Heart Failure: Future Directions

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Cardiovascular Division, Brigham & Women’s Hospital
Boston, Massachusetts

Disclosures: Marc A. Pfeffer, M.D., Ph.D., reports having serves as consultant to Aastrom, Abbott Vascular, Amgen, Cleveland Clinic, Concert, Daiichi Sankyo, Fibrogen, Genzyme, GlaxoSmithKline, Hamilton Health Sciences, Medtronic, Merck, Novartis, Novo Nordisk, Roche, Salix, Sanderling, Sanofi Aventis, Servier, and Teva and having received grant support from Amgen, Celladon, Novartis, and Sanofi-Aventis. The Brigham and Women’s Hospital has patents for the use of inhibitors of the renin-angiotensin system in survivors of MI with Novartis. Dr. Pfeffer’s shares are irrevocably transferred to charity.
Timeline of Landmark Heart Failure RCTs

1990
- V-HeFT
- CONSENSUS

1995
- SOLVD
- SAVE

2000
- RALES
- CIBIS-2
- MERIT-HF
- COPERNICUS
- Val-HeFT
- CHARM
- EPHESUS
- COMPANION

2005
- CARE-HF
- SCD-HeFT
- HeartMate II
- MADIT-CRT
- SHIFT
- RAFT
- EMPHASIS

2010

We need a bigger pole!
Enalapril (n=4212) and LCZ696 (n=4187) Kaplan-Meier Estimate of Cumulative Rates (%).

- **Enalapril**
  - Days After Randomization:
    - 0
    - 180
    - 360
    - 540
    - 720
    - 900
    - 1080
    - 1260
  - Patients at Risk:
    - 4212
    - 3883
    - 3579
    - 2922
    - 2123
    - 1488
    - 853
    - 236

- **LCZ696**
  - Days After Randomization:
    - 0
    - 180
    - 360
    - 540
    - 720
    - 900
    - 1080
    - 1260
  - Patients at Risk:
    - 4187
    - 3922
    - 3663
    - 3018
    - 2257
    - 1544
    - 896
    - 249

- **HR = 0.80 (0.73-0.87)**
- **P = 0.0000002**
- **Number needed to treat = 21**
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees

**HR = 0.84 (0.76-0.93) P<0.0001**

**Kaplan-Meier Estimate of Cumulative Rates (%)**

**Days After Randomization**

**Patients at Risk**

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
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<tr>
<td>180</td>
<td>4056</td>
<td>4051</td>
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<tr>
<td>360</td>
<td>3891</td>
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<td>3282</td>
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<td>720</td>
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<td>900</td>
<td>1716</td>
<td>1726</td>
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<tr>
<td>1080</td>
<td>1005</td>
<td>994</td>
</tr>
<tr>
<td>1260</td>
<td>280</td>
<td>279</td>
</tr>
</tbody>
</table>

**All Cause Mortality**

Enalapril (n=4212)

LCZ696 (n=4187)
• Differences in:
  ❖ Patient Populations
  ❖ Prognosis
  ❖ Responses to Spiro:
    • K+
    • Creatinine
    • Blood Pressure

Rz to spiro associated with reduced CV death and HF hospitalizations, in pts from the Americas
PARAGON-HF: study design

Target patient population: ~4,300 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%

Randomization 1:1

Active run-in period

Screening → Valsartan 80 mg BID* → LCZ696 100 mg BID → up to 2 weeks → 3–8 weeks → LCZ696 200 mg BID → ~240 weeks

Double-blind treatment period

Valsartan 160 mg BID

On top of optimal background medications for co-morbidities (excluding ACEIs and ARBs)

Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)

*Valsartan 40 mg BID (up to 2 weeks) followed by valsartan 80 mg BID as an optional starting run-in dose for those patients being treated with less than the minimum dose of ACEI or ARB at Visit 1.

