Recent Successes in Heart Failure

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FINANCIAL DISCLOSURE:
Research Support: HeartWare Inc, Gambro
Advisory Board: HeartWare Inc

UNLABELED/UNAPPROVED USES DISCLOSURE:
None
Recent Successes in Heart Failure

- Chronic Heart Failure
- Acute Decompensated Heart failure
- Heart Failure with Preserved Ejection Fraction
- Stage D Heart Failure
Heart Failure
Epidemiology/Facts

- Prevalence: ~ 7 million in US (2.5%)
- Incidence: ~ 550,000/year
- Mortality: ~ 300,000/year
- Office visits: ~ 3.4 million (2004)
- Hospital discharges: ~ 1,000,000 (2001)
- Health care costs exceed $30 billion/year
- Single largest expense for Medicare
Heart Failure Prevalence

Heart Failure
Demographic Trends

Elderly U.S. population will double in the next decade

Projected Elderly Population >65 years (millions)

- 31.5 million in 1990 (12.6% total US population)
- 65.6 million in 2030 (21.8% total US population)
Estimated Direct and Indirect Costs of Heart Failure in the US

- Low productivity/mortality*: $2.6
- Home healthcare: $2.2
- Drugs/other medical durables: $2.9
- Physicians/other professionals: $1.9
- Nursing home: $3.6
- Hospitalization: $14.7

Total cost: $27.9 Billion

* Lost future earnings of persons who will die in 2005, discounted by 3%.

The Number of Heart Failure Hospitalizations Is Increasing in Both Men and Women

CDC/NCHS: hospital discharges include patients both living and dead.

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

ANP, BNP

Morbidity and Mortality

Heart Failure Symptoms

Therapies for Chronic HF by NYHA Class

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
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<td>ACE inhibitors</td>
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<td>CRT</td>
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</table>

Adapted from Almeda FQ, Hollenberg SM. *Postgrad Med.* 2003;113:41
MADIT-II
ICD vs. Conventional Rx

Ventricular Dyssynchrony
Effects of CRT on LV Performance

Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine Trial
70% of patients on ivabradine 7.5 mg bid

Mean heart rate reduction

Heart rate (bpm)

Primary composite endpoint
(CV death or hospital admission for worsening HF)

Cumulative frequency (%)

HR = 0.82 (0.75–0.90)
$P < 0.0001$

Placebo

Ivabradine

Hospitalization for HF

Cumulative frequency (%)

HR = 0.74 (0.66–0.83)

$P < 0.0001$


www.shift-study.com
Death from heart failure

Cumulative frequency (%)

HR = 0.74 (0.58–0.94)

$P = 0.014$

Placebo

Ivabradine

26%

Angiotensin-Nephrilysin Inhibition vs. Enalapril in HF (PARADIGM-HF)

A Primary End Point
Hazard ratio, 0.80 (95% CI, 0.73–0.87)  
P<0.001

B Death from Cardiovascular Causes
Hazard ratio, 0.80 (95% CI, 0.71–0.89)  
P<0.001

C Hospitalization for Heart Failure
Hazard ratio, 0.79 (95% CI, 0.71–0.89)  
P<0.001

D Death from Any Cause
Hazard ratio, 0.84 (95% CI, 0.76–0.93)  
P<0.001

No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236

No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279

# Angiotensin-Nephrilysin Inhibition vs. Enalapril in HF (PARADIGM-HF)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LCZ696 Enrol</th>
<th>Enalapril Enrol</th>
<th>Primary Endpoint Hazard Ratio (95% CI)</th>
<th>P-value for interaction</th>
<th>Death from Cardiovascular Causes Hazard Ratio (95% CI)</th>
<th>P-value for interaction</th>
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</table>
Recent Successes in Heart Failure

- Chronic Heart Failure
- **Acute Decompensated Heart failure**
- Heart Failure with Preserved Ejection Fraction
- Stage D Heart Failure
Heart Failure
Outcomes of Hospitalized Patients

