Keynote Presentation

Optimal Medical Management and Device Therapy for Chronic Heart Failure

Chicago, IL

November 22, 2008
7:30 AM – 8:30 AM
Session 9: Keynote: Optimal Medical Management and Device Therapy for Chronic Heart Failure

Learning Objectives

- Discuss clinical data and guideline recommendations for heart failure therapies that offer advantages in terms of morbidity and mortality for specific patient populations.
- Compare emerging therapies that target heart failure.

Faculty

Gregg C. Fonarow, MD
Eliot Corday Professor of Cardiovascular Medicine and Science
Director, Ahmanson-UCLA Cardiomyopathy Center
Codirector, UCLA Preventative Cardiology Program
Associate Chief, UCLA Division of Cardiology
University of California at Los Angeles Medical Center

Dr Fonarow serves as the director of the Ahmanson-UCLA Cardiomyopathy Center and is the director of the Cardiology Fellowship Program at the University of California at Los Angeles. His research interests center on heart failure management and implementing treatment algorithms to improve clinical outcome. Dr Fonarow has published a number of research studies and clinical trials in heart failure management. New therapies and management strategies for advanced heart failure and research into the pathophysiology of this disease are conducted at UCLA under his direction. He wrote the UCLA Clinical Practice Guidelines for heart failure, acute myocardial infarction, atherosclerosis prevention and treatment, and unstable angina. He has also developed and successfully implemented a comprehensive atherosclerosis treatment program at the UCLA Medical Center (Cardiac Hospitalization Atherosclerosis Management Program: CHAMP).

Faculty Financial Disclosure Statement

The presenting faculty report the following:
Dr Fonarow is a member of the speakers bureau for GlaxoSmithKline, Pfizer Inc., and Merck & Co., Inc. He is a consultant for Bristol-Myers Squibb/sanofi-aventis. He receives research grants from Guidant and Medtronic.

Drug and Device Lists

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>captopril</td>
<td>Capoten</td>
<td>DDDR  dual-chamber rate-adaptive pacemaker</td>
</tr>
<tr>
<td>carvedilol</td>
<td>Coreg</td>
<td>VVI   single-chamber ventricular demand pacer</td>
</tr>
<tr>
<td>enalapril</td>
<td>Vasotec</td>
<td>OptiVol Fluid Status Monitoring —</td>
</tr>
<tr>
<td>eplerenone</td>
<td>Inspra</td>
<td>automatic intrathoracic fluid status monitoring</td>
</tr>
<tr>
<td>metoprolol XL</td>
<td>Toprol XL</td>
<td></td>
</tr>
<tr>
<td>ramipril</td>
<td>Altace</td>
<td></td>
</tr>
<tr>
<td>spironolactone</td>
<td>Aldactone</td>
<td></td>
</tr>
</tbody>
</table>

Suggested Reading List


Session 9
Optimal Medical Management and Device Therapy for Chronic Heart Failure

Gregg C. Fonarow, MD
Eliot Corday Professor of Cardiovascular Medicine and Science Director, Ahmanson-UCLA Cardiomyopathy Center Co-director, UCLA Preventive Cardiology Program Associate Chief, UCLA Division of Cardiology

Heart Failure Background

Population Group | Prevalence | Incidence | Mortality | Hospital Discharges | Cost
--- | --- | --- | --- | --- | ---
Total population | 5,200,000 | 550,000 | 50% at 5 years | 1,100,000 | $33.2 billion

- Heart failure (HF) is a major public health problem resulting in substantial morbidity and mortality
- Major cost-driver of HF is high incidence of hospitalizations
- Despite treatment advances large number of eligible patients are not receiving optimal care

Survival after the onset of congestive heart failure in Framingham Heart Study subjects
Ho Circulation 1993;88:107-115