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BID=twice daily; CV=cardiovascular; HF=heart failure; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association
Stages of HF and treatment options for systolic heart failure

Jessup M and Brozena S

1’ Prevention

ACE inhibitors (or ARB) in all patients; Beta blockers in selected patients.
Treat hypertension, dyslipidemia, diabetes. ACE inhibitors (or ARB) in selected patients
Risk factor reduction, patient and family education


Circulation. 2001;104:2996-3007

NYHA Class (I–IV)

NYHA IV

NOMAL

Stage A

No symptoms
Normal exercise
Normal LV

Asymptomatic LV Dysfunction
Stage B

No symptoms
Normal exercise
Abnormal LV

Compensated HF
Stage C

No symptoms
↓ Exercise
Abnormal LV

Decompensated Heart failure
Stage C

Symptoms
↓↓ Exercise
Abnormal LV

Refractory Heart Failure
Stage D

Symptoms not controlled with treatment
The Cycle of Clinical Therapeutics

- Epidemiology
- Hypothesis
- Pathophysiology
- RCT
- Guidelines
- Societies, Regulators, Payers, Practitioners
- Public Health Improved
- Implementation
- Education
- Euro Heart Survey

Adapted from Califf R et al. JACC 2002.
<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home-visiting programs</td>
<td>Home visits by clinicians, such as a nurse or pharmacist, who educate, reinforce self-care instructions, perform physical examination, or provide other care (e.g., physical therapy or medication reconciliation). These interventions are often referred to as nurse case management interventions, but they also can include home visits by a pharmacist or multidisciplinary team.</td>
</tr>
<tr>
<td>Structured Telephone Support</td>
<td>Monitoring, education, or self-care management (or various combinations) using simple telephone technology after discharge in a structured format (e.g., series of scheduled calls with a specific goal, structured questioning, or use of decision-support software).</td>
</tr>
<tr>
<td>Telemonitoring</td>
<td>Remote monitoring of physiologic data (e.g., electrocardiogram, blood pressure, weight, pulse oximetry, or respiratory rate) with digital, broadband, satellite, wireless, or Bluetooth transmission to a monitoring center, with or without remote clinical visits (e.g., video monitoring).</td>
</tr>
<tr>
<td>Outpatient clinic–based</td>
<td>Services provided in one of several types of outpatient clinics: multidisciplinary HF, nurse-led HF, or primary care. The clinic-based intervention can be managed by a nurse or other provider and may also offer unstructured telephone support (e.g., patient hotline) outside clinic hours.</td>
</tr>
<tr>
<td>Primarily educational</td>
<td>Patient education (and self-care training) delivered before or at discharge by various personnel or methods: in person, interactive CD-ROM, or video education. Interventions in this category do not feature telemonitoring, home visits, or STS and are not delivered primarily through a clinic-based intervention. Follow-up telephone calls may occur to ascertain outcomes (e.g., readmission rates) but not to monitor patients’ physiologic data.</td>
</tr>
<tr>
<td>Other</td>
<td>Unique interventions or interventions that do not fit into any of the other categories (e.g., individual peer support for patients with HF).</td>
</tr>
</tbody>
</table>
Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure


**Hazard Ratio (97.5% CI) vs. Placebo**
- Amiodarone vs. placebo: HR 1.06 (0.86–1.30), P = 0.529
- ICD Therapy vs. placebo: HR 0.77 (0.62–0.96), P = 0.007

**Graph:**
- Amiodarone vs. Placebo: HR 1.06 (0.86, 1.30), P = 0.529
- ICD Therapy vs. Placebo: HR 0.77 (0.62, 0.96), P = 0.007
Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure

COMPANION: Death or Hospitalization

12 month event rate reductions:
- CRT = by 18.6%
- CRT-D = by 19.3%

p = .005, CRT-D vs. OPT
p = .015, CRT vs. OPT

12 month OPT Event Rate (1-y) = 67.7%
Trials of implantable monitoring devices in heart failure: which design is optimal?

William T. Abraham, Wendy G. Stough, Ileana L. Piña, Cecilia Linde, Jeffrey S. Borer, Gaetano M. De Ferrari, Roxana Mehran, Kenneth M. Stein, Alphons Vincent, Jay S. Yadav, Stefan D. Anker and Faiez Zannad

Examples of information provided by implanted medical devices:
- RV systolic and diastolic pressure
- Estimated pulmonary artery end-diastolic pressure
- Change in pressure over time
- Pulmonary artery pressure
- Left atrial pressure
- Heart rate
- Patient activity
- Temperature
- Impedance
- Respiratory rate
- Rhythm abnormalities
- Heart rate variability
LONG-TERM USE OF A LEFT VENTRICULAR ASSIST DEVICE FOR END-STAGE HEART FAILURE

ERIC A. ROSE, M.D., ANNETINE C. GELLINS, PH.D., ALAN J. MOSKOWITZ, M.D., DANIEL F. HEITJAN, PH.D.,
LYNNE W. STEVENSON, M.D., WALTER DEMBITSKY, M.D., JAMES W. LONG, M.D., PH.D., DEBORAH D. ASCHEIM, M.D.,
ANITA R. TIERNEY, M.P.H., RONALD G. LEVITAN, M.S.C., JOHN T. WATSON, PH.D., AND PAUL MEIER, PH.D.,
FOR THE RANDOMIZED EVALUATION OF MECHANICAL ASSISTANCE FOR THE TREATMENT OF CONGESTIVE HEART FAILURE
(REMATCH) STUDY GROUP*
Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device

Mark S. Slaughter, M.D., Joseph G. Rogers, M.D., Carmelo A. Milano, M.D., Stuart D. Russell, M.D., John V. Conte, M.D., David Feldman, M.D., Ph.D., Benjamin Sun, M.D., Antone J. Tatooles, M.D., Reynolds M. Delgado, III, M.D., James W. Long, M.D., Ph.D., Thomas C. Wozniak, M.D., Waqas Ghumman, M.D., David J. Farrar, Ph.D., and O. Howard Frazier, M.D., for the HeartMate II Investigators*

As-treated analysis

Log-rank Test p=0.008

Percent Survival

CF LVAD 68±4%

PF LVAD 58±5%

Duration of support (yrs):

Median  Longest

CF LVAD  1.7  3.7
PF LVAD  0.6  2.1

Remaining at risk

133  59
96   32
82   19
69   5
62   2

Months

NEJM 2009;361(23):2241-51.
LONG-TERM USE OF A LEFT VENTRICULAR ASSIST DEVICE FOR END-STAGE HEART FAILURE


Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device

Mark S. Slaughter, M.D., Joseph G. Rogers, M.D., Carmelo A. Milano, M.D., Stuart D. Russell, M.D., John V. Conte, M.D., David Feldman, M.D., Ph.D., Benjamin Sun, M.D., Antoine J. Tatooles, M.D., Reynolds M. Delgado, III, M.D., James W. Long, M.D., Ph.D., Thomas C. Wozniak, M.D., Waqas Ghumman, M.D., David J. Farrar, Ph.D., and O. Howard Frazier, M.D., for the HeartMate II Investigators

Sixth INTERMACS annual report: A 10,000-patient database

James K. Kirklin, MD, a David C. Naftel, PhD, a Francis D. Pagani, MD, PhD, b Robert L. Kormos, MD, c Lynne W. Stevenson, MD, d Elizabeth D. Blume, MD, e Marissa A. Miller, DVM, MPH, f J. Timothy Baldwin, PhD, f and James B. Young, MD g

Intermacs

Implants: June 2006 – December 2013, n = 10542

- Continuous Flow Intracorporeal LVAD Pump
- Pulsatile Flow Intracorporeal TAH
- Pulsatile Flow Intracorporeal LVAD Pump
- Pulsatile Flow Paracorporeal LVAD Pump

Implants per year

2006  2007  2008  2009  2010  2011  2012  2013
Stages of HF and treatment options for systolic heart failure

