Disclosure

- **Consultant:**
  Johnson & Johnson, NILE Therapeutics, Sanofi-Aventis, Servier, Torrent

- **Speaker:**
  AstraZeneca, BMS, GlaxoSmithKline, MSD, Menarini, Sanofi-Aventis, Servier
The success of the neuro hormonal paradigm in HF with low EF:

- ACE I
- ARBs
- Beta blockers
- MRAs
- ARNI
Annual risk of HF death in major HF trials

HF death rate per patient-year of follow-up (%)

- SOLVD: 5.5%
- CIBIS II: 2.6%
- SHIFT: 2.6%

Placebo group
Heart failure mortality in Europe

A) Heart Failure as underlying cause of death

B) Heart Failure as multiple cause of death

The burden of early and recurrent hospitalizations
Acute HF: re-hospitalizations during the follow-up*

Median follow-up 349 days [252-365]

Causes of hospitalization

- Non CV causes: 17.0%
- CV causes non HF: 26.6%
- HF: 56.4%

Maggioni, A, Eur J Heart Fail, 2013
Chronic heart failure: a life-time burden of hospitalization

50 125 patients with HF hospitalization

30-day HF rehospitalization

30-day mortality

Heidenreich PA et al. J Am Coll Cardiol. 2010;56(5):362-8
Can other paradigms do better?
Fréquence cumulée (%)

- Placebo
  - HR = 0.82
  - $p < 0.0001$
  - -18%

- Ivabradine

PARADIGM-HF: Primary Endpoint

Enalapril (n=4212)
HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

LCZ696 (n=4187)
1117
914

Days After Randomization

On going clinical trials
Chronic HF

- Alliskiren (Renin inhibitor)
- Mirabegron (B₃ agonist)
- Levosimendan
- Sildenafil
- Ferric carboxymaltose
- Vericiguat (sGC stimul.)
- Cardiac myosin activator
- Liraglutide (GLP₁ agonist)
Primary: CV Death, MI, Stroke or UA

HR = 1.02 (0.89, 1.17)

Primary + Heart Failure Hosp

HR = 0.97 (0.85, 1.10)

Heart Failure Hospitalization

HR = 0.96 (0.75, 1.23)

All-Cause Death

HR = 0.94 (0.78, 1.13)
HFpEF: a clinical dilemma

Benefit

Too well to benefit

Too sick to benefit

Disease severity
### Clinical trials: HFpEF

<table>
<thead>
<tr>
<th>Negative trials</th>
<th>Ongoing trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>- ACE I</td>
<td>- LCZ 696</td>
</tr>
<tr>
<td>- ARBs</td>
<td>- Anakinra</td>
</tr>
<tr>
<td>- Spironolactone</td>
<td>- Inhaled NO</td>
</tr>
<tr>
<td>- Sildenafil</td>
<td>- Vericiguat</td>
</tr>
<tr>
<td>- Nitrates</td>
<td>- Perhexilline</td>
</tr>
<tr>
<td></td>
<td>- Renal denervation</td>
</tr>
</tbody>
</table>
ACUTE HEART FAILURE
All cause mortality / HF hosp

Acute HF: 35.1%

Chronic HF: 17.2%
FAILURES

- Endothelin antagonists
- Inotropic agents
- AVP antagonists
- Cytokine modulators
- Adenosin receptor antagonists
- Recombinant human natriuretic peptide (Nesiritide)
- Patient heterogeneity.
- Lack of consensus on endpoints and timing.
Clinical trials: Acute HF

- Serelaxin
- Anakinra (IL1 blocker)
# Home Telemonitoring

Inglis et al 2010

**Mortality**

HR 0.66 (0.54-0.87); p<0.0001

**All-Cause Hospitalisation**

HR 0.91 (0.84-0.99); p=0.02

n = 2,710

(Cochrane Review)
OPTILINK HF: PRIMARY ENDPOINT: ALL-CAUSE DEATH OR CV HOSPITALISATION

Hazard ratio = 0.867 (0.72, 1.044)
Stratified log-rank p-value = 0.132

Bohm M, ESC 2015
Non pharmacological approach

Gene therapy?

Stem cell therapy?
Treatment with AAV1/SERCA2a failed to improve the rate of recurrent events (HR, 0.93; 95% confidence interval [CI] 0.53 to 1.65; p=0.81).

