New Strategies For Treating Patients With Chronic Heart Failure

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Disclosures

- Consultant – GSK, Corventis, BiogenIdec
- Speakers Bureau - GSK, Merck, Scios, Novartis
New Strategies For Treating Patients With Chronic Heart Failure

- Prevention
- Pathogenesis and medical therapy
- Emerging role of devices
- Strategies for improving outcomes
- New therapeutic approaches
Heart Failure Rages Through American Cities
Epidemiology of Heart Failure in the US

- Incidence: 10 per 1000 population after age 65
- Over 1 million hosp DCs annually
- More deaths from heart failure than from all forms of cancer combined

Population-Attributable Risks for Development of HF

HTN, diabetes and/or CAD accounts for ~90% of HF

Population-attributable risk defined as:
\[(100 \times \text{prevalence} \times [\text{hazard ratio} - 1]) / (\text{prevalence} \times [\text{hazard ratio} - 1] + 1)\]

CHF = chronic heart failure; AP = angina pectoris; DM = diabetes mellitus; LVH = left ventricular hypertrophy; VHD = valvular heart disease; HTN = hypertension; MI = myocardial infarction

The Boys Go Out For A ‘Heart Healthy’ Lunch…
And Then Walk the Dog For Exercise
Adults With Diagnosed Diabetes*

*Includes women with a history of gestational diabetes.

Adults With Diagnosed Diabetes*

HTN in America

Increased 30% Last Decade

![Bar chart showing increased HTN burden from 1988-1994 to 1999-2000.](chart1)

Majority of U.S. Hypertensives Not at <140 mmHg Goal

![Distribution of SBP range showing high percentage not meeting goal.](chart2)


Treating Hypertension to Prevent HF

- Aggressive blood pressure control:
  - Decreases risk of new HF by ~ 50%
  - 56% in DM2

- Aggressive BP control in patients with prior MI:
  - Decreases risk of new HF by ~ 80%

JAMA 1997;278:212-6 (SHEP)
UKPDS Group. UKPDS 38. BMJ 1998;317:703-713
Management of Patients with Known Atherosclerotic Disease But No HF

- Treatment with ACE inhibitors decreases the risk of CV death, MI, stroke, or cardiac arrest.

NEJM 2000;342:145-53 (HOPE)
Lancet 2003;362:782-8 (EUROPA)
Take Home Messages

• Heart failure is preventable (if we really try)!
Remodeling Is The Major Cause of Progressive Cardiac Dysfunction

6 months post-MI

14 months post-MI
Effect of Remodeling on Survival in HF Patients

Neurohormonal Activation in HF
SOLVD

*Prevention trial: assessed prevention of HF in asymptomatic patients (n=151);
†Treatment trial: assessed reduction in mortality in symptomatic patients (n=81).

ACEIs Inhibit LV Remodeling: SOLVD Echo Sub-study

SOLVD: Changes in LV Dimension (1)

SOLVD: Changes in LV Mass

# ACEIs Reduce Mortality in HF

## Mortality

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

Addition of β-Blockers to ACEIs Reduces Mortality in Heart Failure

**US Carvedilol Trials**
- Carvedilol (n=696)
- Placebo (n=398)

Cumulative Mortality (%)
- Days
- 65% ↓
- \( P < .001 \)

**CIBIS-II**
- Bisoprolol (n=1,327)
- Placebo (n=1,320)

Survival (%)
- Days
- 34% ↓
- \( P < .0001 \)

**MERIT-HF**
- Metoprolol CR/XL (n=1,990)
- Placebo (n=2,001)


**COPERNICUS**
- Carvedilol (n=1,156)
- Placebo (n=1,133)

Survival (%)
- Months
- 35% ↓
- \( P = .0014 \) (adjusted)

# Trials With Aldosterone Antagonists

*Primary Endpoint: All-Cause Mortality*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>Aldosterone Antagonist</th>
<th>Hazard Ratio</th>
<th>Log-rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHESUS</td>
<td>554/3,319</td>
<td>478/3,313</td>
<td>.85</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(.75, .96)</td>
<td></td>
</tr>
<tr>
<td>RALES</td>
<td>386/841</td>
<td>284/822</td>
<td>.70</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(.60, .82)</td>
<td></td>
</tr>
</tbody>
</table>

Take Home Messages

• Most heart failure is preventable (if we really try)!
• Neurohormonal activition causes remodeling – inhibition improves outcomes.
Heart Failure Related Deaths: Impact Of Contemporary Therapy

24 month data from placebo arm of ValHeft

Arrhythmic Death Can Be Prevented
SCD-HeFT: Mortality

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>97.5% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone vs Placebo</td>
<td>1.06</td>
<td>0.86–1.30</td>
<td>.53</td>
</tr>
<tr>
<td>ICD Therapy vs Placebo</td>
<td>0.77</td>
<td>0.62–0.96</td>
<td>.007</td>
</tr>
</tbody>
</table>

ICD=implantable cardioverter defibrillator.