National Trends in Outcomes Among Patients Hospitalized with HF

Trends in Crude and Adjusted Mortality Rates

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>30-day Mortality (%)</th>
<th>1-year Mortality (%)</th>
<th>30-day Mort (OR, 95% CI)</th>
<th>1-year Mort (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>483,560</td>
<td>11.0</td>
<td>32.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1993</td>
<td>509,549</td>
<td>10.8</td>
<td>33.9</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
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<tr>
<td>1994</td>
<td>509,245</td>
<td>10.6</td>
<td>31.7</td>
<td>0.99 (0.98-1.00)</td>
<td>0.91 (0.90-0.92)</td>
</tr>
<tr>
<td>1995</td>
<td>510,929</td>
<td>10.5</td>
<td>31.5</td>
<td>1.00 (0.98-1.01)</td>
<td>0.91 (0.90-0.92)</td>
</tr>
<tr>
<td>1996</td>
<td>505,661</td>
<td>10.3</td>
<td>31.4</td>
<td>0.98 (0.97-1.00)</td>
<td>0.91 (0.90-0.92)</td>
</tr>
<tr>
<td>1997</td>
<td>507,986</td>
<td>10.2</td>
<td>31.7</td>
<td>0.98 (0.97-0.99)</td>
<td>0.92 (0.92-0.93)</td>
</tr>
<tr>
<td>1998</td>
<td>436,257</td>
<td>10.2</td>
<td>31.8</td>
<td>0.99 (0.97-1.00)</td>
<td>0.93 (0.92-0.93)</td>
</tr>
<tr>
<td>1999</td>
<td>494,733</td>
<td>10.3</td>
<td>31.7</td>
<td>1.01 (1.00-1.02)</td>
<td>0.93 (0.92-0.94)</td>
</tr>
</tbody>
</table>

National sample of 3,957,520 Medicare beneficiaries ≥65 who were hospitalized with HF between 1992 and 1999
Kosiborod AJM 2006;119:e1-e7
**Natural History of Heart Failure**

- **Mechanism of Death**
  - Sudden Death: 40%
  - Worsened HF: 40%
  - Other: 20%

- **Left Ventricular Dysfunction and Symptoms**
  - Asymptomatic: 0%
  - Mild: 10-20%
  - Moderate: 25-30%
  - Severe: 35-40%

**Heart Failure Pathophysiology**

- **Myocardial Injury**
- **Activation of RAAS, SNS, ET, and others**
- **Remodeling and progressive worsening of LV function**
- **Peripheral vasoconstriction**
- **Hemodynamic alterations**
- **Heart failure symptoms**

**Fonarow GC. Rev Cardiovasc Med. 2001;2:7–12.**

**Pathophysiologic Effects of Angiotensin II and Epinephrine/Norepinephrine**

- Cardiac Myocyte
  - Hypertrophy
  - Apoptosis
  - Cell Sliding
  - Increased Wall Stress
  - Increased O2 Consumption
  - Impaired Relaxation
  - Fibrosis
  - Collagen Synthesis
  - Hyperplasia
- Fibroblasts
  - Fibrosis
  - Collagen Synthesis
  - Fibroblast Proliferation
- Smooth Muscle
  - Hypertrophy
  - Hyperplasia
- Coronary Artery
  - Vasoconstriction
  - Endothelial Dysfunction
  - Hyperreactivity
  - Atherosclerosis
  - Thrombosis
- Venous Constriction

**ACC/AHA HF Guidelines: Management of Heart Failure (Stage C)**

- **Life Prolonging Therapy**
  - ACE inhibitors (Class I, evidence A) all patients without contraindications or intolerance
  - β-Blockers (Class I, evidence A) all patients without contraindications or intolerance
  - Aldosterone antagonists (Class I, evidence B) all patients with moderately severe or severe symptoms without contraindications or intolerance, when close monitoring can be assured

**Effect of ACE Inhibitors on Mortality and Hospitalizations in Patients with HF**

- **Total Mortality or Hospitalization for Congestive Heart Failure**

  - **Subgroup**
    - Male: 22.9 vs 33.2, OR 0.63
    - Female: 22.2 vs 29.5, OR 0.78
    - <60: 22.2 vs 31.1, OR 0.71
    - ≥60: 24.0 vs 34.8, OR 0.79
    - Class I: 17.5 vs 24.8, OR 0.69
    - Class II: 19.5 vs 28.4, OR 0.68
    - Class III: 22.1 vs 43.2, OR 0.58
    - Class IV: 46.2 vs 59.2, OR 0.69
    - Ischemic: 28.3 vs 40.1, OR 0.63
    - Nonischemic: 23.2 vs 29.0, OR 0.72
    - LVEF >25: 23.6 vs 29.6, OR 0.85
    - LVEF <25: 33.7 vs 48.9, OR 0.53
    - All Patients: 22.4 vs 32.6, OR 0.65

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32 Trials of ACEI in Heart Failure. ACEI (n = 3370); Placebo (n = 3235).

