Management of Heart Failure: State of the Art Update 2015

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Presenter Disclosure Information

“Heart Failure Management”

I will not discuss off label use of medications or devices

DISCLOSURE INFORMATION:
The following relationships exist related to this presentation:

Gregg C. Fonarow, MD, FACC, FAHA
Research: NIHI, AHQR, PCORI
Consultant: Amgen, Bayer, Novartis, Medtronic, Gambro
Heart Failure Background

- Heart failure (HF) is a major public health problem resulting in substantial morbidity, mortality, and healthcare expenditures
- Major cost-driver of HF is high incidence of hospitalizations
- Despite treatment advances large number of eligible patients are not receiving one or more evidence-based HF therapies

<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>5,700,000</td>
<td>870,000</td>
<td>50% at 5 years</td>
<td>1,023,000</td>
<td>$30.7 billion</td>
</tr>
</tbody>
</table>

Prognosis with Heart Failure

Overall
5-year mortality 50%

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

Survival after the onset of congestive heart failure in Framingham Heart Study subjects

AHA, 1998 Heart and Statistical Update
NCHS, National Center for Health Statistics
Ho Circulation 1993;88:107-115
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


### Approach to the Classification of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk</td>
<td>High risk for developing heart failure (HF)</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic HF</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td>D</td>
<td>Refractory end-stage HF</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>High risk for developing heart failure (HF)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Asymptomatic HF</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>Refractory end-stage HF</td>
</tr>
</tbody>
</table>

- Hypertension
- CAD
- Diabetes mellitus
- Family history of cardiomyopathy
- Previous MI
- LV systolic dysfunction
- Asymptomatic valvular disease
- Known structural heart disease
- Shortness of breath and fatigue
- Reduced exercise tolerance
- Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)
## Classification of Heart Failure

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for HF but without structural heart disease or symptoms of HF.</td>
<td>None</td>
</tr>
<tr>
<td>B Structural heart disease but without signs or symptoms of HF.</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current symptoms of HF.</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td>D Refractory HF requiring specialized interventions.</td>
<td>IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
</tbody>
</table>

## Definition of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Heart Failure with Reduced Ejection Fraction (HFrEF)</strong></td>
<td>≤40%</td>
<td>Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td><strong>II. Heart Failure with Preserved Ejection Fraction (HFpEF)</strong></td>
<td>≥50%</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFpEF, Borderline</td>
<td>41% to 49%</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HFpEF.</td>
</tr>
<tr>
<td>b. HFpEF, Improved</td>
<td>&gt;40%</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>

Natural History of Heart Failure

**Left Ventricular Dysfunction and Symptoms**

Survival

- Asymptomatic: 100%
- Progression:
  - Mild: 100% - 90%
  - Moderate: 90% - 70%
  - Severe: 70% - 50%

**Annual Mortality**

-生存率
- 10% 10-20% 20 - 30% 30 - 80%

**Mechanism of Death**

- Sudden Death: 40%
- Worsened HF: 40%
- Other: 20%
Heart Failure Pathophysiology

Myocardial injury → Fall in LV performance → Activation of RAAS, SNS, ET, and others → Myocardial toxicity → Peripheral vasoconstriction → Hemodynamic alterations → Remodeling and progressive worsening of LV function → Heart failure symptoms → Morbidity and mortality

ANP
BNP

Pathophysiologic Effects of Angiotensin II and Epinephrine/Norepinephrine

**Cardiac Myocyte**
- Hypertrophy
- Apoptosis
- Cell Sliding
- Increased Wall Stress
- Increased O2 Consumption
- Impaired Relaxation

**Fibroblast**
- Hyperplasia
- Collagen Synthesis
- Fibrosis

**Peripheral Artery**
- Vasoconstriction
- Endothelial Dysfunction
- Hypertrophy
- Decreased Compliance

**Coronary Artery**
- Vasoconstriction
- Endothelial Dysfunction
- Atherosclerosis
- Restenosis
- Thrombosis
ACC/AHA HF Guidelines: Management of Heart Failure (Stage C)

Life Prolonging Medical Therapy

- ACE inhibitors or ARB (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 A) all patients with Class II-IV HF without contraindications or intolerance, when close monitoring can be assured

