Keynote Presentation

Optimal Medical Management and Device Therapy for Chronic Heart Failure

Dallas, Texas

December 12, 2008
7:30 AM – 8:30 AM
Session 1: 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, University of California at Los Angeles Preventative Cardiology Program
Associate Chief, UCLA Division of Cardiology
UCLA 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</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


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 Preventative Cardiology Program Associate Chief, UCLA Division of Cardiology

Presenter Disclosure Information
“Heart Failure Care”
I will discuss off label use of medications or devices

DISCLOSURE INFORMATION:
The following relationships exist related to this presentation:
Gregg C. Fonarow, MD, FACC – GlaxoSmithKline, Merck, AstraZeneca, Bristol Myers Squibb, Sanofi, Pfizer, Novartis, Scios, Medtronic, and Guidant: Research, Consultant, Speaker

Heart Failure Background

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Hospital Discharges</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>5,200,000</td>
<td>550,000</td>
<td>50% at 5 years</td>
<td>1,100,000</td>
<td>$33.2 billion</td>
</tr>
</tbody>
</table>

- 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

Prognosis with Heart Failure

Overall 5-year mortality 50%
Hospitalized Patients 1-year mortality:
Mild to Moderate Symptoms 10-20%
Severe Symptoms 40-60%

Outcomes During and After HF Hospitalization

- In-hospital
  - Length of stay (mean) 6.2 days
  - Mortality rate 4.1%
- Hospital readmissions
  - 20% at 30 days
  - 50% at 6 months
- Longer-term mortality
  - 11.6% at 30 days
  - 33.1% at 12 months

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>Crude Mortality (%)</th>
<th>Adjusted Mortality (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-day</td>
<td>1-year</td>
<td>30-day</td>
</tr>
<tr>
<td>1992</td>
<td>483,560</td>
<td>11.0</td>
<td>32.5</td>
</tr>
<tr>
<td>1993</td>
<td>509,549</td>
<td>10.9</td>
<td>33.9</td>
</tr>
<tr>
<td>1994</td>
<td>508,245</td>
<td>10.6</td>
<td>31.7</td>
</tr>
<tr>
<td>1995</td>
<td>510,929</td>
<td>10.5</td>
<td>31.5</td>
</tr>
<tr>
<td>1996</td>
<td>505,661</td>
<td>10.3</td>
<td>31.4</td>
</tr>
<tr>
<td>1997</td>
<td>507,066</td>
<td>10.2</td>
<td>31.7</td>
</tr>
<tr>
<td>1998</td>
<td>486,257</td>
<td>10.2</td>
<td>31.8</td>
</tr>
<tr>
<td>1999</td>
<td>494,733</td>
<td>10.3</td>
<td>31.7</td>
</tr>
</tbody>
</table>

National sample of 3,957,520 Medicare beneficiaries ≥65 who were hospitalized with HF between 1992 and 1999
Natural History of Heart Failure

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

Left Ventricular Dysfunction and Symptoms

- Asymptomatic: 0%
- Mild: 10%
- Moderate: 20%
- Severe: 70%

Heart Failure Pathophysiology

- Myocardial injury
- Hypertrophy
- Apoptosis
- Increased Wall Stress
- Increased O2 Consumption
- Impaired Relaxation
- Hypertrophy
- Endothelial Dysfunction
- Atherosclerosis
- Thrombosis

Pathophysiologic Effects of Angiotensin II and Epinephrine/Norepinephrine

- Cardiac Myocyte Hypertrophy, Apoptosis
- Cell Sliding, Increased Wall Stress, Impaired Relaxation
- Fibroblast Fibrosis
- Myocardial toxicity
- Fibrosis
- Vasoconstriction
- Renin Angiotensin System (RAS)
- Angiotensin II
- Bradykinin
- Nitric Oxide (NO)
- Prostaglandins
- Endothelin (ET)
- Norepinephrine
- Vasopressin