Survival Rates in Patients Receiving ACE Inhibitors Across NYHA Classes

ValHeFT: ARB added to Standard HF Care Including ACEI

CHARM-Alternative

ACEI/ARB in Heart Failure

Effects of Aldosterone

RALES: Aldosterone Antagonist Reduces All-Cause Mortality in Chronic HF

*Ejection fraction ≤35%; Class III or IV symptoms at some point in prior 2 months.

### RALES Results: Relative Risks of Various End Points

<table>
<thead>
<tr>
<th>End point</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from Cardiac Causes or Hospitalization for Cardiac Causes</td>
<td>0.86 (0.59-0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from Any Cause or Hospitalization for Any Reason</td>
<td>0.77 (0.69-0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from Any Cause or Hospitalization for Cardiac Causes</td>
<td>0.86 (0.80-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cause of Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Causes</td>
<td>0.89 (0.58-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression of Heart Failure*</td>
<td>0.94 (0.51-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sudden Death†</td>
<td>0.71 (0.54-0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Reason for hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Cardiac Causes</td>
<td>0.70 (0.59-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Worsening Heart Failure</td>
<td>0.85 (0.64-0.77)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* This category includes death due to worsening heart failure defined as increasing symptoms or signs requiring an increase in treatment.
† This category includes sudden death from cardiac causes heralded by abrupt loss of consciousness within 1 hr after the onset of symptoms in a patient in whom death was unexpected.
‡ Some patients were hospitalized for more than one cardiac cause.

### Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS)

**Post AMI, LVEF < 40, Rales or S3**

- **Randomization**
  - Eplerenone Initiation
    - 25 qd, 50 mg at 4wks
  - Matching Placebo
- **Follow-up**

**EPHESUS Co-Primary Endpoint: Total Mortality**

- **Eplerenone + standard care (n=3319)**
  - (16.7%)
- **Placebo + standard care (n=3313)**
  - (14.4%)

- **HR = 0.85 (95% CI, 0.75 to 0.96)**
  - **P = .008**

**HR = hazard ratio.**


### Aldosterone Antagonists in Heart Failure

- **Indicated for patients with moderately severe or severe HF due to LVD (LVEF < 0.40).** (Contraindications: hyperkalemia, Cr > 2.5 in men and > 2.0 in women)
- **Spironolactone 12.5 mg PO qd starting dose (or 6.25 mg in higher risk patients) or Eplerenone 25 mg qd.** Decrease potassium supplementation and loop diuretic dose at time of initiation.
- **Critical to very closely monitor serum potassium and renal function.** Advise checking chemistry panel at 48 hours, 1 week, and 4 weeks.
- **Advance Spironolactone dose at 4 weeks to 25 mg PO qd or Eplerenone 50 mg which is the target dose.** Avoid higher doses due to risk of hyperkalemia.

Hunt SA et al. J Am Coll Cardiol. 2005

### Effect of Digoxin on Mortality in Heart Failure: The Digitalis Investigation Group

- **CV Mortality ≤ 4%**
  - Relative Risk 0.99
  - 95% CI 0.91–1.07
  - **P = .80**
- **HF Hospitalizations ≤ 28%**
- **Total Hospitalizations ≤ 5%**

**DIG (Digitalis Investigation Group):** 6,800 patients with LVEF < 45% randomized to digoxin (n=3,403) or placebo (n=3,397) in addition to therapy with diuretics and ACEI followed for 37 months.

The Use of Beta Adrenergic Blocking Agents in Heart Failure

Initial hemodynamic deterioration followed by reverse remodeling (decrease in EDV and ESV) with improved ventricular function over time (increased LVEF).

Effect of Carvedilol in Heart Failure

US Heart Failure Trials Program

1094 Class II-IV CHF pts on triple therapy (ACEI, digoxin, diuretics), Carvedilol 0.625 bid x 2 weeks, then 1.25 bid, then 2.5 bid vs placebo

Packer NEJM 1996;334:1349-55

Effect of Metoprolol CR/XL in Heart Failure

MERIT-HF

3991 pts with CHF Class II-IV, ave age 64 and LVEF 0.28
Randomized to Metoprolol CR/XL 12.5 mg or 25 mg PO qd, target dose 200 mg qd
Lancet 1999;353:2001-07