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

OR 0.77 (0.67-0.88) p<0.001

32 Trials of ACEI in Heart Failure  ACEI (n = 3870) Placebo (n = 3235)
Collaborative Group on ACE Inhibitor Trails  JAMA 1995;273:1450-1456
## 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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>22.9</td>
<td>33.2</td>
<td>0.63</td>
</tr>
<tr>
<td>Female</td>
<td>20.2</td>
<td>29.5</td>
<td>0.78</td>
</tr>
<tr>
<td>≤ 60</td>
<td>22.2</td>
<td>31.1</td>
<td>0.71</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>24.9</td>
<td>36.9</td>
<td>0.79</td>
</tr>
<tr>
<td>Class I</td>
<td>17.5</td>
<td>24.8</td>
<td>0.69</td>
</tr>
<tr>
<td>Class II</td>
<td>19.5</td>
<td>28.4</td>
<td>0.68</td>
</tr>
<tr>
<td>Class III</td>
<td>22.1</td>
<td>43.2</td>
<td>0.58</td>
</tr>
<tr>
<td>Class IV</td>
<td>46.2</td>
<td>59.2</td>
<td>0.69</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</td>
<td>0.72</td>
</tr>
<tr>
<td>LVEF &gt;25</td>
<td>23.6</td>
<td>29.6</td>
<td>0.85</td>
</tr>
<tr>
<td>LVEF ≤ 25</td>
<td>33.7</td>
<td>48</td>
<td>0.53</td>
</tr>
<tr>
<td>All Patients</td>
<td>22.4</td>
<td>32.6</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 Trails  JAMA 1995;273:1450-1456
## High vs Low Dose ACEI Therapy for Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Low Dose</th>
<th>High Dose</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or Hospitalization</td>
<td>1339/1596</td>
<td>1251/1568</td>
<td>0.88</td>
<td>p=0.002</td>
</tr>
<tr>
<td></td>
<td>83.9%</td>
<td>79.8%</td>
<td>(0.82-0.95)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>717/1596</td>
<td>666/1568</td>
<td>0.92</td>
<td>p=0.128</td>
</tr>
<tr>
<td></td>
<td>44.9%</td>
<td>42.5%</td>
<td>(0.81-1.03)</td>
<td></td>
</tr>
</tbody>
</table>

ATLAS: 8% reduction in death and 14% reduction in death and HF hospitalization
SOLVD: 14% reduction in death and 26% reduction in death and HF hospitalization

3164 patients with Class II-IV CHF ave f/u 46 months
Lisinopril  Low Dose 2.5 to 5.0 mg/d  High Dose 32.5 to 35.0 mg/d
Packer  Circulation 1999;100:1-7
Survival Rates in Patients Receiving ACE Inhibitors Across NYHA Classes

ACE inhibitor arms of CONSENSUS, V-HeFT, and SOLVD trials.
Placebo arms of PRAISE, PROMISE, and DIG trials (all receiving ACE inhibitors).
ValHeFT: ARB added to Standard HF Care Including ACEI

Mortality

CHARM-Alternative

Primary outcome of CV death or CHF hospitalization

HR 0.77 (95% CI 0.67-0.89), \( P=.0004 \)
Adjusted HR 0.70, \( P<.0001 \)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Candesartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1,013</td>
<td>1,015</td>
</tr>
<tr>
<td>1</td>
<td>929</td>
<td>887</td>
</tr>
<tr>
<td>2</td>
<td>831</td>
<td>798</td>
</tr>
<tr>
<td>3</td>
<td>434</td>
<td>427</td>
</tr>
<tr>
<td>3.5</td>
<td>122</td>
<td>126</td>
</tr>
</tbody>
</table>

ACEI/ARB in Heart Failure

- Indicated for all patients with asymptomatic LV dysfunction and for Class I to IV heart failure. (Contraindications: hyperkalemia, angioedema, pregnancy)

- Titrate to target doses (example enalapril 10 mg bid, lisinopril 20 qd, ramipril 10 mg qd, benazepril 40 qd, valsartan 160 mg bid, candesartan 32 mg qd)

- Monitor serum potassium and renal function. Advise checking chemistry panel 1-2 weeks after first dose.

- Use of ACE inhibitor together with ARB reserved as a consideration only in patients not candidates for aldosterone antagonist.

Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

Endogenous vasoactive peptides
(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin

Inactive metabolites

Neprilysin inhibition

Neurohormonal activation
Vascular tone
Cardiac fibrosis, hypertrophy
Sodium retention

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

Enalapril (n=4212)

LCZ696 (n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

Patients at Risk
<table>
<thead>
<tr>
<th></th>
<th>4187</th>
<th>3922</th>
<th>3663</th>
<th>3018</th>
<th>2257</th>
<th>1544</th>
<th>896</th>
<th>249</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>4212</td>
<td>3883</td>
<td>3579</td>
<td>2922</td>
<td>2123</td>
<td>1488</td>
<td>853</td>
<td>236</td>
</tr>
</tbody>
</table>

Days After Randomization
PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

LCZ696 was more effective than enalapril in . . .

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by incremental 20%
- Reducing the risk of HF hospitalization by incremental 21%
- Reducing all-cause mortality by incremental 16%
- Incrementally improving symptoms and physical limitations

LCZ696 was better tolerated than enalapril . . .

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

Sacubitril/Valsartan for Heart Failure

- The fixed-dose combination of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker (ARB) valsartan is indicated to reduce the risk of cardiovascular death and heart failure hospitalization in patients with heart failure with reduced ejection fraction.

- Recommended starting dosage is 49/51 mg twice daily. The dose should be doubled after 2-4 weeks as tolerated to reach the target maintenance dosage of 97/103 mg twice daily. For patients not currently taking an ACEI or ARB, or for those with severe renal impairment (eGFR <30 mL/min/1.73 m2) or moderate hepatic impairment, the starting dosage of is 24/26 mg twice daily.

- ACE inhibitor treatment should be stopped for 36 hours before starting treatment.

- Contraindications: hyperkalemia, pregnancy, symptomatic hypotension or shock, concurrent use with ACEI.

- Side effects: Hypotension and hyperkalemia. Angioedema occurred in 0.5% of patients compared to 0.2% with ACEI.
Effects of Aldosterone

Cardiac Myocyte
- Hypertrophy
- Norepinephrine Release

Fibroblast
- Hyperplasia
- Collagen Synthesis
- Fibrosis

Peripheral Artery
- Vasoconstriction
- Endothelial Dysfunction
- Hypertrophy
- Decreased Compliance

Kidney
- Potassium Loss
- Sodium Retention
RALES: Aldosterone Antagonist Reduces All-Cause Mortality in Chronic HF

Spironolactone (25 mg) + standard care (n = 822)
Placebo + standard care (n = 841)

HR = 0.70 (95% CI, 0.60 to 0.82)

P<.001

HR = hazard ratio; RR = risk reduction.

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

# 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>0.68 (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 (0.68-0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from Any Cause or Hospitalization for Cardiac Causes</td>
<td>0.68 (0.60-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cause of Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Causes</td>
<td>0.69 (0.58-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression of Heart Failure*</td>
<td>0.64 (0.51-0.80)</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><strong>Reason for hospitalization</strong></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>0.65 (0.54-0.77)</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 witnessed 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.
Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms: EMPHASIS HF

Primary Endpoint: CV Mortality and HF Hospitalization

HR = 0.63 (0.54-0.74), $p < 0.001$

Placebo
Eplerenone

No. at Risk
Placebo 1373 848 512 199
Eplerenone 1364 925 562 232

Aldosterone Antagonists in Heart Failure

- Indicated for patients with mild, moderate, 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 (or 12.5 mg in higher risk patients). 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 72 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.

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 6.25 bid test 2 weeks, then 12.5 bid, then 25 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

Survival Proportion

Follow-up (months)

RR 0.66 (0.53-0.81)
P=0.0062
## Major Trials of β-Blockade in Heart Failure

<table>
<thead>
<tr>
<th>Study</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>≤ 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>≤ 35</td>
<td>All-cause mortality: ↓ 34% (P&lt;.0001)</td>
</tr>
<tr>
<td>MDC</td>
<td>383</td>
<td>1</td>
<td>II-III</td>
<td>≤ 40</td>
<td>Death or need for transplant: ↓ 30%, P&lt;0.05</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>3991</td>
<td>1</td>
<td>II-III</td>
<td>≤ 40</td>
<td>All-cause mortality: ↓ 34% (P=.0062)</td>
</tr>
<tr>
<td>US Carvedilol</td>
<td>1094</td>
<td>7.5 months</td>
<td>II-III</td>
<td>≤ 35</td>
<td>All-cause mortality*: ↓ 65% (P=.0001)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2289</td>
<td>10.5 months</td>
<td>IV</td>
<td>≤ 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 4 days) ave age 63, LVEF 0.20
Carvedilol 3.125 bid, q 2 wks titration. 75% to target. withdrawal 16% placebo, 13% carvedilol
Packer NEJM 2001;344:1651-8