Hospital Readmissions
N = 38,702

- 20% at 30 Days
- 50% at 6 Months

Mortality
N = 38,702

- 12% at 30 Days
- 33% at 12 Months
- 60% at 5 Years

Median length of hospital stay: 6 days

References:
Incomplete Relief of Congestion

20% of ADHF patients discharged with weight gain or no change in weight

<table>
<thead>
<tr>
<th>Change in Weight (lbs)</th>
<th>Enrolled Discharges (%)</th>
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<tr>
<td>(-20)</td>
<td>8%</td>
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<td>(-20 to -15)</td>
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<td>(-15 to -10)</td>
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<tr>
<td>(-10 to -5)</td>
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<tr>
<td>(-5 to 0)</td>
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<td>(0 to 5)</td>
<td>15%</td>
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<td>(5 to 10)</td>
<td>3%</td>
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<td>(&gt;10)</td>
<td>2%</td>
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DOSE trial
Bolus vs. Continuous Diuretics

A  Bolus vs. Continuous Infusion
Hazard ratio with continuous infusion, 1.15
(95% CI, 0.83–1.60)
P=0.41

B  Low-Dose vs. High-Dose Strategy
Hazard ratio with high-dose strategy, 0.83 (95% CI, 0.60–1.16)
P=0.28

**ASCEND-HF**

Nesiritide in patients with ADHF

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### A Self-Assessed Change in Dyspnea at 6 and 24 Hours

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<th>Time</th>
<th>Placebo</th>
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<td>6 Hours</td>
<td>42.1</td>
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<td>28.7</td>
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<td>20.3</td>
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*P = 0.03*

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*P = 0.007*

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### B Death from Any Cause or Rehospitalization for Heart Failure at 30 Days

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*Hazard ratio, 0.93 (95% CI, 0.8–1.08)*

---

**Percentage Point Difference (95% CI)**

- Death or Rehospitalization for Heart Failure: -0.7 (-2.1 to 0.7)
- Death: -0.4 (-1.3 to 0.5)
- Rehospitalization for Heart Failure: -0.1 (-1.2 to 1.0)

---

Mechanical Fluid Removal by Ultrafiltration

UF

Vascular Space

Interstitial Space (edema)

H₂O

Na

K

P

PR

Vascular Space

Na

K

Na
Primary End Point
Weight Loss at 48 Hr

Costanzo J Am Coll Cardiol. 2007;49:675-683
CARRESS-HF
UF in ADHF with Cardiorenal Syndrome

CARRESS-HF – UF v. Diuretics

Figure 1. Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).
Recent Successes in Heart Failure

- Chronic Heart Failure
- Acute Decompensated Heart Failure
- Heart Failure with Preserved Ejection Fraction
- Stage D Heart Failure
Prevalence of HFPEF vs. SHF by Age Groups

Tribouilloy *Eur Heart J* 2007; 29:339
Heart Failure Secular Trends in Survival

Owan, *N Engl J Med* 2006; 355; 251
Recent Successes in Heart Failure

- Chronic Heart Failure
- Acute Decompensated Heart Failure
- Heart Failure with Preserved Ejection Fraction
- Stage D Heart Failure
Therapies for End-Stage HF

- Hospice/Palliation
- Inotropes
- IABP
- Heart Transplantation
- Mechanical Assist Devices
ADULT HEART TRANSPLANTATION

All comparisons significant at p < 0.0001


Survival (%)

Years

ISHLT

J Heart Lung Transplant 2008;27: 937-983
Ventricular Assist Devices

A Pulsatile-Flow LVAD

- External battery pack
- Skin entry site
- External system controller
- Percutaneous lead
- Pulsatile-flow LVAD
- Aorta
- Left ventricle
REMATCH Trial

Figure 2. Kaplan–Meier Analysis of Survival in the Group That Received Left Ventricular (LV) Assist Devices and the Group That Received Optimal Medical Therapy.