Major Trials of β-Blockade in Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (n)</th>
<th>Follow-up (yrs)</th>
<th>NYHA Class</th>
<th>LVEF (%)</th>
<th>Effects on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS</td>
<td>641</td>
<td>1.9</td>
<td>II-III</td>
<td>&lt; 35</td>
<td>All-cause mortality: ↓ 22% NS</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>2647</td>
<td>1.3</td>
<td>II-III</td>
<td>&lt; 35</td>
<td>All-cause mortality: ↓ 34% (P&lt;0.001)</td>
</tr>
<tr>
<td>MDC</td>
<td>383</td>
<td>1</td>
<td>II-III</td>
<td>&lt; 40</td>
<td>Death or need for transplant: ↓ 10%, P&lt;0.05</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>3991</td>
<td>1</td>
<td>II-III</td>
<td>&lt; 40</td>
<td>All-cause mortality: ↓ 34% (P&lt;0.002)</td>
</tr>
<tr>
<td>US Carvedilol Trials</td>
<td>1094</td>
<td>7.5 months</td>
<td>II-III</td>
<td>&lt; 35</td>
<td>All-cause mortality*: ↓ 25% (P&lt;0.003)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2289</td>
<td>10.5 months</td>
<td>IV</td>
<td>&lt; 25</td>
<td></td>
</tr>
</tbody>
</table>

Effect of Carvedilol in Severe Heart Failure

COPERNICUS

2289 Class IV CHF pts, LVEF < 0.25, not on inotropes x 4days, ave age 63, LVEF 0.20
Carvedilol 3.125 bid, q 2 wks titration. 75% to target.  withdrawl 16% placebo, 13% carvedilol
Packer NEJM 2001;344:1651-8

Effect of Carvedilol on Mortality

Annual placebo mortality rate (per patient-year)

19.7% Favors treatment

28.5% Favors placebo

Recent or recurrent decompensation
**Safety of Initiating Carvedilol in Patients with Severe Heart Failure**

Permanent Withdrawals

![Graph showing permanent withdrawals over months for Placebo vs Carvedilol](image)

Packer NEJM 2001;344:1651-8

**Early Benefits and Early Safety of Carvedilol in Severe HF: COPERNICUS**

Early Mortality Reduction

![Graph showing early mortality reduction between Placebo and Carvedilol](image)

Lower Risk for Worsening CHF

![Graph showing lower risk for worsening CHF between Placebo and Carvedilol](image)


**Effects of Sympathetic Activation in Heart Failure**

![Diagram showing effects of sympathetic activation with various receptors](image)

Bristow MR. Circulation. 2000;101:558-569.

**Not All β-Blockers Reduce Mortality in HF**

![Graph showing mortality reduction for BEST and SENIORS studies](image)

Bisoprolol1

Bucindolol2

Carvedilol3-5

Metoprolol tartrate6

Metoprolol succinate7

Nebivolol8

Xamoterol9

**COMET: Effect Carvedilol vs Metoprolol Tartrate on Mortality in HF**

![Graph showing mortality rates for Carvedilol vs Metoprolol](image)

Metoprolol Tartrate mean dose: 85 mg OD; Carvedilol mean dose: 42 mg OD.

COMET did not evaluate metoprolol succinate, the agent used in the MERIT-HF Trial.

**Beta Blocker Therapy in Heart Failure**
- Indicated for all patients with asymptomatic LVD dysfunction and for Class I to IV Heart Failure with LVEF < 0.40
- Contraindications: cardiogenic shock, severe reactive airway disease, 2/3rd degree HB
- Use one or more evidence-based beta blockers in HF: eg carvedilol, metoprolol succinate, bisoprolol
- Start at very low HF doses and up-titrate to target doses at two week intervals, or highest dose short of target dose that is well tolerated
- Monitor HR and BP


**Neurohormonal Activation as the Therapeutic Target in Heart Failure**

**Therapies with Demonstrated Benefit in Clinical Trials**

- **Sympathetic Nervous System**
  - Beta Adrenergic Blockers (carvedilol)
- **Renin Angiotensin Aldosterone System**
  - Angiotensin Converting Enzyme Inhibitors (Angiotensin II Receptor Antagonists)
  - Aldosterone Antagonists

**AHeFT: Trial Summary**

43% Decrease in Mortality

Placebo

Fixed-dose HYD/ISDN

Hazard ratio=0.57
P=0.01

Days Since Baseline Visit Date

1,050 African Americans with Class III to IV HF, LVEF 24%, on ACEI, BB, AA

**Device Therapy for Heart Failure**

- Cardiac resynchronization therapy (CRT)
- Implantable cardioverter-defibrillators (ICD)
- Ventricular assist devices
  - Bridge to transplant
  - Destination therapy
- Totally implanted artificial hearts
- Cardiac reshaping devices
- Ultrafiltration devices

