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
• >10% people over 65 yo will develop HF

End-Stage Congestive Heart Failure Scope of Problem

• 1 million hospitalizations/year as #1 Diagnosis,
• 2.5 million as # 2 or 3 Discharge Diagnosis
• Average LOS≈5.7 days
• Highest DRG Volume Dx (days X # pts)
• Highest readmission rate
• Number 1 discharge Diagnosis in pts >63 y.o.
• Increasing age of population will double in 15 yrs

HEART FAILURE Estimated Prevalence by Age & Gender

Demographic Trends

Elderly U.S. population will double with graying of “baby boomer” generation

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
Primary Diastolic Dysfunction

Hypertension is the leading cause
Prevalence Increases in advancing Age
Effects Women > men
ECHO is the best way to make diagnosis
Treatment: control HR and BP
No mortality benefits in Diastolic HF
Rx: Beta Blockers, ARB, ACEI, CCB

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>
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<tr>
<td>80’s</td>
<td>Survival</td>
<td>ACEI/β-Blockers</td>
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<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>
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</tbody>
</table>

Pathophysiology of CHF

ACC/AHA Guidelines on Heart Failure
Drug Treatment

ACEI

Hydral/Nitr

Beta Blocker

Digoxin

Diuretic
Treatment of Heart Failure
Neurohormonal Antagonism

What is the Renin-Angiotensin System (RAS)?

Angiotensinogen → Renin

Angiotensin I → ACE

Angiotensin II NonACE → Angiotensin II

Angiotensin II Receptors (Subtype AT1)

Vasodilation

Blood Pressure

Sympathetic activation

Aldosterone secretion

Inactive fragments

ACE Inhibitors – Mechanism of Action

ACE Inhibitor

IPA
Prostaglandins
Vasodilation

Bradykinin, Substance P
ACE

Angiotensinogen

Angiotensin I

Angiotensin II

Chymase
CAGE
Cathepsin G

Bradykinin
Substance P
Enkephalins

Angiotensin II
Receptors

Kinase II

Vasoconstriction
Aldosterone
Vasopressin
Sympathetic

Cumulative Mortality in V-HeFT II Enalapril and Hydralazine/Isosorbide Dinitrate Study

Treatment of Heart Failure
HOPE - Secondary Endpoint Results

7.4
16
3.8
9.4
18.4
5.5
22% Risk Reduction
p<0.0005
15% Risk Reduction
p=0.0013
31% Risk Reduction
p<0.01

20
25

% with an event

All Heart Failure
Asy Revascularization Procedure
New Onset of Diabetes Mellitus

7.4
9.4
3.8
10
15
20
25

90
80
70
60
50
40
30
20
10
0

Months

Enalapril
Hydralazine/Isosorbide dinitrate

Control
Prevention
Treatment

Control
Prevention
Treatment

Control
Prevention
Treatment

Control
Prevention
Treatment

Control
Prevention
Treatment

Control
Prevention
Treatment
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 cardiac ejection fract.
- May not be as effective in Afr.-Americans
- Genotype may influence response
- May be a dose maximum – alternative pathway

Pathophysiology of CHF
Renin Angiotensin System
Alternate Pathway – ARB’s

Angiotensinogen
Renin
Caspase
Cathepsin
Angiotensin I
ACE(I)
Angiotensin II
ARBl
Receptor
ATl
Constriction
Growth
ATII
Vasodilation
Antiprolit.

Val-HeFT
Study Design

HF patients
≥18 yr; EF<40%; NYHA II-IV
Receiving Standard Therapy
ACEI, diuretics, digoxin, β-blockers (stratified)
Randomized to
Val-HeFT
Placebo

Valsartan
40 mg bid titrated
to 160 mg bid
906 deaths (events reported)

CHARM: ADDED Trial
Cumulative Event Outcome

P=0.011

Candesartan
n=1272
Placebo
n=1276

Proportion with Cardiovascular Death or Hospital Admission for CHF (%)

Limitations
ARB’s

- No significant benefit over ACEI (or difference)
- Addition to ACEI decreases hospitalizations, and may improve survival
  Better tolerated than ACEI’s
- Use of High dose ACEI(>20 mg/d) may lead to conversion of ANG I-II via alternative pathway

Sympathetic Activation and Increased Heart Failure Mortality

PNE = Plasma norepinephrine
Spillover of Norepinephrine to Plasma (% of normal)

- Total
- Heart
- Gut & Liver
- Lungs
- Kidney

Norepinephrine Spillover in Heart Failure

- Esler et al. Hypertension 1988

Adrenergic Receptor Densities in Human LV Myocardium

- Non-failing
- Failing (IDC)

* P < 0.05 vs. non-failing
IDC = Idiopathic Dilated Cardiomyopathy

Antiadrenergic Therapy - 
β-blockade

- β1 receptors
- β2 receptors
- α1 receptors

Sympathetic activation

Remodelling Effects

Metoprolol
Propranolol
Carvedilol

Beta Blockers in CHF
Effect of Dose on Ejection Fraction
MOCHA Trial

Carvedilol Dose-Response Trial (MOCHA)
Effect of Carvedilol Dose on Mortality

- Linear Trend: p = 0.0005
- p < 0.05
- NS
- p < 0.001

Bristow et al., Circulation 2001;104:1-142
Beta Blockers in CHF
Role of Norepinephrine
Moxonidine (Moxcon) Study

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

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

Improving survival in CHF
1-year mortality

SOLVD-T (1991)
RRR 21%

MERIT (1999)
RRR 33%

CHARM-Added (2003)
β blocker subgroup
RRR 30%

Sympathetic Nervous Blockade
Failed MOXCON Trial

Placebo (n=875)
Moxonidine (n=918)

