Constriction
Growth

ARB Receptor
ATⅡ
Vasodilation
Antiprolit.

Val-HeFT
Study Design

HF patients
≥18 yr; EF<40%; NYHA II–IV

Randomized to
Receiving Standard Therapy
ACEI, diuretics, digoxin, β-blockers (stratified)

PLACEBO

Valsartan
40 mg bid titrated
to 160 mg bid

906 deaths (events reported)


CHARM Program

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

<table>
<thead>
<tr>
<th>CHARM Alternative</th>
<th>n=2028</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≤40%</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td></td>
</tr>
<tr>
<td>intolerant</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHARM Added</th>
<th>n=2548</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≤40%</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td></td>
</tr>
<tr>
<td>treated</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHARM Preserved</th>
<th>n=3025</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &gt;40%</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td></td>
</tr>
<tr>
<td>treated/not treated</td>
<td></td>
</tr>
</tbody>
</table>

Primary outcome for each trial: CV death or CHF hospitalization
Primary outcome for Overall Program: All-cause death

Improving survival in CHF
1-year mortality

SOLVD-T (1991)  RRR 21%
MERIT (1999)   RRR 33%
CHARM-Added (2003) (β-blocker subgroup)  RRR 30%
ACC/AHA Guidelines on Heart Failure
Angiotensin Receptor Blockers

<table>
<thead>
<tr>
<th>ARB</th>
<th>Initial Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>25 mg/day</td>
<td>50 – 10 mg/d</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 mg BID</td>
<td>160 mg BID</td>
</tr>
<tr>
<td>Candesartan</td>
<td>20 mg/day</td>
<td>40mg/day</td>
</tr>
</tbody>
</table>

Limitations
ARB’s

- No significant benefit over ACEI (or difference)
- Addition to ACEI does not change survival, but decreases hospitalizations
- Better tolerated than ACEI’s
- No limitation of alternative pathway

Sympathetic Activation and Increased Heart Failure Mortality

\[ \text{PNE < 400 pg/mL} \]
\[ \text{PNE 400-800 pg/mL} \]
\[ \text{PNE > 800 pg/mL} \]


Norepinephrine Spillover in Heart Failure

<table>
<thead>
<tr>
<th>Spillover of Norepinephrine to Plasma (% of normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Heart</td>
</tr>
<tr>
<td>Gut &amp; Liver</td>
</tr>
<tr>
<td>Lungs</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
</tbody>
</table>

Eister et al. Hypertension 1988

Adrenergic Receptor Densities in Human LV Myocardium

\[ \beta_1 \]
\[ \beta_2 \]
\[ \alpha \]

\* P < 0.05 vs. non-failing

IDC = Idiopathic Dilated Cardiomyopathy
### Antiadrenergic Therapy - Beta Blockade

- **Sympathetic activation**
  - $\beta_1$ receptors
  - $\beta_2$ receptors
  - $\alpha_1$ receptors

- **Remodelling Effects**
  - Metoprolol
  - Propranolol
  - Carvedilol

### ACC/AHA Guidelines on Heart Failure

<table>
<thead>
<tr>
<th>Beta Blockers</th>
<th>Initial Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>3.125 mg</td>
<td>25 mg BID</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>12.5 – 25 mg</td>
<td>150 mg/d</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>10 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

- Side Effects: hypotension, bradycardia, fluid retention, fatigue

### Limitations of Medical Rx of HF

- Fairly Consistent Survival Benefit
  - Relative Risk Reduction 25-65%
  - Absolute Risk Reduction 7-9%
  - (on top of ACE, Dig, Diuretic)
- Significant increase E.F.
- Primarily Class II-III HF, but also Class IV
- May be less effective in Afr.-Americans
- Class effect, but also unique individual agents
Beta Blockers in CHF
Role of Norepinephrine
Moxonidine (Moxcon) Study

Moxonidine: Central acting agent (Clonipin) causes a decrease in norepinephrine

Study: 1,950 patients enrolled (4,500 goal)
All on ACE, Dig, Diuretic + Moxonidine vs Placebo

Stopped due to increase mortality in moxonidine arm
? Too rapid a reduction NE

Complications of Diuretic Therapy for Heart Failure

The RALES Trial: Effect of Spironolactone on Survival in CHF

Treatment of Heart Failure
Aldactone Inhibitors

The RALES Trial: Effect of Spironolactone on Survival in CHF

Total mortality ↓ 30% (p < 0.001)


Spironolactone
Placebo

Probability of Survival
Months

Initial Dose Target Dose
Aldactone 12.5 mg 25-50 mg
Use instead of oral K+ supplements
• Caution in use with ACEI or ARB due to additive effect of inducing hyperkalemia
• Requires K+ checks @week 1,3
• Eplerenone-more expensive, + remodeling

DIG Study

Cause of Death Risk Ratios Confidence Intervals P value
All cause mortality 1.00 (0.93-1.09) 0.92
Cardiovascular 1.03 (0.95-1.12)
Pump failure 0.86 (0.76-0.99)
Sudden death 1.12 (0.96-1.31) 0.13
Limitations of Oral HF Therapy

- Neutral Endopeptidase Inhibitor (NEP) decreases breakdown, increases circulating BNP levels
- ACE Inhibitor
- OVERTURE Study—no benefit over ACEI
- ?? Biologically effective BNP in vivo

Treatment of Advanced HF

Vesnarinone (VEST) Trial

Outcome

- Stopped early by D.S.M.C.
- 60 mg dose: 26% increase mortality (p=0.007) vs placebo
- 30 mg dose: 14% increase mortality (p=0.165)

No improvement in quality of life
### Pathophysiology of CHF

**Mediators of Vascular Tone**

<table>
<thead>
<tr>
<th>Vasodilators</th>
<th>Vasoconstrictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old</td>
<td>Old</td>
</tr>
<tr>
<td>New</td>
<td>New</td>
</tr>
<tr>
<td>Natriuretic Peptides</td>
<td>Endothelin</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>Adrenomedullin</td>
<td></td>
</tr>
<tr>
<td>Bradykinin</td>
<td></td>
</tr>
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### New Therapeutic Agents for HF

- Levosimendan-calcium sensitiz inotrope
- Vasopressin Antagonists
- Anemia
- Immunomodulation
- Clenbuterol
- Gene and Stem Cell Therapies

### Limitations of Drug Therapy for HF

**Factors Affecting Outcome**

- Age
- Race
- Dose
- Pharmacogenomics
- Genomics
- Compliance
Limitations of Oral HF Therapy

Summary

• Many issues that effect the response to a given oral HF drug
• ACEI’s, ARB’s, and BB’s remain the most consistent drugs to favorably alter survival
• Most promising new drugs have not been shown to have a survival benefit
• Device therapies will likely play a significant role in HF therapy in the future

Pharmacogenomics

Varying response to drugs between patients based on:

• Genetic variation in metabolic pathways (e.g. CYP450 genes)
• Genetic variation at the target protein(s) (e.g. Beta2-adrenergic receptor-CHF, asthma)
• Genetic variation at off target protein(s) (e.g. Sodium & Potassium channel genes; LQTS, LPL-Rapa)
• Genetic factors related to the etiology of the disorder (e.g. AGTR1, AGT, IL-10, TNF α)

Pharmacogenomics

2D6 polymorphisms can markedly decrease 2D6 activity (poor metabolizer; PM)
• The frequency of PM’s varies from 1% to 30%
• 2D6 metabolized about 20% of prescribed drugs