**Cardiac Resynchronization Therapy for Heart Failure**

- In patients with heart failure 27 to 53% of patients have IVCDs (RBBB, LBBB, IVCD)
- Abnormal conduction contributes to abnormal ventricular activation/contraction and subsequent dysynchrony between the RV and LV
  - Reduced systolic performance
  - Mechanical inefficiency
  - Worsened prognosis

Aarronson Circulation 1997;96. Grines Circulation 1989;79
Xiao Int J Cardiol 1996;53

**Cardiac Resynchronization Therapy: Weight of Evidence**

- >4,000 patients evaluated in randomized controlled trials
- Consistent improvement in quality of life, functional status, and exercise capacity
- Strong evidence of reverse remodeling
  - ↓ LV volumes and dimensions
  - ↑ LVEF
  - ↓ Mitral regurgitation
- Reduction in HF and all-cause morbidity and mortality

**CRT Improves QoL and NYHA Functional Class**

Average Change in QoL Score (MLWHF)

- CRT Improves QoL and NYHA Functional Class

NYHA: Proportion Improving 1 or More Class (%)

P<0.001

<table>
<thead>
<tr>
<th></th>
<th>Control N=63</th>
<th>CRT N=61</th>
<th>CRT N=63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
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</tbody>
</table>

*P<.05.

**CARE-HF: Effect of CRT Without an ICD on All-Cause Mortality**

Event-Free Survival

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>0</th>
<th>500</th>
<th>1,000</th>
<th>1,500</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT plus meds</td>
<td>400</td>
<td>370</td>
<td>351</td>
<td>213</td>
</tr>
<tr>
<td>Medical Rx</td>
<td>404</td>
<td>363</td>
<td>321</td>
<td>192</td>
</tr>
</tbody>
</table>

HR: 0.64 (95% CI: 0.48-0.85)

P=.0019

**CARE-HF: Clinical Outcomes**

**Death + CV Hospitalization**

<table>
<thead>
<tr>
<th>OMT (n=404)</th>
<th>CRT + OMT (n=409)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>225 (55%)</td>
<td>159 (39%)</td>
<td>0.63 (.51 to .77)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**CV Hospitalization**

<table>
<thead>
<tr>
<th>OMT (n=404)</th>
<th>CRT + OMT (n=409)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>184 (46%)</td>
<td>125 (31%)</td>
<td>0.61 (.49 to .77)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**All-Cause Death**

<table>
<thead>
<tr>
<th>OMT (n=404)</th>
<th>CRT + OMT (n=409)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 (30%)</td>
<td>82 (20%)</td>
<td>0.64 (.48 to .85)</td>
<td>&lt;.002</td>
</tr>
</tbody>
</table>

**CARE-HF: Effect of CRT on the Primary End Point in Predefined Subgroups**

**CARE-HF: Hemodynamic, Echocardiographic, and Biochemical Assessments**

**Variable**

<table>
<thead>
<tr>
<th>Difference in Means at 3 Mo (95% CI)</th>
<th>P Value</th>
<th>Difference in Means at 18 Mo (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>+1.1 (-1.3 to 3.4)</td>
<td>.33</td>
<td>+1.2 (-1.6 to 4.0)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>+5.8 (3.5 to 8.2)</td>
<td>&lt;.001</td>
<td>+6.3 (3.6 to 9.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>+1.5 (0.1 to 2.9)</td>
<td>.03</td>
<td>+1.3 (-1.8 to 4.4)</td>
</tr>
<tr>
<td>Interventricular mechanical delay, ms</td>
<td>-21 (-25 to -16)</td>
<td>&lt;.001</td>
<td>-21 (-25 to -17)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>+3.7 (3.0 to 4.4)</td>
<td>&lt;.001</td>
<td>+6.8 (5.6 to 8.1)</td>
</tr>
<tr>
<td>Left ventricular end-systolic volume, mL/m²</td>
<td>-18.2 (-21.2 to -15.1)</td>
<td>&lt;.001</td>
<td>-26.0 (-30.0 to -22.4)</td>
</tr>
<tr>
<td>Mitral regurgitation area?</td>
<td>-0.061 (-0.073 to -0.049)</td>
<td>&lt;.001</td>
<td>-0.42 (-0.71 to -0.13)</td>
</tr>
<tr>
<td>N-terminal pro-BNP, pg/mL</td>
<td>-225 (-705 to 250)</td>
<td>.36</td>
<td>-1122 (-1815 to -429)</td>
</tr>
</tbody>
</table>