Survival Proportion

Follow-up (months)

HR 0.65 (0.52-0.81)
P=0.0001

n=1133
n=1156
Early Benefits and Early Safety of Carvedilol in Severe HF: COPERNICUS

Early Mortality Reduction

Risk Reduction ↓25%
(-35% to –59%)

All Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks</td>
<td>(n=1,133)</td>
<td>(n=1,156)</td>
</tr>
<tr>
<td>0-2</td>
<td>6.4</td>
<td>5.1</td>
</tr>
<tr>
<td>2-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Event rates: Placebo 2.3%; Carvedilol 1.7%

Lower Risk for Worsening CHF

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest-Risk Subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=316)</td>
<td>11.4</td>
<td>8.8</td>
</tr>
<tr>
<td>(n=308)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effect of $\beta$-Blockade on Hospitalizations

Only carvedilol and metoprolol CR/XL are FDA approved for HF therapy in the U.S.

Effect of Carvedilol Dose on Mortality in Patients with Heart Failure

Carvedilol Dose-Response Trial (MOCHA)

Dose Response of Carvedilol in moderate heart failure patients on all cause mortality
Bristow  Circulation 1996;94:2807
Effects of Sympathetic Activation in Heart Failure

↑ CNS sympathetic outflow

↑ Cardiac sympathetic activity

β₁-receptors
β₂-receptors
α₁-receptors

Myocyte death
Increased arrhythmias

Vasoconstriction
Sodium retention

Disease progression

α₁- β₁-

Activation of RAS

Bristow MR. Circulation. 2000;101:558-569.
Not All β-Blockers Reduce Mortality in HF

**BEST**
- **Follow-Up (months)**
  - 2,708 patients (CHF Class III–IV, average age 60, LVEF .23) randomized to placebo or bucindolol (3 mg titrated to 50 mg po BID).
  - Number of events: bucindolol 411 (30%); placebo 449 (33%).
  - **Risk Reduction**: ↓10% (-2%, 22%) with **p = .105**.

**SENIORS**
- **Follow-Up (months)**
  - 2,128 patients (CHF Class II–III, average age 76, average LVEF .36 with approximately 65% of patients with LVEF ≤.35) randomized to Placebo or nebivolol (1.25 mg titrated to 10 mg po QD). All-cause mortality was a secondary endpoint.
  - Number of events: nebivolol 169 (15.8%); placebo 192 (18.1%).
  - **Risk Reduction**: ↓12% (-8%, 29%) with **p = .214**.

---

<table>
<thead>
<tr>
<th>β-Blockers</th>
<th>Long-Term Effects on Mortality in HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol(^1)</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Bucindolol(^2)</td>
<td>No effect</td>
</tr>
<tr>
<td>Carvedilol(^3-^5)</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Metoprolol tartrate(^6)</td>
<td>Not well studied</td>
</tr>
<tr>
<td>Metoprolol succinate(^7)</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Nebivolol(^8)</td>
<td>No effect</td>
</tr>
<tr>
<td>Xamoterol(^9)</td>
<td>Harmful</td>
</tr>
</tbody>
</table>

COMET: Effect Carvedilol vs Metoprolol Tartrate on Mortality in HF

Metoprolol tartrate mean dose: 85 mg QD; Carvedilol mean dose: 42 mg QD.
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 the 3 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

**Renin Angiotensin Aldosterone System**
- Angiotensin Converting Enzyme Inhibitors
- (Angiotensin II Receptor Antagonists)
- Aldosterone Antagonists
AHeFT: Trial Summary

43% Decrease in Mortality

Survival (%)

Days Since Baseline Visit Date

Hazard ratio = 0.57
P = .01

Fixed-dose HYD/ISDN

Placebo

1050 African Americans with Class III to IV HF, LVEF 24%, on ACEI, BB, AA
AHeFT: Trial Summary

- **All-Cause Mortality (%):**
  - Placebo + Standard Therapies: 6.2, n=32
  - Hyd/Nit + Standard Therapies: 10.2, n=54
  - P = 0.012

