A CRITICAL ANALYSIS OF TREATMENT OPTIONS FOR HEART FAILURE

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ALAN B MILLER MD

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- I have financial relationships to disclose:
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Heart failure: An increasing public health burden

Affects 5 million US residents
- 2.2% of the population
- 550,000 new cases annually

Annual impact on healthcare resources
- ~3 million office visits
- ~1 million hospital discharges
- No.1 cause of hospitalizations in the elderly
- Direct and indirect costs: $28.8 billion

AHA. *Heart and Stroke Statistics—2004 Update.*
## Classification of HF: ACC/AHA stage vs NYHA class

<table>
<thead>
<tr>
<th>ACC/AHA HF stage</th>
<th>NYHA functional class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for HF but without structural heart disease or symptoms</td>
<td>None</td>
</tr>
<tr>
<td>B Structural heart disease but without HF</td>
<td>I Asymptomatic</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current HF symptoms</td>
<td>II Symp. with moderate exertion</td>
</tr>
<tr>
<td>D Refractory HF requiring specialized interventions</td>
<td>III Symp. with minimal exertion</td>
</tr>
<tr>
<td></td>
<td>IV Symptomatic at rest</td>
</tr>
</tbody>
</table>

Pathophysiology of Heart Failure

Cardiac injury → Increased load → Activation of RAA System, SNS, and cytokines → Reduced systemic perfusion →

- Altered gene expression
- Growth and remodeling
- Ischemia and energy depletion
- Direct toxicity → Apoptosis → Necrosis → Cell death

Adapted from: Eichhorn EJ, Bristow MR. Circulation. 1996;94:2285-2296.
**Neurohormonal Activation in HF**

*SOLVD*

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**Median Plasma Norepinephrine (pg/mL)**
- Control: n=56
- Prevention*: n=151
- Treatment†: n=81

**Median Plasma ANF (pg/mL)**
- Control: n=56
- Prevention*: n=151
- Treatment†: n=81

**Median Plasma Renin Activity (pg/mL)**
- Control: n=56
- Prevention*: n=151
- Treatment†: n=81

**Median Plasma AVP (pg/mL)**
- Control: n=56
- Prevention*: n=151
- Treatment†: n=81

*Prevention trial: assessed prevention of HF;† Treatment trial: assessed reduction in mortality*

Hypertrophy, apoptosis, ischemia, arrhythmias, remodeling, fibrosis

Angiotensin II  Norepinephrine
## Effect of ACE Inhibitors on Mortality Reduction in Patients With Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mortality</th>
<th></th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACEI</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>Chronic CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS I</td>
<td>39%</td>
<td>54%</td>
<td>0.56 (0.34–0.91)</td>
</tr>
<tr>
<td>SOLVD (Treatment)</td>
<td>35%</td>
<td>40%</td>
<td>0.82 (0.70–0.97)</td>
</tr>
<tr>
<td>SOLVD (Prevention)</td>
<td>15%</td>
<td>16%</td>
<td>0.92 (0.79–1.08)</td>
</tr>
<tr>
<td>Post MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td>20%</td>
<td>25%</td>
<td>0.81 (0.68–0.97)</td>
</tr>
<tr>
<td>AIRE</td>
<td>17%</td>
<td>23%</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>TRACE</td>
<td>35%</td>
<td>42%</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>SMILE</td>
<td>5%</td>
<td>6.5%</td>
<td>0.75 (0.40–1.11)</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>21%</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>
Aldosterone’s Role in Heart Failure

- **Aldosterone**
  - ↑ Na⁺
  - ↑ LV mass & fibrosis
  - ↓ K⁺  ↓ Mg⁺⁺
    - ↑ Fibrosis
    - ↓ Norepinephrine Uptake
    - ↓ Heart rate variability
  - ↓ Arterial compliance
  - ↓ Baroreceptor function
  - ↓ Norepinephrine uptake
  - ↓ Endothelial function
  - ↑ PAI-1