* Differences were not adjusted for the higher mortality rate in the medical therapy group. A plus sign indicates a greater value, and a minus sign a smaller value, in the cardiac resynchronization group than in the medical therapy group.
**Improved Survival with Prophylactic ICD Therapy Patients with Prior MI and LVEF < 30: MADIT-II**

Subgroup Analyses Influencing Payment Approval

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1040</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>Age &lt;60 yr</td>
<td>370</td>
<td></td>
</tr>
<tr>
<td>Age 60-69 yr</td>
<td>426</td>
<td></td>
</tr>
<tr>
<td>Age ≥70 yr</td>
<td>436</td>
<td></td>
</tr>
</tbody>
</table>

**SCD-HeFT: Trial Design**

2521 Ischemic or Non-ischemic Chronic HF on Standard HF Medications

EF ≤35%

NYHA Class II or III

Placebo Amiodarone ICD

Mean age 60%, 71% male, Ischemic 54%, LVEF 0.24

ACE: 85%, BB: 19%, Ald Ant 19%, Statin 38%

**SCD-HeFT Trial: Survival**

Amiodarone vs Placebo: 1.06, 0.86-1.30, P = 0.53

ICD vs Placebo: 0.77, 0.62-0.96, P = 0.007

2521 patients with ischemic or non-ischemic NYHA class II-III heart failure and LVEF ≤35% or less

**COMPANION: Secondary Endpoint of All-Cause Mortality**

CORT vs OPT: HR=0.91, P=0.003 (Critical boundary: 0.94)

CRT-D vs OPT: HR=0.36, P=0.002 (Critical boundary: 0.50)

**SCD-HeFT and Other ICD Device Trials in HF**

<table>
<thead>
<tr>
<th>HF Etiology</th>
<th>MADIT II</th>
<th>COMPANION</th>
<th>DEFINITE</th>
<th>SCD-HeFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>HR 0.77</td>
<td>HR 0.89</td>
<td>HR 0.64</td>
<td>HR 0.77</td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>HR 0.81</td>
<td>HR 0.80</td>
<td>HR 0.63</td>
<td>HR 0.81</td>
</tr>
<tr>
<td>NYHA Class I/II/III</td>
<td>20%/60%/20%</td>
<td>17%/61%/22%</td>
<td>15%/61%/23%</td>
<td>17%/61%/22%</td>
</tr>
<tr>
<td>LVEF ≤35%</td>
<td>HR 0.73</td>
<td>HR 0.75</td>
<td>HR 0.64</td>
<td>HR 0.73</td>
</tr>
</tbody>
</table>

**Important Comorbidities in Heart Failure**

- Cardiovascular
  - Hypertension
  - Coronary artery disease
  - Peripheral vascular disease
  - Cerebral vascular disease
  - Hyperlipidemia
  - Atrial fibrillation
- Non-Cardiovascular
  - Obesity
  - Diabetes
  - Anemia
  - Chronic kidney disease
  - Thyroid disease
  - COPD / Asthma
  - Smoking
  - Sleep disordered breathing
  - Liver disease
  - Arthritis
  - Cancer
  - Depression

Horwich and Fonarow: Chapter 40: Impact and Treatment of Comorbidities in Heart Failure
ACC/AHA Guidelines for HF Comorbidities and Related Risks

- Control of systolic and diastolic hypertension in accordance with recommended guidelines
  - Appropriate antihypertensive regimen frequently consists of several drugs used in combination
  - Drugs that are useful for the treatment of both hypertension and HF are preferred (eg, ACE inhibitors, β-blockers, aldosterone antagonists, diuretics)
- Treat lipid disorders
- Encourage smoking cessation and regular exercise
- Discourage alcohol intake/illicit drug use

Heart Failure with Normal Systolic Function

Treatment of patients with predominantly diastolic dysfunction heart failure has not been well studied

- Control hypertension
- Diuretics should be used cautiously, at low dose initially, recognizing that the stiff heart is highly dependent on adequate preload
- Rate control for atrial fibrillation
- ACE inhibitors, calcium channel blockers, and beta blockers have favorable effects upon hemodynamics but their impact on longer term outcome is not known

