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New horizons in HF: potential of new drugs

FINANCIAL DISCLOSURE:
Disclosures: Dr. Pfeffer receives honoraria and/or research grants, or serves as a consultant for Affectis, Amgen, Anthera, Baxter, Boehringer, Boston Scientific, Bristol-Myers Squibb, Celladon, Daiichi Sankyo, Gilead, GlaxoSmithKline, Medtronic, Mirabila, Nicox, Novartis, Roche, Salutria, Sanofi-Aventis, Servier, and the University of Oxford. Dr. Pfeffer is a co-inventor of a patent awarded to BWH regarding the use of inhibitors of the renin-angiotensin system in selected survivors of MI. A licensing agreement with Boehringer Ingelheim and Novartis is not linked to sales.
What’s in the pipeline

- **Patients with low LVEF HF:**
  - SHIFT – ivabradine √
  - EMPHASIS-HF – eplerenone √
  - RED-HF – darbepoetin
  - ATMOSPHERE – aliskiren
  - PARADIGM-HF – LCZ696 (an ARNi)

- **Patients with preserved LVEF HF:**
  - TOPCAT - spironolactone

- **Patients with acute HF:**
  - ASCEND-HF – nesiritide √
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators*

*Lancet 2010; 376: 875–85*
SHIFT: Primary endpoint – CV death or HF hospitalization

HR 0.82 (95% CI 0.75–0.90), p<0.0001

Number at risk
Placebo group 3264 2868 2489 2061 1089 439
Ivabradine group 3241 2928 2600 2173 1191 447
SHIFT: Components of primary endpoint

Cardiovascular death

HF hospitalization

Months of follow-up
The issue:

- Two drugs acting through the same pathway

The questions:

- Were the patients in CHARM-Added treated with an “optimal” dose of ACE inhibitor?
- Could the same effect be obtained by giving a bigger dose of ACE inhibitor?
EMPHASIS-HF

• **Hypothesis:** Aldosterone antagonism with eplerenone will be of benefit in patients with mild HF and LV systolic dysfunction

• **Population:** 2737 patients ≥60 years with NYHA II HF and LVEF ≤30% (or LVEF 31-35% and QRS duration >130 msec.). CV hospitalisation within 90 days (or BNP ≥250 pg/ml or NT-proBNP ≥500 pg/ml in men/ ≥750 pg/ml in women.

• **Intervention:** Eplerenone (50 mg) vs Placebo

• **Primary endpoint:** CV death or HF hospitalisation – event driven (813 events)

*Terminated early: 27 May 2010*
EMPHASIS-HF: Primary outcome

HR 0.63 (0.54-0.74) P<0.001
The missing piece of the aldosterone-antagonist jigsaw

LVSD/HF after AMI  Mild CHF  Severe CHF

Beta-blockers (87%)

EPHESUS  EMPHASIS-HF  RALES
Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist
Hypothesis: Spironolactone will reduce morbidity and mortality in mild HF and preserved LV function

Population: 3200 patients >50 yrs with NYHA II HF (and admission or elevated BNP), EF ≥45%

Intervention: Spironolactone (15-45 mg) vs placebo

Primary endpoint: CV death, RSD, HF hospitalisation

Status: Recruitment started 2008; expected 2012
Heart failure and CKD

A treatment to improve renal function
Rolofylline, an Adenosine $A_1$–Receptor Antagonist, in Acute Heart Failure

Barry M. Massie, M.D., Christopher M. O’Connor, M.D., Marco Metra, M.D., Piotr Ponikowski, M.D., John R. Teerlink, M.D., Gad Cotter, M.D., Beth Davison Weatherley, Ph.D., John G.F. Cleland, M.D., Michael M. Givertz, M.D., Adriaan Voors, M.D., Paul DeLucca, Ph.D., George A. Mansoor, M.D., Christina M. Salerno, M.S., Daniel M. Bloomfield, M.D., and Howard C. Dittrich, M.D., for the PROTECT Investigators and Committees*

N ENGL J MED 363;15  NEJM.ORG  OCTOBER 7, 2010
Hypothesis: Nesiritide will improve dyspnoea/self assessment (at 3 and 24 hours) and reduce morbidity and mortality in acute "decompensated" HF (at 30 and 180 days)

Population: ~7000 pts ≥18 yrs with clinical evidence of HF and supportive evidence e.g. chest X-ray, BNP, echo

Intervention: IV nesiritide (1-7 days) vs placebo

Primary endpoint: Dyspnoea. Death or HF hospitalisation

Status: AHA /NEJM November 2010
ASCEND-HF Co-Primary outcome: 30-day all-cause mortality or HF re-hospitalization