- ↑ Edema
- ↑ Remodeling
- ↑ Arrhythmia
- ↑ Ischemic Events

Progression of HF
Sudden cardiac death
Randomized Aldactone Evaluation Study (RALES)

Placebo vs. Spironolactone over time:
- Probability of Survival
- Months

P < .001

Relative Risk of Total Mortality

Cumulative Incidence (%)

RR = 0.85 (95% CI, 0.75-0.96)

Placebo vs Eplerenone

Placebo: 331 3064 298 283 241 180 121 709 323 99 2 0 0

Eplerenone: 331 3125 304 209 246 185 126 728 336 110 0 0

P = 0.008
CHARM-Overall
CV death or CHF hosp.

Placebo
1310 (34.5%)
1150 (30.2%)

Candesartan

HR 0.84 (95% CI 0.77-0.91), p<0.0001
Adjusted HR 0.82, p<0.0001

Number at risk
Candesartan 3803 3563 3271 2215 761
Placebo 3796 3464 3170 2157 743
Adrenergic Pathway in Heart Failure Progression

- CNS sympathetic outflow
- Cardiac sympathetic activity
  - $\beta_1$ receptors
  - $\beta_2$ receptors
  - $\alpha_1$ receptors
- Sympathetic activity to kidneys and blood vessels
- Myocyte hypertrophy + death, dilatation, ischemia + arrhythmias
- Vasoconstriction, sodium retention
## Major Trials of β-Blockade in Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (n)</th>
<th>Follow-up (yrs)</th>
<th>Target Dosage (mg)</th>
<th>Mean Dosage Achieved (mg/day)</th>
<th>Effects on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS</td>
<td>641</td>
<td>1.9</td>
<td>5 qd</td>
<td>3.8</td>
<td>All-cause mortality: NS</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>2647</td>
<td>1.3</td>
<td>10 qd</td>
<td>7.5</td>
<td>All-cause mortality: ↓34% (P&lt;.0001)</td>
</tr>
<tr>
<td>MDC</td>
<td>383</td>
<td>1</td>
<td>50 to 75 bid</td>
<td>108</td>
<td>Death or need for transplant (primary end point): NS</td>
</tr>
<tr>
<td>MERIT-HF†</td>
<td>3991</td>
<td>1</td>
<td>200 qd</td>
<td>159</td>
<td>All-cause mortality: ↓34% (P=.0062)</td>
</tr>
<tr>
<td>US Carvedilol Trials†</td>
<td>1094</td>
<td>7.5 months</td>
<td>6.25 to 50 bid</td>
<td>45</td>
<td>All-cause mortality*: ↓65% (P=.0001)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2289</td>
<td>10.5 months</td>
<td>25 bid</td>
<td>37</td>
<td>All-cause mortality: ↓34% (P=.00013)</td>
</tr>
</tbody>
</table>

*Not a planned end point.
†Carvedilol and metoprolol CR/XL are the only agents with β-blockade approved by the FDA for the treatment of mild to moderate heart failure.
Hazard ratios (95% CI) for clinical outcomes by $\beta_1$ and $\alpha_{2c}$ genotype in the BEST genetic substudy

<table>
<thead>
<tr>
<th>End point</th>
<th>$\beta_1$ 389 Arg/Arg + $\alpha_{2c}$ 322-325 WT or DEL carrier, n=493</th>
<th>$\beta_1$ 389 Gly carrier + $\alpha_{2c}$ 322-325 WT/WT, n=413</th>
<th>$\beta_1$ 389 Gly carrier + $\alpha_{2c}$ 322-325 DEL carrier, n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.62 (0.39–0.99)$^a$</td>
<td>0.75 (0.48–1.17)</td>
<td>1.04 (0.43–2.54)</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.52 (0.31–0.88)$^a$</td>
<td>0.60 (0.36–0.97)$^a$</td>
<td>1.11 (0.45–2.78)</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.56 (0.39–0.82)$^b$</td>
<td>0.77 (0.53–1.13)</td>
<td>0.73 (0.35–1.53)</td>
</tr>
</tbody>
</table>