- **First HF Hospitalization (%):**
  - Placebo + Standard Therapies: 24.4, n=130
  - Hyd/Nit + Standard Therapies: 16.4, n=85
  - P < 0.001

- **Patient Reported Functional Status:**
  - Placebo + Standard Therapies: n=532
  - Hyd/Nit + Standard Therapies: n=518
  - P < 0.01

1050 African Americans with Class III to IV HF, LVEF 24%, on ACEI, BB, AA
GISSI HF: *All-cause Mortality*

Adjusted HR (95% CI)  
0.91 (0.833 – 0.998)  P value 0.041

NNT = 56  
ARR = 1.8%

HR = hazard ratio; CI=confidence interval; NNT=number needed to treat; ARR=absolute risk reduction
**β-Blocker Dose and Heart Rate Reduction in Patients with Chronic Heart Failure**

Results of univariable meta-regressions evaluating the effect of individual covariates on the potential mortality benefits of β-blockers in heart failure

<table>
<thead>
<tr>
<th>Potential Modifier</th>
<th># Trials</th>
<th># Subjects</th>
<th>Ratio of Relative Risks (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate reduction</td>
<td>17</td>
<td>17,831</td>
<td>0.82 (0.71-0.94) per 5 bpm</td>
<td>0.006</td>
</tr>
<tr>
<td>β-blocker dose</td>
<td>17</td>
<td>17,660</td>
<td>1.02 (0.93-1.10) per increment</td>
<td>0.69</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>19</td>
<td>17,981</td>
<td>1.07 (0.88-1.32) per 5 bpm</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Meta-analysis of 17 randomized trials in subjects with heart failure to examine whether the β-blocker dose or the magnitude of heart rate reduction could account for differences in treatment effects among heart failure β-blocker trials, 1966-2008.

### Ivabradine and Outcomes in Chronic Heart Failure (SHIFT)

SHIFT: Hazard ratios for primary and individual outcomes, ivabradine vs placebo groups

<table>
<thead>
<tr>
<th>Outcomes in SHIFT</th>
<th>Ivabradine, n=3241 (%)</th>
<th>Placebo, n=3264 (%)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or HF hospitalization</td>
<td>24</td>
<td>29</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>3</td>
<td>5</td>
<td>0.74 (0.58-0.94)</td>
<td>0.014</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>16</td>
<td>21</td>
<td>0.74 (0.66-0.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death, HF hospitalization, or admission for nonfatal MI</td>
<td>25</td>
<td>30</td>
<td>0.82 (0.74-0.89)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The benefit of ivabradine appeared to go up with increasing heart rate (HR<77 HR 0.93; HR≥77 HR 0.75)

6558 patients with LVEF ≤35%, Sinus rhythm ≥70 bpm
Swedberg et al. Lancet 2010
Ivabradine for Heart Failure

- Indicated to reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with LVEF ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

- Starting dose is 5 mg twice daily. After 2 weeks of treatment, adjust dose based on heart rate. The maximum dose is 7.5 mg twice daily. In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, initiate dosing at 2.5 mg twice daily.

- Contraindications: acute decompensated HF, BP < 90/50 mmHg, SSS or 3rd degree AV block, unless a functioning demand pacemaker is present, resting heart rate less than 60 bpm prior to treatment, severe hepatic impairment.

- Most common adverse reactions occurring in ≥ 1% of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes).
Effect of Digoxin on Mortality in Heart Failure: The Digitalis Investigation Group

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.

Diuretic Therapy in Chronic Heart Failure

- Loop diuretics are mainstay of therapy for CHF (Given to > 85% of patients)

- Beneficial effects of diuretic therapy:
  - ↓ Dyspnea and other congestive symptoms
  - ↓ Volume overload
  - Facilitate successful initiation and titration of ACE inhibitors, β-blockers, vasodilators

No outcome studies of diuretic therapy in chronic HF and effects on morbidity and mortality unknown
### Pharmacological Therapy for Management of Stage C HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional supplements as treatment for HF are not recommended in HFrEF</td>
<td>III: No Benefit</td>
<td>B</td>
</tr>
<tr>
<td>Hormonal therapies other than to replete deficiencies are not recommended in HFrEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
<tr>
<td>Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn</td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td>Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation</td>
<td>III: Harm</td>
<td>C</td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocking drugs are not recommended as routine in HFrEF</td>
<td>III: No Benefit</td>
<td>A</td>
</tr>
</tbody>
</table>

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

Cardiac Resynchronization Therapy: Weight of Evidence

- >8,000 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: Effect of CRT Without an ICD on All-Cause Mortality

Event-Free Survival

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

P = .0019

Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Days 0</th>
<th>Days 500</th>
<th>Days 1,000</th>
<th>Days 1,500</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT plus meds</td>
<td>409</td>
<td>376</td>
<td>351</td>
<td>213</td>
</tr>
<tr>
<td>Medical Rx</td>
<td>404</td>
<td>365</td>
<td>321</td>
<td>192</td>
</tr>
</tbody>
</table>

# CARE-HF: Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<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>0.63 (0.51 to 0.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CV Hospitalization</td>
<td>184 (46%)</td>
<td>125 (31%)</td>
<td>0.61 (0.49 to 0.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>133 (33%)</td>
<td>72 (18%)</td>
<td>0.48 (0.36 to 0.64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>All-Cause Death</td>
<td>120 (30%)</td>
<td>82 (20%)</td>
<td>0.64 (0.48 to 0.85)</td>
<td>&lt;.002</td>
</tr>
</tbody>
</table>

OMT=optimal medical therapy.
Effect of CRT on Mortality in Patients with NYHA Class II HF

1798 Patients is LVEF ≤ 30%, QRS duration 120 ms or above and NYHA Class II on optimal medical therapy. RAFT. NEJM 210 363:2385-2395
SCD-HeFT and Other ICD Device Trials in HF

<table>
<thead>
<tr>
<th>HF Etiology</th>
<th>Ischemic: 100%</th>
<th>Ischemic: 59% Non-ischemic: 41%</th>
<th>Non-ischemic: 100%</th>
<th>Ischemic: 52% Non-ischemic: 48%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class</td>
<td>I/II/III (35%/35%/30%)</td>
<td>III/IV (87%/13%)</td>
<td>I/II/III (20%/60%/20%)</td>
<td>II/III (71%/29%)</td>
</tr>
<tr>
<td>LVEF</td>
<td>≤ 30%</td>
<td>≤ 35%</td>
<td>≤ 35%</td>
<td>≤ 35%</td>
</tr>
<tr>
<td>No. Pts</td>
<td>1232</td>
<td>1520</td>
<td>458</td>
<td>2521</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>20 months</td>
<td>12 months</td>
<td>24 months</td>
<td>45 months</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.69</td>
<td>0.64</td>
<td>0.66</td>
<td>0.77</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

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

Heart Failure with Preserved Ejection Fraction

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

ARB in HF with Preserved EF

I-PRESERVE: Primary Endpoint Death or CV hospitalization

HR (95% CI) = 0.95 (0.86-1.05)
Log-rank p=0.35

Massie BM et al. NEJM 2008;359(23):2456-2467.
Clinical Effectiveness of Beta-Blockers in Heart Failure: CMS Matched Cohort

HF with LVEF < 40%

n = 3001

Adjusted HR 0.77 (95% CI 0.68-0.87)

HF with LVEF ≥ 40%

n = 4153

Adjusted HR 0.94 (95% CI, 0.84-1.07)

7154 patients hospitalized with HF, eligible for beta-blockers, and previously not treated. 3421 (49%) were newly initiated on beta-blocker therapy.

Spironolactone in HFpEF: TOPCAT
1° Outcome: CV Death, HF Hosp, or Resuscitated Cardiac Arrest

Implantable Wireless Heart Sensor

No batteries or internal power source, sensor is powered by RF-energy provided by an external electronics module.

Coil and a pressure sensitive capacitor encased in a hermetically sealed silica capsule covered by silicone. The device has no leads or batteries. Two nitinol loops at the ends of the capsule serve as anchors in the pulmonary artery. The coil and capacitor form an electrical circuit that resonates at a specific frequency, and pressure applied to the sensor causes deflections of the pressure-sensitive surface. An external antenna provides power to the device, continuously measuring its resonant frequency, which is then converted to a pressure waveform. The interrogating device has an atmospheric barometer which automatically subtracts the ambient pressure from that measured from the implanted sensor.
Wireless Pulmonary Artery Hemodynamic Monitoring in Chronic Heart Failure: CHAMPION

Wireless Pulmonary Artery Hemodynamic Monitoring in Chronic Heart Failure: CHAMPION

550 patients with NYHA Class III HF, irrespective of LVEF, and a previous HF hospital admission were enrolled in 64 centers the US

Randomly assigned to management with a wireless implantable hemodynamic monitoring (W-IHM) system (treatment group) or to a control group for at least 6 months

Clinicians used daily measurement of pulmonary artery pressures in addition to standard of care versus standard of care alone in the control group, with goal of keeping PAD pressures normal and specific recommendations provided

The primary efficacy endpoint was the rate of HF related hospitalizations at 6 months

Wireless Pulmonary Artery Hemodynamic Monitoring in Chronic Heart Failure: CHAMPION

Other Findings from CHAMPION

• Mean PAP fell substantially over 6 months in the sensor-guided-therapy group and rose in the control group (p=0.008).

• Quality of life at six months, as assessed by the MLWHFQ, was better in the PAP-guided therapy group (p=0.024).

• The length of stay for HF-related hospitalizations was significantly shorter in the treatment group than in the control group (2.2 days [SD 6.8] vs 3.8 days [11.1], p=0.02).

• Significant reduction in the rate of HF-related hospitalizations for preserved (0·16 vs 0·33, p<0·0001) and reduced systolic function (0·36 vs 0·47, p=0·007) patients during 6 months.

• Incremental cost-effectiveness ratio of integrating W-IHM into standard of care for management of the HF is estimated to be $13,979 per QALY gained.

HeartMate II LVAS

- A surgically implanted, rotary continuous-flow device in parallel with the native left ventricle
  - Left ventricle to ascending aorta
- Percutaneous driveline
- Electrically powered
  - Batteries & line power
- Fixed speed operating mode
- Home discharge
Destination VAD Therapy Trials

Figure 1. Survival Rates in Two Trials of Left Ventricular Assist Devices (LVADs) as Destination Therapy.

The curves labeled 2009 are those reported by Slaughter and colleagues in this issue of the *Journal*; those labeled 2001 were reported for the REMATCH trial.¹

NEJM 2009;361(23):2241-51.
Mechanical Circulatory Support (MCS) Indications

- Failure to wean off CPB (post-cardiotomy syndrome)
- ESHD pt with inadequate organ perfusion despite optimal medical management (BT Tx)
- Acute myocarditis/post-partum CMY (BT Recovery)
- Acute, massive MI with shock
- Destination therapy (DT) for non-transplant candidates with end stage HD
- Incessant VT/cardiac arrest

CPB, cardiopulmonary bypass; ESHD, end-stage heart disease; BTT, bridge to transplant; CMY, cardiomyopathy; BTR, bridge to recovery; VT, ventricular tachycardia.
### Evidence-Based Heart Failure Therapies

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>Relative Risk Reduction in Mortality</th>
<th>Number Needed to Treat for Mortality (standardized to 36 months)</th>
<th>NNT for Mortality</th>
<th>Relative Risk Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17%</td>
<td>22 over 42 months</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>ARNI</td>
<td>16%</td>
<td>36 over 27 months</td>
<td>27</td>
<td>21%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>34%</td>
<td>28 over 12 months</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>30%</td>
<td>9 over 24 months</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>43%</td>
<td>25 over 10 months</td>
<td>7</td>
<td>33%</td>
</tr>
<tr>
<td>CRT</td>
<td>36%</td>
<td>12 over 24 months</td>
<td>8</td>
<td>52%</td>
</tr>
<tr>
<td>ICD</td>
<td>23%</td>
<td>14 over 60 months</td>
<td>23</td>
<td>NA</td>
</tr>
</tbody>
</table>

- Academic detailing or educational outreach visits are useful to facilitate the implementation of practice guidelines

- Chart audit and feedback of results can be effective to facilitate implementation of practice guidelines

- The use of reminder systems can be effective to facilitate implementation of practice guidelines

- The use of performance measures based on practice guidelines may be useful to improve quality of care

IMPROVE HF Primary Results: Improvement in Quality Measures at 24 Months (Patient Level Analysis)