Jessup M and Brozena S

ACE inhibitors (or ARB) in all patients; Beta blockers in selected patients.
Treat hypertension, dyslipidemia, diabetes. ACE inhibitors (or ARB) in selected patients
Risk factor reduction, patient and family education
Gene therapy using an adenovirus vector
Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients With Advanced Heart Failure

The CUPID 2 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b)

Barry Greenberg, MD,* Alex Yaroshinsky, PhD,† Krisztina M. Zsebo, PhD,‡ Javed Butler, MD, MPH,§ G. Michael Felker, MD,¶ Adriaan A. Voors, MD,∥ Jeffrey J. Rudy, BS,∫ Kim Wagner, MA,‡ Roger J. Hajjar, MD#
Celladon Reports Negative Results for CUPID2 Trial of MYDICAR(R) in Advanced Heart Failure

- Investigational gene therapy fails to meet primary and secondary endpoints –
- SAN DIEGO, April 26, 2015 (GLOBE NEWSWIRE) -- Celladon Corporation (Nasdaq:CLDN) today announced that its Phase 2b CUPID2 trial did not meet its primary and secondary endpoints. CUPID2 is a randomized, double-blind, placebo-controlled, multinational trial evaluating a single, one-time, intracoronary infusion of the cardiovascular gene therapy agent MYDICAR® (AAV1/SERCA2a) versus placebo added to a maximal, optimized heart failure drug and device regimen.

In the study, the primary endpoint comparison of MYDICAR to placebo resulted in a hazard ratio of 0.93 :95%CI (0.53, 1.65)
Bone marrow cells regenerate infarcted myocardium

Donald Orlic†, Jan Kajstura*, Stefano Chimenti*, Igor Jakoniuk†,
Stacie M. Anderson†, Baosheng Li†, James Pickel†, Ronald McKay†,
Bernardo Nadal-Ginard†, David M. Bodine†, Annarosa Leri†
& Piero Anversa†
Metaanalysis of Bone Marrow Stem Cells post AMI
Change in EF at 3-6 months

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruan</td>
<td>2005</td>
<td>20</td>
<td>6.03 (-0.73, 18.76)</td>
</tr>
<tr>
<td>Ge</td>
<td>2006</td>
<td>20</td>
<td>2.30 (-4.21, 8.81)</td>
</tr>
<tr>
<td>Huang RC</td>
<td>2006</td>
<td>40</td>
<td>3.60 (-0.12, 7.32)</td>
</tr>
<tr>
<td>Janssens</td>
<td>2006</td>
<td>60</td>
<td>2.70 (-2.26, 7.66)</td>
</tr>
<tr>
<td>Lunde</td>
<td>2006</td>
<td>100</td>
<td>-0.20 (4.17, 3.77)</td>
</tr>
<tr>
<td>Meyer</td>
<td>2006</td>
<td>60</td>
<td>4.70 (-1.60, 11.00)</td>
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<tr>
<td>Schachinger</td>
<td>2006</td>
<td>187</td>
<td>3.90 (0.54, 7.26)</td>
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<tr>
<td>Huang</td>
<td>2007</td>
<td>40</td>
<td>4.40 (0.81, 7.99)</td>
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<tr>
<td>Penicka</td>
<td>2007</td>
<td>24</td>
<td>-2.00 (-8.41, 4.41)</td>
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<tr>
<td>Suarez de Lezo</td>
<td>2007</td>
<td>20</td>
<td>13.00 (5.54, 20.46)</td>
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<tr>
<td>Huikuri</td>
<td>2008</td>
<td>72</td>
<td>3.00 (-2.62, 8.62)</td>
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<td>Meluzin</td>
<td>2008</td>
<td>40</td>
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<tr>
<td>Cao</td>
<td>2009</td>
<td>85</td>
<td>2.70 (1.14, 4.25)</td>
</tr>
<tr>
<td>Piepol</td>
<td>2009</td>
<td>38</td>
<td>5.30 (3.93, 6.67)</td>
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<tr>
<td>Plewka</td>
<td>2009</td>
<td>56</td>
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<td>Silva</td>
<td>2009</td>
<td>20</td>
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<td>Tendera</td>
<td>2009</td>
<td>66</td>
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<td>Grajec</td>
<td>2010</td>
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<td>Hirsh</td>
<td>2010</td>
<td>127</td>
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<tr>
<td>Roncalli</td>
<td>2010</td>
<td>92</td>
<td>-2.00 (-6.08, 2.08)</td>
</tr>
<tr>
<td>Traverse</td>
<td>2010</td>
<td>40</td>
<td>-2.80 (-9.07, 3.47)</td>
</tr>
<tr>
<td>Wohrle</td>
<td>2010</td>
<td>40</td>
<td>-5.10 (+13.37, 1.17)</td>
</tr>
</tbody>
</table>