Rose E et al NEJM 2001:345;1435-43.
Ventricular Assist Devices

HeartMate II

HeartWare
Outcomes with LVAD vs. OMM

* N Engl J Med 2001; 345:1435-43

HeartMate II Survival by Era

Implant dates | n  | 30 d | 6 Mo | 12 mo |
---|---|---|---|---|
a Apr '08 - Oct '10 | 1496 | 95% | 89% | 85% |
b Apr '08 - Aug '08 | 169 | 96% | 90% | 85% |
c Mar '07 - Apr '08 | 205 | 95% | 86% | 80% |
d Mar '05 - Mar '07 | 281 | 92% | 82% | 73% |
e Mar '05 - May '06 | 133 | 89% | 75% | 68% |

Post-Trial^a
Post-Approval Study^b
Late Trial^c
Early-mid Trial^d
Early Trial^e

References:
- John et al STS 2011
- Starling et al JACC (in press)
- Pagani et al JACC 2009
- Miller et al NEJM 2007

John, Naka, Smedira et al: Presented at STS 2011
Improvement in Functional Class

Rogers, J Am Coll Cardiol. 2010 27;55(17):1826-34
Improvement in QOL (KCCQ)
Partial Support
Circulite

Investigational Device
LVAD Offered on ebay!

Thoratec Heartmate II System Controller w/Ventriassist

- Item condition: Used
- Quantity: 1
- Price: US $400.00
- Seller Information: bobussi5 (10332, 99.8% positive feedback)

Shipping: $20.00 - Standard Shipping
Item location: Pittsburgh, Pennsylvania, United States
Delivery: Estimated between Tue, Jan. 17 and Mon, Jan. 23
Payments: PayPal®, Bill Me Later, Pay on pickup
Returns: No returns or exchanges, but item is covered by eBay Buyer Protection.

eBay Buyer Protection
Covers your purchase price plus original shipping.

See more Items Just like this

JBL MSC1 Studio Monitor System Controller w/ RMC Room Mode Correction MSC 1 NEW
Buy It Now $299.00 5d 10h
Advances in Heart Failure Therapy

- Chronic Heart Failure √ √
- Acute Decompensated Heart failure X
- Heart Failure with Preserved Ejection Fraction X X X
- Stage D Heart Failure √ √ √ √
The one-year survival rate for heart failure is worse than that for cancer of the breast, uterus, prostate & bladder.
Prognosis
Heart Failure vs. Cancer Mortality

Mortality Rates

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>30</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>50</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>80</td>
</tr>
<tr>
<td>Class IV Heart Failure with OMM</td>
<td>100</td>
</tr>
</tbody>
</table>

Thank You
Back-Up Slides
Hemodynamic Profile Assessment

Congestion at Rest

- No
  - Warm & Dry
  - Low Perfusion at Rest
- Yes
  - Warm & Wet
  - Signs/symptoms of congestion
    • Orthopnea/PND
    • JVD
    • Ascites
    • Edema
    • Rales (rare in HF)

Possible evidence of low perfusion
- Narrow pulse pressure
- Sleepy/obtundled
- Low serum sodium
- Cool extremities
- Hypotension with ACE inhibitor
- Renal dysfunction (one cause)

Patient Selection and Treatment

**Congestion at Rest**

<table>
<thead>
<tr>
<th>Low Perfusion at Rest</th>
<th>Warm &amp; Dry</th>
<th>Cold &amp; Dry</th>
<th>Warm &amp; Wet</th>
<th>Cold &amp; Wet</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PCWP normal</td>
<td>PCWP low/normal</td>
<td>PCWP elevated</td>
<td>PCWP elevated</td>
<td></td>
</tr>
<tr>
<td>CI normal</td>
<td>CI decreased</td>
<td>CI decreased</td>
<td>CI normal</td>
<td></td>
</tr>
</tbody>
</table>