WT = wild type
DEL = deletion

$^a$ p<0.05
$^b$ p<0.01

O'Connor CM et al. Heart Failure Society of America Scientific Meeting; September 22, 2008; Toronto.
Medication use in HF by office-based physicians

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>39%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>19%</td>
</tr>
<tr>
<td>Positive inotropes</td>
<td>14%</td>
</tr>
<tr>
<td>β-blockers</td>
<td>10%</td>
</tr>
<tr>
<td>K supplements</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>13%</td>
</tr>
</tbody>
</table>

HF Clinic Medications

- ACEI/ARB: 92%
- Aldo Blocker: 82%
- B-B: 77%
- Statin: 51%
- CCB: 38%
- Digoxin: 25%
- Nitrates: 15%
Vasodilation

Platelet Inhibition

Anti-inflammatory Actions

Inhibit SMC Proliferation

Tissue Perfusion

Oxygen/ROS Consumption

ROS=reactive oxygen species; SMC=smooth muscle cell.
Adapted from Vita JA. J Card Fail. 2003;9:S200.
The NO Paradigm in HF

A System Out of Balance in AAs?

Vasoconstricting and growth promoting

- Norepinephrine
- Angiotensin II
- Endothelins
- Arginine vasopressin

Worsen hemodynamics, progressive remodeling

Vasodilating and growth inhibiting

- Natriuretic peptides
- Bradykinin
- NO

Improve hemodynamics, prevent remodeling

Yancy CW. Heart Failure in African Americans: The State of the Art. Presented at 8th Annual Scientific Meeting of the Heart Failure Society of America. September 12, 2004; Toronto, Canada.
Cardiovascular NO-Superoxide Production in HF: BiDil NO-Enhancing Effects

Components of Composite Score

**Death**
- Placebo: 10.2% (n=54)
- Fixed-dose HYD/ISDN: 6.2% (n=32)
- Difference: 4.0%
- P-value: 0.02

**First HF Hospitalization**
- Placebo: 24.4% (n=130)
- Fixed-dose HYD/ISDN: 16.4% (n=85)
- Difference: 8.0%
- P-value: 0.001

**Change in Quality of Life**
- Placebo: -2.7
- Fixed-dose HYD/ISDN: -5.6
- Difference: 2.9
- P-value: 0.02

Baseline clinical characteristics were similar between the treatment groups, with 46% of patients having dilated cardiomyopathy and 38% with ischemic heart disease. Mean LV ejection fraction was 25%.

Of the 409 patients randomized to the CRT device, 95% had a successful implantation.

The primary endpoint of all-cause mortality or hospitalization for a major cardiovascular event occurred less frequently in the CRT group than the medical therapy alone group (hazard ratio [HR] 0.63, 95% CI 0.51-0.77).

The major secondary endpoint of all-cause mortality was also lower in the CRT group (HR 0.64, 95% CI 0.48-0.85).
SURGICAL OPTIONS FOR ISCHEMIC CARDIOMYOPATHY

- STICH trial
- Surgical Treatment for ischemic heart failure
- Pts randomized to:
  - 1. medical therapy
  - 2. medical therapy + CABG
  - 3. medical therapy + CABG + SVR
Rapid Assessment of Hemodynamic Status

Congestion at Rest

- **Low Perfusion at Rest**
  - **NO**
    - A: Warm & Dry
  - **YES**
    - B: Warm & Wet
    - L: Cold & Dry (Low Profile)
    - C: Cold & Wet (Complex)

**Signs/Symptoms of Congestion:**
- Orthopnea / PND
- JV Distension
- Hepatomegaly
- Edema
- Rales (rare in chronic heart failure)
- Elevated est. PA systolic
- Valsalva square wave

**Possible Evidence of Low Perfusion:**
- Narrow pulse pressure
- Sleepy / obtundated
- Low serum sodium
- Cool extremities
- Hypotension with ACE inhibitor
- Renal Dysfunction (one cause)
Limitations of Current Therapies for Acute CHF: Positive Inotropes

- **Increased mortality**
  - Milrinone 1,2
  - Enoximone 3
  - Imazodan 4
  - Vesnarinone 5
  - Dobutamine 6,7
  - Xamoterol 8
  - Ibopamine 9

- **Increased risk of hospitalization** 1

- **Aggravation and induction of arrhythmias (need telemetry)**
  - Milrinone 10,11
  - Dobutamine 12
  - Dopamine 13

- **Tachycardia** 14

- **Tachyphylaxis** (dobutamine) 15

- **Neurohormonal activation and/or lack of suppression** 16

- **Physiologic effects antagonized by b-blockade** (dobutamine, dopamine)

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Vicious Circle of Myocardial Dysfunction

Myocardial Injury

↓ Left Ventricular Performance

↑ Ventricular Pre- and Afterload
Myocardial Hypertrophy and Ischemia

Systemic Vasoconstriction and Renal Sodium and Water Retention

↓ Cardiac Output

Neurohumoral Response
Sympathetic Nervous System
Renin-Angiotensin-Aldosterone System
Nonosmotic AVP Release

AVP Receptor Antagonist

Changes in Body Weight and Serum Sodium by Visit

Body Weight (kg)

Serum Na⁺ (mEq/L) (baseline <134 mEq/L)
Rolofylline Early Clinical Study Results: Increased Glomerular Filtration Rate and Increased Renal Plasma Flow

- Patients with congestive heart failure and reduced kidney function
  - Randomized, two-way crossover study (n=23)
  - Background treatment with furosemide
Aquapheresis™/Aquadex™ FlexFlow™ Observations

<table>
<thead>
<tr>
<th>Treatment Detail</th>
<th>Average or Typical Value*</th>
</tr>
</thead>
</table>
| Patient selection         | • ≥5 lb over dry weight, diuretic resistant within 12 h of hospitalization  
                           | • Before any significant administration of IV diuretics and/or vasoactive drugs |
| Fluid removal rate (UF rate) | 250 mL/h (= 6 L in 24 h) |
| Blood flow rate (blood flow) | 30-40 mL/min            |
| Treatment time            | 20 h                     |
| Anticoagulation           | 2 times normal           |
| Venous access             | Peripheral or central    |
| Salt removal              | Approximately 3200 mg/L  |

*Monitor patient for clinical signs of hypovolemia and hypotension.

### GISSI-HF omega-3 fatty acid study: Primary and secondary outcomes

<table>
<thead>
<tr>
<th>End point</th>
<th>Omega-3 fatty acids, n=3494 (%)</th>
<th>Placebo, n=3481 (%)</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end points</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mortality</td>
<td>27.3</td>
<td>29.1</td>
<td>0.91 (0.833–0.998)</td>
</tr>
<tr>
<td>• All-cause mortality or hospitalization for cardiovascular causes</td>
<td>56.7</td>
<td>59.0</td>
<td>0.92 (0.849–0.999)</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Death from cardiovascular causes</td>
<td>20.4</td>
<td>22.0</td>
<td>0.90 (0.81–0.99)</td>
</tr>
<tr>
<td>• Sudden cardiac death</td>
<td>8.8</td>
<td>9.3</td>
<td>0.93 (0.79–1.08)</td>
</tr>
<tr>
<td>• Patients admitted for cardiovascular causes</td>
<td>46.8</td>
<td>48.5</td>
<td>0.93 (0.87–0.99)</td>
</tr>
<tr>
<td>• Patients with fatal and nonfatal MI</td>
<td>3.1</td>
<td>3.7</td>
<td>0.82 (0.63–1.06)</td>
</tr>
<tr>
<td>• Patients with fatal and nonfatal stroke</td>
<td>3.5</td>
<td>3.0</td>
<td>1.16 (0.91–1.53)</td>
</tr>
</tbody>
</table>