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

- Total Mortality: -23
- Death or Hospitalization: -35
- CHF Hospitalization: -31

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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ACE Inhibitor</th>
<th>Controls</th>
<th>OR  95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>22.4</td>
<td>35.5</td>
<td>0.65</td>
</tr>
<tr>
<td>LVEF &gt; 325</td>
<td>23.4</td>
<td>33.7</td>
<td>0.53</td>
</tr>
<tr>
<td>LVEF ≤ 325</td>
<td>23.3</td>
<td>33.7</td>
<td>0.53</td>
</tr>
<tr>
<td>Class I</td>
<td>22.2</td>
<td>31.1</td>
<td>0.71</td>
</tr>
<tr>
<td>Class II</td>
<td>24.0</td>
<td>34.6</td>
<td>0.73</td>
</tr>
<tr>
<td>Class III</td>
<td>24.6</td>
<td>36.9</td>
<td>0.79</td>
</tr>
<tr>
<td>Class IV</td>
<td>22.2</td>
<td>33.1</td>
<td>0.68</td>
</tr>
<tr>
<td>Ischemic</td>
<td>28.3</td>
<td>40.1</td>
<td>0.63</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>23.2</td>
<td>29.3</td>
<td>0.72</td>
</tr>
<tr>
<td>LVEF &gt; 25</td>
<td>23.3</td>
<td>29.3</td>
<td>0.72</td>
</tr>
<tr>
<td>LVEF ≤ 25</td>
<td>23.7</td>
<td>35.5</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Total Mortality or Hospitalization for Congestive Heart Failure

32 Trials of ACEI in Heart Failure  ACEI (n = 3870) Placebo (n = 3235)
Collaborative Group on ACE Inhibitor Trials  JAMA 1995;273:1450-1456
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
**RALES Results: Relative Risks of Various End Points Related to Death or Hospitalization in the Spironolactone Group**

<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 (0.80-0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cause of Death</td>
<td>0.86 (0.80-0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac Causes</td>
<td>0.89 (0.58-0.22)</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 (0.54-0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>Reason for hospitalization</td>
<td>0.70 (0.59-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All Cardiac Causes</td>
<td>0.85 (0.78-0.93)</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 medication.
†This category includes sudden death from cardiac causes heralded by abrupt loss of consciousness within one hour after the onset of symptoms in a patient in whom death was unexpected.
| Some patients were hospitalized for more than one cardiac cause.

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

- **Eplerenone + standard care (n = 3319)**
  - Cumulative Incidence (%): 22
  - HR: 0.85 (95% CI: 0.75 to 0.96)
  - P = .008
- **Placebo + standard care (n = 3313)**
  - Cumulative Incidence (%): 16.7

**Early Benefits of Eplerenone When Added to Standard Post MI Patient Care**

- **30 Days**
  - All Cause Mortality
  - Cardiovascular Mortality
  - Sudden Cardiac Death
  - Heart Failure Hospitalization
  - HR: 0.85 (95% CI: 0.75 to 0.96)
  - P = .008

**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 to 4 weeks to 25 mg PO qd or Eplerenone 50 mg which is the target dose.** Avoid higher doses due to risk of hyperkalemia.

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

- **CV Mortality**
  - 4%
- **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.

**Pitt N Engl J Med 2003;348:1309-1321.**
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

Effect of Carvedilol in Severe Heart Failure

COPERNICUS

Effect of Carvedilol on Mortality

Annual placebo mortality rate (per patient-year)

Favors treatment

Favors placebo

Major Trials of β-Blockade in Heart Failure

Patients (n) Follow-up (yrs) NYHA Class LVEF (%) Effects on Outcomes
CIBIS 641 1.9 II-III < 35 All-cause mortality:
↓ 22% NS
CIBIS-II 2647 1.3 II-III < 35 All-cause mortality:
↓ 34% (P<0.0001)
MDC 363 1 II-III < 40 Death or need for transplant:
↓ 30%, P<0.05
MERIT-HF 3991 1 II-III < 40 All-cause mortality:
↓ 34% (P<0.002)
US Carvedilol Trials 1094 7.5 months II-III < 35 All-cause mortality*:
↓ 65% (P<0.001)
COPERNICUS 2289 10 months IV < 25