Significant Improvement in 6 of 7 Quality Measures at 12 and 24 Months
Pre-specified Primary Objective Met: Relative Improvement ≥ 20% in 3 Quality Measures

* P<0.001 vs. baseline

Improved Adherence to HF Guidelines Translates to Improved Clinical Outcomes in Real World Patients

- Each 10% improvement in ACC/AHA heart failure guideline recommended composite care was associated with a 13% lower odds of 24-month mortality (adjusted OR 0.87; 95% CI, 0.84 to 0.90; \( P<0.0001 \)).
Cumulative Benefits of Established, Guideline-Recommended HF Therapies

Heart Failure Therapies

- Beta-blocker: -39% (P < 0.0001)
- Beta-blocker + ACEI/ARB: -63% (P < 0.0001)
- Beta-blocker + ACEI/ARB + ICD: -76% (P < 0.0001)
- Beta-blocker + ACEI/ARB + ICD + HF education: -81% (P < 0.0001)
- Beta-blocker + ACEI/ARB + ICD + HF education + anticoagulation for AF: -83% (P < 0.0001)
- Beta-blocker + ACEI/ARB + ICD + HF education + anticoagulation for AF + CRT: -81% (P < 0.0001)

Fonarow GC et al J Am Heart Assoc 2012;1:16-26
## Potential Impact of Optimal Implementation of Evidence-Based HF Therapies on Mortality

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>HF Patient Population Eligible for Treatment, n*</th>
<th>Current HF Population Eligible and Untreated, n (%)</th>
<th>Potential Lives Saved per Year</th>
<th>Potential Lives Saved per Year (Sensitivity Range*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>2,459,644</td>
<td>501,767 (20.4)</td>
<td>6516</td>
<td>(3336-11,260)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>2,512,560</td>
<td>361,809 (14.4)</td>
<td>12,922</td>
<td>(6616-22,329)</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>603,014</td>
<td>385,326 (63.9)</td>
<td>21,407</td>
<td>(10,960-36,991)</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>150,754</td>
<td>139,749 (92.7)</td>
<td>6655</td>
<td>(3407-11,500)</td>
</tr>
<tr>
<td>CRT</td>
<td>326,151</td>
<td>199,604 (61.2)</td>
<td>8317</td>
<td>(4258-14,372)</td>
</tr>
<tr>
<td>ICD</td>
<td>1,725,732</td>
<td>852,512 (49.4)</td>
<td>12,179</td>
<td>(6236-21,045)</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>-</td>
<td>67,996</td>
<td>(34,813-117,497)</td>
</tr>
</tbody>
</table>

## Cumulative Impact of Clinical Trial Evidence Based Heart Failure Therapies

<table>
<thead>
<tr>
<th></th>
<th>Relative-risk</th>
<th>2 yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>↓ 23%</td>
<td>27%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>↓ 35%</td>
<td>18%</td>
</tr>
<tr>
<td>Aldosterone Ant</td>
<td>↓ 30%</td>
<td>13%</td>
</tr>
<tr>
<td>CRT-D (EF&lt;35, QRS&gt;120)</td>
<td>↓ 36%</td>
<td>8.3%</td>
</tr>
<tr>
<td>ARNI</td>
<td>↓ 16%</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction if all evidence-based therapies are used: 80%
Absolute risk reduction: 28.1%, NNT = 3.6

Heart Failure Prevention

Patients at risk for heart failure:

- Treat systolic and diastolic hypertension according to guidelines
- Treat diabetes according to guidelines
- Treat atherosclerosis according to guidelines
- Treat lipid disorders according to guidelines
- Encourage smoking cessation
- Encourage exercise
- Discourage heavy alcohol intake, illicit drug use
- Consider ACEI/ARB and beta blocker use in those at risk for HF

Advances in the Treatment of HF

- Increased attention to prevention
- ACEI / β-blocker / aldosterone antagonist combination established as the “cornerstone” of therapy
- ARNI further reduce morbidity and mortality
- 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

The economic burden of HF continues to grow and HF is one of the single most expensive and deadly health care problems.

Medical therapies and nonpharmacologic measures for HF that can impact patients' need for re-hospitalization, costs of care, and survival are underutilized in conventional practice settings.

Every efforts should be made to implement evidence-based HF therapies when indicated and optimize care of HF.