New Therapies for Heart Failure

- Vasopeptidase inhibitors
- Natriuretic peptides
- Cytokine Antagonists
- Phosphodiesterase-5 inhibitors
- Cardiac resynchronization therapy (class 1)
- Ventricular constraint devices
- Statins
- Erythropoietin
- Immune modulation
- Peripheral ultrafiltration

Evidence-Based Treatment Across the Continuum of LVD and HF

Reduce Mortality

- ACEI or ARB
- β-Blocker
- Aldosterone Antagonist
- CRT ± an ICD
- Hyd/ISDN

Control Volume

- Salt Restriction
- Diuretics

Treat Residual Symptoms

- Digoxin

Treat Comorbidities

- Aspirin
- Warfarin
- Statin

Patient Education is Essential in HF

Patient Instructions

- Monitor daily weights
- Salt restricted diet (e.g. 2-3 gm sodium diet)
- Medications, need for adherence
- Activity Rx
- Smoking Cessation Advice/Counseling
- What to do if HF symptoms worsen
- Close follow-up and monitoring

Long-Term Trends in Mortality With Heart Failure

Temporal Trends in Age-Adjusted Mortality After the Onset of Heart Failure

<table>
<thead>
<tr>
<th>Period</th>
<th>30-Day Mortality</th>
<th>1-Year Mortality</th>
<th>5-Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>1970–1979</td>
<td>15 (7-23)</td>
<td>16 (6-24)</td>
<td>41 (29-51)</td>
</tr>
<tr>
<td>1980–1989</td>
<td>12 (5-16)</td>
<td>10 (4-16)</td>
<td>33 (23-42)</td>
</tr>
<tr>
<td>1990–1999</td>
<td>11 (4-17)</td>
<td>10 (3-15)</td>
<td>28 (18-36)</td>
</tr>
</tbody>
</table>

Survival Trends in HF Patients With and Without Preserved EF

A. Patients With Reduced Ejection Fraction

B. Patients With Preserved Ejection Fraction

Utilization of Evidence-based HF Therapies

IMPROVEMENT International Survey

ADHERE Quality of Care
Conformity to JCAHO HF Performance Indicators

All Patients (n = 54,639)

Patients at Academic Hospitals (n = 18,934)

Patients at Non-Academic Hospitals (n = 35,705)

P value †

Failure” of Usual Care in HF

- Failure to prescribe evidence-based medications
- Failure to discontinue medications that may exacerbate HF
- Failure to titrate medications to target doses
- Failure to adhere to prescribed medications
- Failure to address co-morbidities adequately
- Failure to consider device therapies
- Failure to provide adequate dietary counseling
- Failure to comply with dietary regimen
- Failure to seek early care with escalating symptoms
- Failure to provide adequate discharge planning
- Failure to provide adequate follow-up
- Failure to provide adequate monitoring
- Failure to identify patient social support systems
- Failure to address patient and caregiver needs

**Clinical IIb III 0 III III II III 07 1 06 6 08 5 II 07 0 IIb III III IIb III IIb 08 6 04 6 0 0 0**

**J Am Coll Cardiol. Fonarow GC. et al. Total medical costs: Pre ($18,808) vs Post ($9,555),**

- National guidelines
- Clinical trial evidence

**C**

---

**HF Disease Management Program:**

- Impact on Hospitalizations

- **Pre** vs conventional management
- **95** vs **92**

---

**Randomized Trials of Disease Management Programs for Heart Failure**

- Sensitivity analysis: Mortality, All-cause readmission, HF-related readmission
- OR CI OR CI OR CI

---

**Why a Hospital-based System for Heart Failure Management?**

- **Patients**
  - Patient capture point
  - Have patients/family attention: “teachable moment”
  - Predictor of care in community

- **Hospital structure**
  - Standardized processes/protocols/orders/teams
  - JCAHO-ORYX Core Measures
  - Process improvement examples
  - Centers for Medicare and Medicaid Services—peer review organizations
  - NEDIS (post discharge)

---

**Institutional Heart Failure Discharge Medication Program Reduces Readmissions and Mortality**

- **Pre-Intervention (n=11,038)**
- **Post-Intervention (n=8,045)**
Outpatient Adherence to β-Blocker Therapy Post Acute MI

Optimize-HF: Change in HF Performance Measures Over Time

Impact of Evidence-Based HF Therapy Use at Hospital Discharge on Treatment Rates During F/U: OPTIMIZE-HF

Impact of Discharge Use of Beta Blocker on Early Clinical Outcomes in Heart Failure

Challenges to Implement a Heart Failure Performance Improvement System
Key Elements to Quality Improvement: Why Do Some Programs Succeed?