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

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. 16% placebo, 13% carvedilol
Packer NEJM 2001;344:1651-8

Recent or recurrent decompensation

19.7%

28.5%

All patients

Favors treatment

Favors placebo
Safety of Initiating Carvedilol in Patients with Severe Heart Failure

Permanent Withdrawals

% Patients Permanently Withdrawn

Packer NEJM 2001;344:1651-8

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

Early Mortality Reduction

Lower Risk for Worsening CHF


Effects of Sympathetic Activation in Heart Failure

β-Blockers Differ in Their Long-Term Effects on Mortality in HF

COMET: Effect Carvedilol vs Metoprolol Tartrate on Mortality in HF
**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 of the 3 evidence-based beta blockers in HF: eg carvedilol, metoprolol succinate, bisoprolol
- Start at very low HF doses and up-titrato 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
- Fixed-dose HYD/ISDN
- Placebo

Hazard ratio=0.57

P<.01

Days Since Baseline Visit Date

100 African Americans with Class II to IV HF, LVEF 25%, 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

Aaronson 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

CARE-HF: Hemodynamic, Echocardiographic, and Biochemical Assessments

<table>
<thead>
<tr>
<th>Variable</th>
<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 (-2.5 to 0.3)</td>
<td>.35</td>
<td>-1.3 (-2.6 to 0.0)</td>
<td>.09</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>+6.0 (5.0 to 7.0)</td>
<td>&lt;.001</td>
<td>+7.3 (6.5 to 8.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>+1.5 (0.1 to 2.9)</td>
<td>.83</td>
<td>+1.3 (-0.8 to 4.4)</td>
<td>.42</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>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>+3.7 (2.8 to 4.4)</td>
<td>&lt;.001</td>
<td>+6.5 (5.6 to 7.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left ventricular end-systolic volume index, mL/m²</td>
<td>-1.8 (-2.0 to -1.5)</td>
<td>&lt;.001</td>
<td>-2.0 (-2.3 to -1.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mitral regurgitation area²</td>
<td>-0.001 (-0.007 to -0.000)</td>
<td>.001</td>
<td>-0.001 (-0.007 to -0.000)</td>
<td>.003</td>
</tr>
<tr>
<td>N-terminal pro-BNP, pg/mL</td>
<td>-225 (-705 to 250)</td>
<td>.36</td>
<td>-1120 (-1815 to -429)</td>
<td>&lt;.002</td>
</tr>
</tbody>
</table>

Notes:
- 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 therapy group than in the medical therapy group.
- Mitral regurgitation area² was calculated as the area of the color-flow Doppler regurgitant jet divided by the area of the left atrium in systole, both in square centimeters.


CARE-HF: Clinical Outcomes

<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>Death + CV Hospitalization</td>
<td>225 (55%)</td>
<td>159 (39%)</td>
<td>.63 (.51 to .77)</td>
</tr>
<tr>
<td>CV Hospitalization</td>
<td>184 (46%)</td>
<td>125 (31%)</td>
<td>.61 (.49 to .77)</td>
</tr>
<tr>
<td>All-Cause Death</td>
<td>120 (30%)</td>
<td>82 (20%)</td>
<td>.64 (.48 to .85)</td>
</tr>
</tbody>
</table>


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

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

<table>
<thead>
<tr>
<th>Event-Free Survival (%)</th>
<th>0</th>
<th>.05</th>
<th>.10</th>
<th>.15</th>
<th>.20</th>
<th>.25</th>
<th>.30</th>
<th>.35</th>
<th>.40</th>
<th>.45</th>
<th>.50</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT plus meds</td>
<td>400</td>
<td>370</td>
<td>351</td>
<td>321</td>
<td>292</td>
<td>262</td>
<td>231</td>
<td>201</td>
<td>171</td>
<td>141</td>
<td>111</td>
<td>100</td>
</tr>
<tr>
<td>Medical Rx</td>
<td>404</td>
<td>305</td>
<td>221</td>
<td>152</td>
<td>71</td>
<td>0</td>
<td>.8</td>
<td>2.0</td>
<td>3.2</td>
<td>4.4</td>
<td>5.6</td>
<td>8.0</td>
</tr>
</tbody>
</table>

CARE-HF: Effect of CRT on Ventricular Function in Heart Failure: MIRACLE Trial

<table>
<thead>
<tr>
<th>Left Ventricular End Diastolic Diameter (LVEDD)</th>
<th>Control N=63</th>
<th>CRT N=61</th>
<th>P&lt;.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centimeters</td>
<td>6.65</td>
<td>6.75</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>20</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Abraham ACC 2001

CARE-HF: Effect of CRT and NYHA Functional Class

<table>
<thead>
<tr>
<th>Average Change in QoL Score (MLWHF)</th>
<th>15</th>
<th>-10</th>
<th>-5</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA: Proportion Improving 1 or More Class (%)</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>***</td>
</tr>
<tr>
<td>Control</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>60</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

MIRACLE (1) MUSTIC SR (2) MUSTIC AF (3) CONTAK CD... MIRACLE IC...
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>Age &lt;60 yr</td>
<td>370</td>
<td></td>
</tr>
<tr>
<td>60-69 yr</td>
<td>426</td>
<td></td>
</tr>
<tr>
<td>≥70 yr</td>
<td>436</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>1040</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>LVEF ≤30%</td>
<td>611</td>
<td></td>
</tr>
<tr>
<td>&gt;30%</td>
<td>441</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>481</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>742</td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>490</td>
<td></td>
</tr>
</tbody>
</table>

**Survival**

**Female**

**Male**

**Controlled**

**Uncontrolled**

**Hazard Ratio**

**No ICD**

**ICD**

**MADIT-II**

**Placebo**

**Amiodarone**

**ICD**

**Mean age 60, 77% male, ischemic 52%, LVEF 0.24**

**ACEI 85%, BB 69%, Ald Ant 19%, Statin 38%**

**SCD-HeFT**

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

**EF ≤35%**

**NYHA Class II or III**

**Placebo**

**Amiodarone**

**ICD**

**Mean age 60, 77% male, ischemic 52%, LVEF 0.24**

**ACEI 85%, BB 69%, Ald Ant 19%, Statin 38%**

**SCD-HeFT Trial: Survival**

**Amiodarone vs Placebo**

**ICD vs Placebo**

**MADIT-II**

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

**CRT-D vs OPT**

**CRT vs OPT**

**OPT**

**CRT**

**CRT-D**


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

**SCD-HeFT**

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

**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 β-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
- 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

Enhance Adherence

- Education
- Disease Management
- Performance Improvement Systems
- Aspirin
- Warfarin
- Statin

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>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970–1979</td>
<td>15 (7-23)</td>
<td>16 (6-24)</td>
<td>41 (29-51)</td>
<td>28 (17-38)</td>
<td>75 (65-83)</td>
<td>59 (45-69)</td>
</tr>
<tr>
<td>1990–1999</td>
<td>11 (4-17)</td>
<td>10 (3-15)</td>
<td>28 (18-38)</td>
<td>24 (14-33)</td>
<td>59 (47-68)</td>
<td>43 (33-55)</td>
</tr>
</tbody>
</table>

*All values were adjusted for age (<55, 55–64, 65–74, 75–84, and ≥85 years).

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

ADHERE Quality of Care
Conformity to JCAHO HF Performance Indicators

“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 II IIb II III IIb III II IIb III IIb III IIb III IIb III II 06 6 10 3 07 0 IIb III 08 6 08 5 IIb III 07 5 04 6

Adapted from the American Heart Association. Get With The Guidelines. 2001


Total medical costs: Pre ($18,808) vs Post ($9,555), 214 Patients, 6 months conventional treatment pre- vs 6 months post-comprehensive management.

Comprehensive Heart Failure Patient Management Program
- Optimization of heart failure medical regimen
- Detailed patient and family education
- Daily measuring and recording of weights
- Sodium restricted diet with detailed guidelines
- Two liter (64 oz) fluid restriction (if congestion)
- Patient self-monitored flexible-loop diuretic regimen
- Alcohol and smoking abstinence
- Progressive walking exercise program
- Vigilant follow-up by clinical nurse specialists and physicians

HF Disease Management Program: Impact on Hospitalizations

$P<0.001 vs conventional management

HF Management System at Discharge
HF Management 6 Months Post-comprehensive

Cumulative Hospitalizations (6 months)
Conventional vs comprehensive Rx

HF Disease Management Program

Randomized Trials of Disease Management Programs for Heart Failure

Sensitivity analysis Mortality All-cause readmission HF-related readmission

Pre-intervention (n=11,038) Post-intervention (n=8,045)

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

Institutional Heart Failure Discharge Medication Program Reduces Readmissions and Mortality

Intermountain Health Care: 13 Hospitals Pre 10/6-12/31 $11,038 to 1/98-3/00 $8,045

Pearson Circulation 2001;104:8-38
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

- This will not work in a community practice or hospital
- The cardiologists will not agree to this
- We cannot get a consensus
- The managed care organization will not pay for it
- Patients do not want to be on a lot of medications
- There is not enough time
- It will cost too much
- It may not be safe to start β-blocker medications in heart failure patients
- This will benefit the competition
- The administration will not pay for it
- What about the liability?
- It will take too much time
- All my patients are too complex for this
- The patients should all be followed by someone else
- It is too hard to get things through the practice committee
- The physicians at my office do not like cookbook medicine
- We do not have anyone to do this
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


Preliminary Results with GWTG-HF: Performance Measures

<table>
<thead>
<tr>
<th>DIO Instructions</th>
<th>LVF Measurement</th>
<th>ACE/ARB</th>
<th>Beta Blocker</th>
<th>Smoking Cessation</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>70</td>
<td>74</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>Q1</td>
<td>61</td>
<td>82</td>
<td>61</td>
<td>91</td>
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<td>Q2</td>
<td>83</td>
<td>82</td>
<td>86</td>
<td>89</td>
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<tr>
<td>Q3</td>
<td>78</td>
<td>82</td>
<td>61</td>
<td>91</td>
</tr>
<tr>
<td>Q4</td>
<td>87</td>
<td>87</td>
<td>67</td>
<td>94</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

P<0.001, P=0.127, P=0.036, P=0.046

Congestion Precedes Hospitalization

P=0.029

Poor Sensitivity of Weight and BNP Changes Prior to Clinical Decompensation

<table>
<thead>
<tr>
<th>Condition</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

RR = 0.79 (95%CI = 0.64 - 0.98)
P<0.029

21% trend for reduction in the relative risk of HF hospitalization (p=0.27)
32% reduction in the proportion of patients with worsening HF
32% reduction in HF events overall
41% reduction in HF-related events among patients with NYHA class 3 HF (p=0.03)

Impedance Prior to HF Admission

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

Pulmonary Fluid Detection Monitoring

Devices as Patient Care Monitors

Auricchio and Abraham Circulation 2004; 109: 300-307

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

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

Cumulative Impact of Heart Failure Therapies

Relative-risk 2 yr Mortality

None | - | 35%
ACE Inhibitor | 23% | 27%
Aldosterone Ant | 30% | 19%
Beta Blocker | 35% | 12%
CRT +/- ICD | 36% | 8%

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