**Vasodilators**
- Nitroprusside
- Nitroglycerin

**Inotropic Drugs**
- Dobutamine
- Milrinone

### Similarities Between Acute MI and Acute Decompensated HF

<table>
<thead>
<tr>
<th></th>
<th>Acute MI</th>
<th>ADHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>1 million per year</td>
<td>1 million per year</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital</td>
<td>3–4%</td>
<td>3–4%</td>
</tr>
<tr>
<td>After discharge (60–90 d)</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Pathophysiological target(s)</strong></td>
<td>Clearly defined (coronary thrombosis)</td>
<td>Uncertain</td>
</tr>
<tr>
<td><strong>Clinical benefits of interventions in published clinical trials</strong></td>
<td>Beneficial</td>
<td>Minimal/no benefit or deleterious compared with placebo</td>
</tr>
<tr>
<td><strong>ACC/AHA recommendations</strong></td>
<td>Many Level A</td>
<td>None***</td>
</tr>
</tbody>
</table>

Cost of End-Stage HF

- REMATCH Trial (OMM)
  - Mean cost last 2 yrs: $156,169
    - $78,880 (50% last 6 mos)
  - 1 in 4 days in last 6 months spent in the hospital
  - 79% of all costs were for inpatient costs
    - 28% for ICU care,
    - 18% for outpatient care,
    - 3.5% for MD professional fees

LVAD costs compared with other life-saving therapies

- LVAD implantation is both life-saving and resource-intensive.
- Costs are very similar to other high-tech interventions that society pays

Annual Medicare budget per heart transplant ($175,000) from deLissovoy, Health Affairs, 1998
Annual Medicare payment for kidney dialysis ($53,000) from CMS, 2002
Twelve month cost of mAb-based chemotherapy based on AWP for colon cancer ($161,000) from Schrag, NEJM, 2004
Average LVAD hospitalization costs ($128,084) for two of the highest-volume DT-accredited facilities (Miller et al, 2006)
Natural History of Systolic HF

With each event, hemodynamic alterations/myocardial injury contribute to progressive ventricular dysfunction and dilatation.

Jain P et al., Am Heart J. 2003;145:S3-S17
Survival After Hospitalization

Miller, Guglin  *J Am Coll Cardiol.* 2013;61(12):1209-21
Heart Failure
Risk Stratification

Cardiopulmonary Exercise Testing

Prognostic Significance of Oxygen Consumption

Albouaini Heart 2007;93:1285-1292
Mancini Circulation 1991;83:778-786
Ivabradine significantly reduces major risks associated with heart failure:

- 18% reduction in CV death or hospital admission for worsening HF
- 26% reduction in death from heart failure
- 26% reduction in hospital admission for worsening heart failure

Benefits are apparent early, are consistent in predefined subgroups, and have been demonstrated on top of recommended therapy.

Treatment is well tolerated.

Continuous Flow Physiology

- No PULSE
- Measurement of Blood Pressure
### Angiotensin-Nephrilysin Inhibition vs. Enalapril in HF (PARADIGM-HF)

#### Table 2. Primary and Secondary Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo†</td>
<td>-2.99±0.36</td>
<td>-4.63±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation‡</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function§</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

* Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons.
† Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as the least-squares mean (±SE) of the between-group difference.
‡ A total of 2670 patients in the LCZ696 group and 2638 patients in the enalapril group who did not have atrial fibrillation at the randomization visit were evaluated for new-onset atrial fibrillation during the study.
§ A decline in renal function was defined as end-stage renal disease or a decrease of 50% or more in the estimated glomerular filtration rate (eGFR) from the value at randomization or a decrease in the eGFR of more than 30 ml per minute per 1.73 m², to less than 60 ml per minute per 1.73 m².
Angiotensin-Neprilysin Inhibition vs. Enalapril in HF (PARADIGM-HF)

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with systolic blood pressure &lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P=0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P=0.56).
† Angioedema was adjudicated in a blinded fashion by an expert committee.