## GISSI-HF statin study: Primary outcomes

<table>
<thead>
<tr>
<th>End point</th>
<th>Rosuvastatin 10 mg, n=2285 (%)</th>
<th>Placebo, n=2289 (%)</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>29.0</td>
<td>28.0</td>
<td>1.00 (0.898–1.122)</td>
</tr>
<tr>
<td>All-cause mortality or hospitalization for cardiovascular causes</td>
<td>57.0</td>
<td>56.0</td>
<td>1.01 (0.908–1.112)</td>
</tr>
</tbody>
</table>

CHF: Two Broad Categories

SHF
- Eccentric Remodeling
- Increased LV Volume
- Progressive LV Dilation
- Increased V/M
- Systolic Dysfunction

DHF
- Concentric Remodeling
- Normal Volume
- Increased LV Mass
- Decreased V/M
- Diastolic Dysfunction
Diastolic Heart Failure: Diagnosis

Required:
1. Signs and symptoms of CHF,
2. Normal LV ejection fraction,
3. r/o non cardiac causes

Confirmatory:
4. Abnormal diastolic function,
5. Abnormal LV structure
   Concentric remodeling
   LA enlargement
## Proposed Criteria for Diastolic Heart Failure

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>• CHF signs/symptoms</td>
<td>• CHF signs/symptoms</td>
</tr>
<tr>
<td>• EF ≥ 45%</td>
<td>• EF ≥ 50%</td>
</tr>
<tr>
<td>• Hemodynamic or echo evidence of diastolic dysfunction</td>
<td>• Hemodynamic evidence of diastolic dysfunction</td>
</tr>
<tr>
<td>– Slow isovolumic LV relaxation</td>
<td>– Definite or probable if within 72 h of CHF</td>
</tr>
<tr>
<td>– Slow early LV filling</td>
<td>– Possible if not</td>
</tr>
<tr>
<td>– Reduced LV diastolic distensibility</td>
<td>• Hemodynamic evidence of diastolic dysfunction</td>
</tr>
<tr>
<td>– Increased LV chamber stiffness or muscle stiffness</td>
<td>– Definite: abnormal diastolic indices on cardiac catheterization</td>
</tr>
<tr>
<td></td>
<td>– Probable or possible if no evidence</td>
</tr>
</tbody>
</table>
# HF Due to Diastolic Dysfunction Treatment

<table>
<thead>
<tr>
<th>Treatment Goal</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ LV volume &amp; edema:</td>
<td>diuretics, ↓ salt, nitrates</td>
</tr>
<tr>
<td>Rx systolic HTN:</td>
<td>diuretics, ACEI, ARB, CA, BB</td>
</tr>
<tr>
<td>Reverse LVH:</td>
<td>ACEI, ARB, most anti-hypertensives</td>
</tr>
<tr>
<td>Prevent fibrosis:</td>
<td>ACEI, ARB, spironolactone</td>
</tr>
<tr>
<td>Prevent ischemia:</td>
<td>BB, CA, nitrates</td>
</tr>
<tr>
<td>↓ HR, prevent AF:</td>
<td>BB, rate lowering CA</td>
</tr>
<tr>
<td>Enhance relaxation:</td>
<td>? Verapamil</td>
</tr>
</tbody>
</table>
PILOT STUDY OF EPLERENONE IN DIASTOLIC HF

HOSPITALIZATION WITH HF SIGNS AND SYMPTOMS
CHEST X-RAY – PULMONARY CONGESTION
TREATMENT WITH IV MEDS
EJECTION FRACTION > 45% WITHIN 72 HRS
OUTCOME—CARDIAC MRI ANALYSIS