ICD Use in Patients Hospitalized With History of Chronic HF and LVEF $\leq$ 30%

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

- Abnormal ventricular conduction resulting in a mechanical delay
- Present in 15% to 30% (or more) of HF patients
- Wide QRS (IVCD); typically LBBB morphology
  - Impaired systolic and diastolic function
  - Worsening mitral regurgitation

IVCD=interventricular conduction delay; LBBB=left bundle branch block.
CARE-HF: CRT Long-Term Outcomes

- Median LV ejection fraction was 25%
- Of the 409 patients randomized to the CRT device, 95% had a successful implantation
- The primary endpoint of all-cause mortality or hospitalization for a major CV event occurred less frequently in the CRT group than in the medical therapy alone group (HR 0.63, 95% CI 0.51-0.77)
- The major secondary endpoint of all-cause mortality was also lower in the CRT group (HR 0.64, 95% CI 0.48-0.85)

CRT: Areas of Uncertainty

- Atrial fibrillation
- RBBB
- Mild (NYHA Class II) or end-stage HF
- Efficacy in patients with narrow QRS
- Prospectively defining who will and who won’t respond to CRT

RBBB=right bundle branch block; CRT=cardiac resynchronization therapy.

Take Home Messages

• Most heart failure is preventable (if we really try)!
• Neurohormonal antagonists inhibit remodeling and improve HF outcomes.
• Devices provide incremental benefits when added to optimal medical therapy.
46,272 patients hospitalized with HF; prior known diagnosis of systolic dysfunction HF; outpatient medical regimen.

Outpatient Adherence to β-Blocker Therapy Post–Acute MI

ACEI/ARB, β-blocker, and aldosterone antagonist use in eligible patients with LVSD; statin in HF patients with a history of CAD, PVD, CVD and/or diabetes; and warfarin use in patients with HF and atrial fibrillation.

Intra-Thoracic Impedance Changes
With Lung Wetness

“Wetter” Lungs - Reduced Impedance

“Dryer” Lungs - Increased Impedance
Correlation of Impedance with Net Fluid Loss During HF Hospitalization

\[
y = -1.5x - 1.4 \\
r = -0.70; p < 0.0001
\]
Tracking Intrathoracic Impedance

More Fluid

Less Fluid

Days Before Hospitalization

Impedance (Ω)

Relative Baseline

CHF Admission
Take Home Messages

• Most heart failure is preventable (if we really try)!
• Neurohormonal antagonists inhibit remodeling and improve HF outcomes.
• Devices provide incremental benefits when added to optimal medical therapy.
• New strategies are available to better manage HF patients.
Mechanical Therapy

- Smaller devices
- Less infection?
- Opportunity for explant
REMATCH Trial: All Cause Mortality

% Event Free Survival

- LV Assist Device (n=68)
- Control (n=61)

P=0.001

RR 0.52 (0.34, 0.78)

N Engl J Med 2001; 345: 1435
Limitations of Current LVAD Therapy

- Very expensive.
- Major commitment on the part of physicians, nurses and hospitals for continuing care.
- Small increase in survival rates after 2 years.
- Substantial risk of bleeding, infection and device malfunction requiring in-hospital care.
Mechanical Unloading Reverses The Heart Failure Phenotype
Cell Transplantation For Treating HF

Possible Graft
- neonatal/adult CM
- embryonic stem cell
- bone marrow stem cell
- skeletal myoblast
- others
  - GM fibroblast
  - cardiac stem cells

Undefined mechanisms

Functional recovery of diseased hearts
animals, human

End stage heart failure

New Myocytes
BOOST Results

Wollert KC et al. Lancet, July 2004
Cell Transplantation

• Which type of cell works best?
• Where, when and how to deliver?
• What can we do to enhance homing of transplanted cells and improve their survival?
• How does therapy improve cardiac function?
• Is cell transplantation safe?
Calcium Cycling Mediated by SERCA2a is Key to Cardiac Contraction

- End stage HF: reduced SERCA2a results in reduced contractility & elevated intracellular Ca$^{2+}$
- Cardiac function correlates with SERCA2a level or function
  - Recovery after LVAD or with β-blockers
MYDICAR™: SERCA2a Gene Therapy for Heart Failure
### Sheep Pacing Model of Heart Failure

**Absolute Median Change After 1 Month**

Sheep are paced at 180 bpm for 2 mo, gene transfer using V-Focus#
percutaneous coronary artery infusion at 1 mo, evaluation at 2 mo

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MYDICAR™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional Shortening</td>
<td>-1%</td>
<td>+11%</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>-2%</td>
<td>+19%</td>
</tr>
<tr>
<td>Slope of ESPVR</td>
<td>-0.7 mmHg/mL</td>
<td>+1.2 mmHg/mL</td>
</tr>
<tr>
<td>+dP/dt</td>
<td>-259 mmHg/sec</td>
<td>-25 mmHg/sec</td>
</tr>
</tbody>
</table>

Take Home Messages

• Most heart failure is preventable (if we really try)!
• Neurohormonal antagonists inhibit remodeling and improve HF outcomes.
• Devices provide incremental benefits when added to optimal medical therapy.
• New strategies are required to better implement effective HF treatment.
• HF treatment continues to evolve with the development of new drugs and devices.