Hazard ratio, 0.93 (95% CI, 0.53-1.65)  
P=0.81

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Days Since Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>122 122 120 119 114 108 103 83 72 57 45 27 11 9 4</td>
</tr>
<tr>
<td>AAV1/SERCA2a</td>
<td>121 119 115 113 109 104 102 81 67 55 40 24 13 6 1</td>
</tr>
</tbody>
</table>
## Cell Therapy Trials in Heart Failure

### A) Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cells Events</th>
<th>No cells Events</th>
<th>Total Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assmus 2013</td>
<td>5</td>
<td>43</td>
<td>5</td>
<td>0.79 (0.25, 2.28)</td>
</tr>
<tr>
<td>Bartunek 2013</td>
<td>1</td>
<td>21</td>
<td>1</td>
<td>0.36 (0.04, 3.59)</td>
</tr>
<tr>
<td>Boll 2011</td>
<td>0</td>
<td>15</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Chen 2006</td>
<td>2</td>
<td>22</td>
<td>4</td>
<td>0.52 (0.11, 2.57)</td>
</tr>
<tr>
<td>Dib 2008</td>
<td>0</td>
<td>12</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Feltner 2014 (BMSC)</td>
<td>0</td>
<td>19</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Heidmann 2014 (MSC)</td>
<td>1</td>
<td>19</td>
<td>1</td>
<td>0.59 (0.04, 3.38)</td>
</tr>
<tr>
<td>Honold 2012</td>
<td>0</td>
<td>22</td>
<td>1</td>
<td>0.18 (0.01, 3.81)</td>
</tr>
<tr>
<td>Hu 2011</td>
<td>1</td>
<td>29</td>
<td>2</td>
<td>0.50 (0.06, 5.20)</td>
</tr>
<tr>
<td>Menasche 2008</td>
<td>0</td>
<td>4</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Nassir 2014</td>
<td>1</td>
<td>28</td>
<td>1</td>
<td>0.93 (0.00, 14.09)</td>
</tr>
<tr>
<td>Pabin 2014</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Perin 2014</td>
<td>3</td>
<td>21</td>
<td>2</td>
<td>0.43 (0.06, 2.00)</td>
</tr>
<tr>
<td>Pokushalov 2010</td>
<td>6</td>
<td>55</td>
<td>21</td>
<td>0.29 (0.02, 2.00)</td>
</tr>
<tr>
<td>Seth 2006</td>
<td>10</td>
<td>41</td>
<td>14</td>
<td>0.70 (0.35, 1.43)</td>
</tr>
<tr>
<td>Turan 2011</td>
<td>0</td>
<td>33</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Vitrok 2011</td>
<td>8</td>
<td>55</td>
<td>19</td>
<td>0.42 (0.20, 0.88)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>459</strong></td>
<td><strong>373</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.48 (0.34, 0.68)</strong></td>
</tr>
</tbody>
</table>

**Total events:** 30, **73**

Heterogeneity: Tau^2 = 0.00, Chi^2 = 4.38, df = 10 (P = 0.93), I^2 = 0%

Test for overall effect: Z = 3.97 (P = 0.0001)

### B) Rehospitalization

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cells Events</th>
<th>No cells Events</th>
<th>Total Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assmus 2013</td>
<td>9</td>
<td>43</td>
<td>20</td>
<td>0.41 (0.21, 0.79)</td>
</tr>
<tr>
<td>Boll 2011</td>
<td>1</td>
<td>16</td>
<td>0</td>
<td>1.41 (0.06, 30.87)</td>
</tr>
<tr>
<td>Heldmann 2014 (BMSC)</td>
<td>0</td>
<td>19</td>
<td>1</td>
<td>0.18 (0.01, 4.13)</td>
</tr>
<tr>
<td>Heldmann 2014 (MSC)</td>
<td>0</td>
<td>19</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Honold 2012</td>
<td>0</td>
<td>22</td>
<td>10</td>
<td>0.10 (0.01, 1.63)</td>
</tr>
<tr>
<td>Menasche 2008</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>0.39 (0.09, 2.45)</td>
</tr>
<tr>
<td>Pabin 2014</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>143</strong></td>
<td><strong>99</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.39 (0.22, 0.79)</strong></td>
</tr>
</tbody>
</table>

**Total events:** 11, **26**

Heterogeneity: Tau^2 = 0.00, Chi^2 = 1.79, df = 4 (P = 0.77), I^2 = 0%

Test for overall effect: Z = 3.17 (P = 0.002)
Thank You!