P=0.31  Hazard Ratio 0.93 (95% CI: 0.8, 1.08)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Nesiritide</th>
<th>Risk Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day Death/HF Rehospitalization</td>
<td>10.1</td>
<td>9.4</td>
<td>-0.7 (-2.1; 0.7)</td>
</tr>
<tr>
<td>30-day Death</td>
<td>4.0</td>
<td>3.6</td>
<td>-0.4 (-1.3; 0.5)</td>
</tr>
<tr>
<td>HF Rehospitalization</td>
<td>6.1</td>
<td>6.0</td>
<td>-0.1 (-1.2; 1.0)</td>
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</tbody>
</table>
Treating anaemia in HF with an ESP?
Design of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): a Phase III, anaemia correction, morbidity–mortality trial

John J.V. McMurray¹*, Inder S. Anand², Rafael Diaz³, Aldo P. Maggioni⁴, Christopher O’Connor⁵, Marc A. Pfeffer⁶, Krishna R. Polu⁷, Scott D. Solomon⁶, Yan Sun⁸, Karl Swedberg⁹, Michal Tendera¹⁰, Dirk J. van Veldhuisen¹¹, Scott M. Wasserman⁷, and James B. Young¹² on behalf of the RED-HF Committees and Investigators†
**Hypothesis:** Darbepoetin will improve outcomes in patients with HF and anaemia

**Population:** 3400 patients with LVEF ≤0.35 and NYHA class III-IV HF/class II and CV admission/ER visit within 12 months

**Anaemia:** Hb ≥9.0 g/dL and ≤12.0 g/dL

**Intervention:** Darbepoietin sc vs placebo; target Hb 13.0-14.5 g/dL

**Primary endpoint:** Death or HF hospitalisation

**Status:** Started summer 2006
Iron supplementation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D., Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D., Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,* Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D., Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D., Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D., Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D., for the FAIR-HF Trial Investigators†

## FAIR-HF Trial

### Death

<table>
<thead>
<tr>
<th></th>
<th>Ferric Carboxymaltose (n = 305)</th>
<th>Placebo (n = 154)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (incidence /100 patient-years)</td>
<td>5 (3.4)</td>
<td>4 (5.5)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Estimated exposure: 459 patients * 24 weeks = 212 patient-years

*Anker et al. NEJM 2009;361(25): 2436*
Too premature to leap
HF and Anemia studies as of 08/25/2010
www.clinicaltrials.gov

Anemia AND “HF”
22 studies

Therapeutic intervention
15

Iron Supplementation
7

6 RCTs, 1 open label
VO₂, ΔHgb, QOL
3165 patients

PRBC post MI
M/M endpoint
92 patients

Erythropoietin Stimulating Agents
7

Non M/M
ΔHgb, VO₂, QOL,
remodeling
580 patients (largest 300)

Observational, Case-control
7

Mortality/Morbidity

RED-HF Trial
REDUCTION OF EVENTS WITH EPOETIN ALFA IN HEART FAILURE TRIAL
Renin-Angiotensin Aldosterone System

- **Angiotensinogen**
- **Renin**
- **Angiotensin I**
- **Angiotensin II**
- **Aldosterone**
- **ACE**
- **AT_1**
- **AT_2**

**Non-ACE Pathways** (e.g., chymase)
- Vasoconstriction
- Cell growth
- Na/H_2O retention
- Sympathetic activation

**Cough, Angioedema Benefits?**

**Bradykinin**
- Vasodilation
- Antiproliferation (kinins)
- Inactive Fragments
Over a Quarter century of inhibiting the RAS

- Inhibiting RAS major role in prevention and treatment of CV diseases
- ACE-I 1975
- ARB 1995
- DRI 2002
- Optimal combinations still being evaluated
RAS blockers

ACE inhibitor  ARB  Renin inhibitor
RAS blockers

ACE inhibitor  ARB  Renin inhibitor
Direct Renin Inhibitors across CV Disease Spectrum

HBP/VASCULAR
  allay
  (APOLLO)

MI
  aspire

HF
  aloft
  (ASTRONAUT)
  (ATMOSPHERe)

DM Renal
  avoid
  (ALTITUDE)
Primary outcome: CV death or heart failure hospitalization
(event driven: 2162 patients)

- **Open-label run-in**
  - Enalapril
  - Enalapril + aliskiren

- **Randomization**
  - Enalapril 10 mg twice daily (n=2,200)
  - Aliskiren 300 mg once daily (n=2,200)
  - Aliskiren 300 mg/enalapril 20 mg Daily (n=2,200)