Relationship Between LV Remodeling and CV Events Post-MI

Relationship Between LV Size and Outcome in CHF

2-D echocardiography obtained at a mean of 11.1 ± 3.2 days after acute MI and 1 year later

Remodeling: CARMEN Trial
Effect of ACEI vs BB on LVEDV

Baseline Month 6 Month 12 Month 18
$\Delta$ LVEDV (ml/m2)

P values for $\Delta$BL to M6, M12, M18

- Carvedilol & Enalapril
- Carvedilol
- Enalapril

$P < 0.002$

$P < 0.05$

Limitations of Medical Rx of HF
Beta Blockers

- 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

Use of Evidence-Based Therapies in Heart Failure
LVEF Documented at < 0.40

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline (n=65)</th>
<th>Month 6 (n=63)</th>
<th>Month 12 (n=63)</th>
<th>Month 18 (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>44.3</td>
<td>40.9</td>
<td>68.0</td>
<td>31.9</td>
</tr>
<tr>
<td>ARB</td>
<td>9.0</td>
<td>10.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Blocker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
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Patients Receiving Therapy (%)

Outpatient HF Medication

Excludes patients with documented contraindications.

Complications of Diuretic Therapy for Heart Failure

Diuretic Therapy

- Hyponatremia
- Saluresis and Diuresis
- Plasma Volume
- Cardiac Output
- Renal Blood Flow
- GFR
- Proximal Reabsorption
- Distal Reabsorption
- Calcium Clearance
- Aldosterone
- Kaliuresis
- Hyperkalemia
- Glucose Intolerance

Cardiovascular Effects of Aldosterone

Aldosterone + Na+

Blood vessels

- Endothelial dysfunction
- Vascular inflammation
- Vascular remodeling

Brain (and other peripheral tissues)

- Vascular damage
- Endothelial dysfunction
- Vascular inflammation
- Renal fibrosis

Kidney

- Hypertension
- Stroke
- Hypertension
- Heart failure

Heart failure

- Diabetes Mellitus
- Heart failure
The RALES Trial: Effect of Spironolactone on Survival in CHF

![Graph showing the effect of Spironolactone on survival in CHF.](image)

- **Total mortality ↓ 30% (p < 0.001)**
- **Placebo**
  - Number at risk: 841, 775, 723, 698, 669, 639, 608, 526, 419, 316, 193, 122, 43
- **Spironolactone**
  - Number at risk: 822, 766, 739, 698, 669, 639, 608, 526, 419, 316, 193, 122, 43

**Pitt B, et al.**

### DIG Study

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Risk Ratio</th>
<th>Confidence Intervals</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>1.00</td>
<td>(0.93-1.09)</td>
<td>0.92</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.03</td>
<td>(0.95-1.12)</td>
<td></td>
</tr>
<tr>
<td>Pump failure</td>
<td>0.86</td>
<td>(0.76-0.99)</td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>1.12</td>
<td>(0.96-1.31)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

### Pathophysiology of CHF Natriuretic Peptides

- **NP’s**
  - ANP (atria)
  - CNP (endothelium)
  - BNP (ventricle)
  - DNP (kidney)

### Effects of Nesiritide

- **VASODILATION**
- **RENAL**
- **HEMODYNAMIC**
- **CARDIAC INDEX**
- **NATRIURESIS DIURESIS**
- **Fluid volume**
- **Preload**
- **Diuretic usage**
- **Preload Afterload PCWP**
- **Dyspnea**
- **Aldosterone Endothelin Norepinephrine**
- **CARDIAC**
  - No increase in HR
  - Not proarrhythmic
- **SYMPATHETIC AND NEUROHORMONAL SYSTEMS**

### The Effect of Anemia on Survival in CHF Patients Outside the Clinical Trial Setting

- **Hb quartiles**
  - [Hb] >14.4g/dL (n=113)
  - [Hb] 13.3-14.4g/dL (n=114)
  - [Hb] 11.8-13.2g/dL (n=107)
  - [Hb]<11.8g/dL (n=102)

Data courtesy Dr. G. Fonarow (UCLA) adjusted for age, sex, BMI, LVEF, LVEDD, SCr, etiology, DM.
Effect of Anemia Treatment on Regression of LVH*

![Graph showing the relationship between LVMI and Hct before and after treatment.](image)

*Note: Normal LVMI² = 125 g/m²


Pathophysiology of CHF Mediators of Vascular Tone

**Vasodilators**
- Old
  - Alpha Adrenergic Recept.
- New
  - Nitric Oxide
  - Adrenomedullin
  - Bradykinin

**Vasoconstrictors**
- Old
  - Beta Adrenergic Recept.
- New
  - Endothelin
  - Angiotensin II

Limitations of Drug Therapy for HF Factors Affecting Outcome

- Age - ELITE, HOPE
- Race - ACEI, Beta Blockers, Hydral/Nit
- Gender - DIG Trial
- Etiology - PRAISE (CCB)
- Dose - ATLAS
- Genomics - BETA 2AR, iNOS, ACE I/D
- Pharmacogenomics - Metoprolol

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

Stem Cell Therapy in AMI: TOPCARE Study

- 20 pts
  - 3-6 days post MI
- 9 pts: Bone marrow aspiration
- 11 pts: 250 cc peripheral blood drawn
- Memonuclear cells isolated
- Ex vivo EPC expansion in cell culture (3 days)
- Intracoronary Infusion

Assmus et al. Circulation 2002;106:3009-17
TOPCARE-AMI

University of Frankfurt

4 Month Follow-up:
- Improved EF
- Improved wall motion
- Reduced end-systolic diameter

No change in matched reference group
No difference b/w BM or PB groups
No Placebo group

Assmus et al, Circulation 2002;106:3009-17