N = 1317

Tests for heterogeneity: p = 0.003, I-squared = 50.3%
Test for overall effect: p < 0.001
<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Completed</td>
<td>Cardiac Stem Cell Infusion in Patients With Ischemic Cardiomyopathy (SCiPIO)</td>
</tr>
</tbody>
</table>

**Conditions:**
- Coronary Artery Disease
- Congestive Heart Failure
Which Cells/Factors?

How administer?

How many?

When?

To whom?
Regenerative Strategies

Safe and Effective Therapeutic Product

CSC GMP Facility (making a reproducible product)

Dose and Regimen

Regulatory Business Development

Regenerative Strategies
Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy

F. Waagstein, Å. Hjalmarson, E. Varnauskas, and I. Wallentin

British Heart Journal

1975

PROLONGATION OF SURVIVAL IN CONGESTIVE CARDIOMYOPATHY BY BETA-RECEPTOR BLOCKADE

Karl Swedberg
Finn Waagstein
Åke Hjalmarson
I. Wallentin

THE LANCET

1979

Beneficial effects of long-term beta-blockade in congestive cardiomyopathy

Karl Swedberg, Åke Hjalmarson, Finn Waagstein, Ingemar Wallentin

British Heart Journal

1980

Adverse effects of beta-blockade withdrawal in patients with congestive cardiomyopathy

K Swedberg, Å Hjalmarson, F Waagstein, I Wallentin

British Heart Journal

1980
Beta Blockers Decrease Mortality in Systolic HF

**MERIT-HF**
- **Placebo**
- **ER Metoprolol Succinate**
- Cumulative mortality (%)
  - $P=.0062$ (adjusted)
  - $P=.00009$ (nominal)
- Follow-up (months)
- Mortality: 34%

**CIBIS-II**
- **Bisoprolol**
- **Placebo**
- Log rank $P=.00006$
- Probability of survival
- Time (days)
- Mortality: 34%

**COPERNICUS**
- **Carvedilol**
- **Placebo**
- Survival (%)
  - $P=.00014$ (unadjusted)
  - $P=.0014$ (adjusted)
- Months
- Mortality: 35%


ER, extended release.
Heart Failure Therapies

Improve -phenome-genotype
by harvesting molecular biology
Novel therapies will be better targeted
Long-Term Trends in First Hospitalization for Heart Failure and Subsequent Survival Between 1986 and 2003: A Population Study of 5.1 Million People
Pardeep S. Jhund, Kate MacIntyre, Colin R. Simpson, James D. Lewsey, Simon Stewart, Adam Redpath, James W.T. Chalmers, Simon Capewell and John J.V. McMurray

First Hospitalization rate (per 100,000 population)

Year
REMARKS ON ANGINA PECTORIS.

BY JOHN WARREN, M. D.

In our inquiries into any particular subject of Medicine, our labours will generally be shortened and directed to their proper objects, by a knowledge of preceding discoveries.
Risk factor reduction, patient and family education

Treat hypertension, dyslipidemia, diabetes. ACE inhibitors (or ARB) in selected patients.

ACE inhibitors (or ARB) in all patients; Beta blockers in selected patients.

1’ Prevention

Risk factor reduction, patient and family education