- Access to current and accurate data on treatment and outcomes
- Have stated goals
- Administrative support
- Support among clinicians
- Use of care maps and pathways
- Use of data to provide feedback

AHA GWTG-HF Web Based Patient Management Tool

Preliminary Results with GWTG-HF: Performance Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC Instructions</td>
<td>70%</td>
<td>72%</td>
<td>70%</td>
<td>73%</td>
<td>79%</td>
</tr>
<tr>
<td>LVF Measurement</td>
<td>91%</td>
<td>92%</td>
<td>92%</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>83%</td>
<td>83%</td>
<td>82%</td>
<td>84%</td>
<td>89%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>87%</td>
<td>88%</td>
<td>87%</td>
<td>84%</td>
<td>90%</td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>75%</td>
<td>82%</td>
<td>92%</td>
<td>83%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Data from 97 GWTG-HF hospitals and 18,516 HF patients were collected from 1/05-3/06
Fonarow GC et al. HFSA 2006

Congestion Precedes Hospitalization

<table>
<thead>
<tr>
<th>Days Relative to the Event</th>
<th>Pressure Change</th>
<th>Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Baseline -7</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>Baseline -6</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>Baseline -5</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>Baseline -4</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>Baseline -3</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>Baseline -2</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>Baseline -1</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>Recovery</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Poor Sensitivity of Weight and BNP Changes Prior to Clinical Decompensation

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2 Kg Weight Gain over 48-72 hours</td>
<td>9%</td>
<td>97%</td>
</tr>
<tr>
<td>&gt; 2% Weight Gain over 48-72 hours</td>
<td>17%</td>
<td>94%</td>
</tr>
<tr>
<td>&gt; 100 pg/mL increase in BNP</td>
<td>47%</td>
<td>77%</td>
</tr>
</tbody>
</table>


Implantable Hemodynamic Monitoring to Guide Heart Failure Care: COMPASS

<table>
<thead>
<tr>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.79 (0.64 - 0.98)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

21% trend for reduction in the relative risk of HF hospitalization. (p=0.27)
33% reduction in the proportion of patients with worsening HF.
32% reduction in HF-related overall.
41% reduction in HF-related events among patients with NYHA class 3 HF. (p=0.03)
Bourge et al. Presented at ACC 2006
Impedance Prior to HF Admission

Yu CM et al. Circulation. 2005;112:841-8

Devices as Patient Care Monitors

Auricchio and Abraham Circulation 2004; 109: 300-307

Implantable Devices Offer Unique Means to Monitor HF Patients

- Objectively track fluid accumulation and/or hemodynamics longitudinally over time
- Multiple measurements per day are averaged to give a truer picture of that day’s trends
- Acute changes are compared to the patient’s own expected baseline
- Intrathoracic impedance is not affected by respiration or any complicating factors such as electrode placement that impact external systems
- No compliance issues as with patient weights
- Wealth of other valuable information

AF Diagnostics

You want to know the following:
- Number of AF episodes
- % of time spent in AF
- Longest duration of AF
- Average ventricular rate during AF

Cumulative Impact of Heart Failure Therapies

Relative-risk 2 yr Mortality

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Relative-risk</th>
<th>2 yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>- -</td>
<td>35%</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>23%</td>
<td>27%</td>
</tr>
<tr>
<td>Aldosterone Ant</td>
<td>30%</td>
<td>19%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>CRT +/- ICD</td>
<td>36%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction if all four therapies are used: 77%
Absolute risk reduction: 27%, NNT = 4

Adapted from Fonarow GC. Rev Cardiovasc Med. 2000;1:25-33
Advances in the Treatment of HF

- Increased attention to prevention
- ACEI / β-blocker / aldosterone antagonist combination established as the “cornerstone” of therapy
- Evidence that β-blockers’ effects are not homogeneous
- Downgrade in recommendation for use of digoxin
- Integration of CRT and ICD device therapy into the standard therapeutic regimen
- Recognition that “special populations” of HF patients may benefit from or require different approaches
- New strategies to improve utilization of evidence based therapies and monitor patients


Key Aspects for Improving Outcomes

- Optimization of medical therapy
- Optimization of device therapy
- Education for both inpatients and outpatients
  - Reasonable expectations being given to patients
  - Consistent information being given to patients
- Increased outpatient access to healthcare professionals
- Long term patient follow-up
- Routine communication between HF and EP