- **Double-blind**
  - ~48 weeks (event driven)
Design Overview

Randomization

Primary outcome: CV death or HF hospitalization at 6 months (381 events)

Acute HF
LVEF < 40%
BNP > 400 pg/mL
SBP ≥ 110 mmHg
~1,800 patients

Aliskiren 150 mg

Aliskiren 300 mg

Placebo

Conventional therapy‡

In-hospital entry and initiation → 2 weeks → ~15 months (event-driven)*

‡ Except concomitant use of an ACEI and ARB

* Follow-up at Week 2, Month 1, 2 and 3, with on-going assessments every 3 months thereafter
Effect of the direct renin inhibitor aliskiren on left ventricular remodelling following myocardial infarction with systolic dysfunction

Scott D. Solomon¹*, Sung Hee Shin¹, Amil Shah¹, Hicham Skali¹, Akshay Desai¹, Lars Kober², Aldo P. Maggioni³, Jean L. Rouleau⁴, Roxzana Y. Kelly⁵, Allen Hester⁵, John J. V. McMurray⁶,⁷, and Marc A. Pfeffer¹, for the Aliskiren Study in Post-MI Patients to Reduce Remodeling (ASPIRE) investigators
Primary Outcome:
Left Ventricular End-Systolic Volume at Baseline and Final Echo visit

Baseline and Final LVESV

<table>
<thead>
<tr>
<th>Placebo (n=329)</th>
<th>Aliskiren (n=343)</th>
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<tbody>
<tr>
<td>Baseline LVESV</td>
<td>Final LVESV</td>
</tr>
<tr>
<td>84.4</td>
<td>82.4</td>
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<tr>
<td>80.9</td>
<td>78.0</td>
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</table>

Delta LVESV

Difference: 0.90 (-1.6, 3.4)
P = 0.44

Solomon et al. EHJ 2011
LCZ 696

Molecular complex of:

- An ARB - valsartan
- A NEP inhibitor – AHU 377
**PARADIGM-HF**

A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction

**Primary objectives**
Evaluate if LCZ696 is superior in delaying time to first occurrence of either **CV mortality or HF hospitalization** in CHF pts (NYHA Class II – IV) with reduced ejection fraction

**Secondary objectives**
- All cause mortality
- Renal progression (eGFR change)
- Clinical summary score (assessed by KCCQ)

**Patient population**
- 7980 patients with CHF NYHA class II – IV and reduced ejection fraction (LVEF < 40%)
- BNP>150 pg/ml (NTproBNP > 600 pg/ml) or BNP > 100 pg/ml (NTproBNP > 400 pg/ml) and hospitalization within the last 12 months
Recombinant adeno-associated viral vectors (AAV):
- Non-pathogenic, non-replicating & non-integrating
- Long-term (>4 yrs) skeletal muscle expression in man

MYDICAR\(^\circledR\) (AAV1/SERCA2a):
- DNA: Inverted Terminal Repeats (ITR) derived from AAV2, CMV promoter, human SERCA2a cDNA, PolyA
  (10-minute intracoronary infusion)
CUPID Met Primary Efficacy Endpoint for High dose vs. Placebo

1. **Group-level analysis success**: Improvement in 6MWT (p=0.14), ESV (p=0.057) with no clinically significant worsening in any endpoint and numerical superiority in all other endpoints

2. **Individual-level analysis success**: The mean individual efficacy “score” for MYDICAR is greater than that for Placebo, p=0.052

3. **Time-to-event (death, LVAD implantation or heart transplant)**: MYDICAR numerically better than Placebo

4. **Duration of CV hospitalizations**: duration for MYDICAR less than that for Placebo, 2.1 ± 3 in placebo versus high dose 0.2 ± 0.7 days p=0.08.

*The probability of achieving above outcomes by chance alone is <0.1% based on permutation test*
In this phase 2 study of patients with advanced HF, MYDICAR® was found to be safe and associated with benefit in the following:

- Clinical outcomes
- Symptoms
- Functional status
- NT-proBNP
- Cardiac structure

These encouraging results support further studies to determine the value of genetically targeted enzyme replacement of SERCA2a in advanced heart failure.

Placebo 14 vs. 25 treated.
Mesenchymal stem cells in cardiac research

Heldman et al. JACC 2011;57;466-468
HF Rx: Half Empty / Half Full

The impossible task of developing a new treatment for heart failure
Packer J Card Fail 2002

New therapies for the failing heart: trans-genes versus trans-cells
Lionetti and Recchia Translational Research 2010
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials