Heart failure medical treatment in 2017: An update

Prof. Marco Metra
Cardiology, University of Brescia
Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland

Men

Women

Survival

Years since diagnosis

Prostate cancer
Lung cancer
Colorectal cancer
Bladder cancer
Heart failure

Breast cancer
Colorectal cancer
Lung cancer
Ovarian cancer
Heart failure

Burden of new hospitalization for heart failure: a population-based investigation from Italy

Giovanni Corrao, Arianna Ghirardi, Buthaina Ibrahim, Luca Merlino, and Aldo Pietro Maggioni

Pro capite costs of HHF patients, euros/year

- Initial hospitalization: 4300
- Subsequent rehospitalizations: 5900
- Drugs: 400
- Visits, procedures, labs: 500

Corrao et al. Eur J Heart Fail 2014; 16, 729–736
Algorithm for the treatment of HFrEF

1. **Diuretics for symptom relief**

2. **New onset heart failure**
   - ACE inhibitor or ARB\* if ACE inhibitor not tolerated; ARNI↑
   - β blocker and MRA

3. **Chronic heart failure**
   - ACE inhibitor or ARB; substitute with ARNI↑
   - β blocker and MRA

4. **Persistent NYHA class II-IV symptoms and LVEF <35%**

5. **If sinus rhythm with heart rate ≥70 bpm, add ivabradine**

6. **If ambulatory and QRS <120–150 ms, consider implantable cardioverter defibrillator**

7. **If QRS >120 ms plus left bundle branch block or QRS ≥150 ms, consider CRT-P or CRT-D**

8. **If persistent NYHA class III-IV symptoms and LVEF <35%, consider digoxin, hydralazine, and nitrates§**

9. **If end-stage or advanced heart failure, consider left ventricular assist device, heart transplantation, or both**

---

Metra, Teerlink. The Lancet DOI: (10.1016/S0140-6736(17)31071-1)
Thirty years of progress in HF-rEF

Positive drug, device and other trials 2001-2014

[Diagram showing timeline and outcomes of various trials and interventions]
Combined AT₁ Receptor Neprilysin Inhibition (ARNI) for the treatment of Heart Failure

LCZ696

Natriuretic peptides BK, ADM, Subst.P, VIP, CGRP

Vasodilation
Diuresis – natriuresis
Inhibition of hypertrophy

sacubitril

Neprilysin

Degradation products

valsartan

Angiotensin II

AT₁ receptor

Vasoconstriction
Sodium-water retention
Hypertrophy/ fibrosis
Dual Angiotensin Receptor and Neprilysin inhibition (ARNI) as an alternative to ACE inhibition in patients with chronic systolic HF. Design of the PARADIGM-HF Trial

- Aged ≥ 18 years
- NYHA II-IV
- LVEF ≤ 40%
- BNP/NTproBNP ≥ 150 / 600 pg/mL

McMurray et al. European Journal of Heart Failure; 15: 1062-73
Kaplan–Meier Curves for Key Study Outcomes, According to Study Group

Effect of LCZ696 compared with enalapril on mode of death in heart failure patients

Sudden cardiac death

Worsening HF death

Mortality (%) after a first event or in patients with no event.

Effect of sacubitril/valsartan versus enalapril for each outcome.

- Primary End Point (2031): 0.80 (0.73-0.87)
- CV death (1251): 0.80 (0.71-0.89)
- HF hospitalization (1295): 0.79 (0.71-0.89)
- Expanded composite (2309): 0.79 (0.73-0.86)
- Intensification with no other event (203): 0.81 (0.61-1.07)
- ED visit with no other event (48): 0.54 (0.30-0.98)

Persistent improvement in KCCQ scores with sacubitril/valsartan vs enalapril through 36 months

Effect of LCZ696 on Clinical Outcomes: The MAGGIC Risk Score Category

Kaplan-Meier event curves for the primary endpoint in patients subdivided according to different SBP subgroups

Bohm et al. Eur Heart J. Published online February 01, 2017. doi:10.1093/eurheartj/ehw570
Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial

Orly Vardeny¹, Brian Claggett², Milton Packer³, Michael R. Zile⁴, Jean Rouleau⁵, Karl Swedberg⁶, John R. Teerlink⁷, Akshay S. Desai², Martin Lefkowitz⁸, Victor Shi⁸, John J.V. McMurray⁹, Scott D. Solomon², for the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Investigators
Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial

Vardeny et al. European Journal of Heart Failure 10 JUN 2016 DOI: 10.1002/ejhf.580
## Cost – efficacy of sacubitril/valsartan versus enalapril in HFrEF

### Table 1: Model parameters: clinical characteristics, event probabilities, costs and utility values.

<table>
<thead>
<tr>
<th>Input</th>
<th>Value (range)</th>
<th>Parameter distribution</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (range)</td>
<td>71 (60.0–80.0)</td>
<td>Normal</td>
<td>Senni et al. (2014)¹</td>
</tr>
<tr>
<td>Female, %</td>
<td>33.6%</td>
<td>Beta</td>
<td>Senni et al. (2014)¹</td>
</tr>
<tr>
<td>Race and region, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>100%</td>
<td>NA</td>
<td>Assumption</td>
</tr>
<tr>
<td>Western Europe</td>
<td>100%</td>
<td>NA</td>
<td>Assumption</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3.5%</td>
<td>NA</td>
<td>Kristensen et al. (2016)⁹</td>
</tr>
<tr>
<td>II</td>
<td>77.1%</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>19%</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0.4%</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>LV EE, %, mean (range)</td>
<td>31.6% (31.1–32.1%)</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Event probabilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality: sacubitril/valsartan HR</td>
<td>0.80 (0.71–0.89)</td>
<td>LogNormal</td>
<td>PARADIGM-HF trial⁷,⁸</td>
</tr>
<tr>
<td>Hospitalization: sacubitril/valsartan HR</td>
<td>0.84 (0.78–0.91)</td>
<td>LogNormal</td>
<td>PARADIGM-HF trial⁷,⁸</td>
</tr>
<tr>
<td>Monthly probability of hospitalization (enalapril)</td>
<td>0.044 (0.038–0.051)</td>
<td>Beta</td>
<td>PARADIGM-HF trial⁷,⁸</td>
</tr>
<tr>
<td>Discontinuation: sacubitril/valsartan HR</td>
<td>0.89 (0.81–0.99)</td>
<td>LogNormal</td>
<td>PARADIGM-HF trial⁷,⁸</td>
</tr>
<tr>
<td>Monthly probability of discontinuation (enalapril)</td>
<td>0.0104 (0.0050–0.0210)</td>
<td>Beta</td>
<td>PARADIGM-HF trial⁷,⁸</td>
</tr>
<tr>
<td>Costs, €</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan, per month</td>
<td>126.36</td>
<td>NA</td>
<td>Italian Medicines Agency⁹</td>
</tr>
<tr>
<td>Enalapril, per month</td>
<td>9.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background therapy, per month</td>
<td>23.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per hospitalization</td>
<td>4898.11 (3673.58–6122.63)</td>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>HF management, per month</td>
<td>52.42 (39.32–65.53)</td>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>Utility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline utility</td>
<td>0.78 (0.663–0.897)</td>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>Utility effect of sacubitril/valsartan</td>
<td>+0.011 (+0.004–+0.017)</td>
<td>Beta</td>
<td></td>
</tr>
</tbody>
</table>

Incremental costs (€) and quality-adjusted life years (QALYs) gained in comparisons of sacubitril/valsartan with enalapril

**Recommendations for diagnostic tests in patients with heart failure**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient’s suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- haemoglobin and WBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- sodium, potassium, urea, creatinine (with estimated GFR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- liver function tests (bilirubin, AST, ALT, GGTP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- glucose, HbA1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- lipid profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- TSH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ferritin, TSAT = TIBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- natriuretic peptides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Class**: I, IIa

**Level**: C, C
### 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iron deficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin &lt;100 μg/L, or ferritin between 100–299 μg/L and transferrin saturation &lt;20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.</td>
<td>IIA</td>
<td>A</td>
</tr>
</tbody>
</table>
Prevalence of iron deficiency (ID) in CHF
ID: ferritin <100 µg/dL, or 100-299 µg/dL with TSat <20%

Role of iron deficiency in the pathogenesis of exercise intolerance

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials

Ewa A. Jankowska, Michał Tkaczyszyn, Tomasz Suchocki, Marcin Drozd, Stephan von Haehling, Wolfram Doehner, Waldemar Banasiak, Gerasimos Filippatos, Stefan D. Anker, and Piotr Ponikowski

Table 1 Continued

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Placebo</td>
<td>Treatment</td>
<td>Placebo</td>
<td>Treatment</td>
</tr>
<tr>
<td>Number of patients randomized</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>304</td>
</tr>
<tr>
<td>No. of patients who completed the study (≥ reached endpoint)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>Age (years)</td>
<td>76 ± 7</td>
<td>74 ± 8</td>
<td>64 ± 5</td>
<td>62 ± 11</td>
<td>68 ± 70</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>NT-proBNP (ng/mL)</td>
<td>291 ± 126</td>
<td>287 ± 118</td>
<td>291 ± 126</td>
<td>287 ± 118</td>
<td>32 ± 6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>21 ± 4</td>
<td>21 ± 4</td>
<td>21 ± 4</td>
<td>21 ± 4</td>
<td>3.5 ± 0.5</td>
</tr>
<tr>
<td>NYHA class</td>
<td>60</td>
<td>65</td>
<td>60</td>
<td>65</td>
<td>75</td>
</tr>
<tr>
<td>Iron target (%)</td>
<td>72 ± 30</td>
<td>71 ± 31</td>
<td>72 ± 30</td>
<td>71 ± 31</td>
<td>80.6</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>10.3 ± 0.6</td>
<td>10.3 ± 0.3</td>
<td>10.3 ± 0.6</td>
<td>10.3 ± 0.3</td>
<td>12.6 ± 2.2</td>
</tr>
<tr>
<td>Anaemia (%)</td>
<td>50</td>
<td>65</td>
<td>50</td>
<td>65</td>
<td>65</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± standard deviation of the mean.

- Given zero events in both the iron and placebo arm, this study was excluded from the analysis.
- Complete data mean ± SD regarding the change from baseline not available for the treatment and control arms separately.
- Data from the meta-analysis of Kasper et al.
- 304 patients were randomized to FCM but one patient assigned to the placebo group received FCM instead and therefore the number of patients treated was 305.
- Mean NYHA class as a continuous variable was calculated by the authors of this meta-analysis.
Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials

<table>
<thead>
<tr>
<th>EQ-5D score</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean difference</th>
<th>MD</th>
<th>95% CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Total Mean</td>
<td>SD</td>
<td>Total Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Anker et al. 2009</td>
<td>285 9.1</td>
<td>17.43</td>
<td>146 3.4</td>
<td>18.80</td>
<td>5.70 [2.04; 9.36]</td>
<td>50.7%</td>
</tr>
<tr>
<td>5. Ponikowski et al. 2015</td>
<td>114 6.2</td>
<td>13.57</td>
<td>106 3.8</td>
<td>14.64</td>
<td>2.40 [-1.34; 6.14]</td>
<td>49.3%</td>
</tr>
<tr>
<td>Random effects model</td>
<td>399 252</td>
<td></td>
<td></td>
<td></td>
<td>4.07 [0.84; 7.31]</td>
<td>100% z = 2.4686 P=0.0136</td>
</tr>
<tr>
<td>Heterogeneity: I² = 24.6%, tau² = 1.882, p = 0.2163</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q = 1.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KCCQ score</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean difference</th>
<th>MD</th>
<th>95% CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Total Mean</td>
<td>SD</td>
<td>Total Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Ponikowski et al. 2015</td>
<td>114 6.55</td>
<td>15.386</td>
<td>106 2.15</td>
<td>14.517</td>
<td>4.40 [0.45; 8.35]</td>
<td>49.1%</td>
</tr>
<tr>
<td>Random effects model</td>
<td>400 251</td>
<td></td>
<td></td>
<td></td>
<td>5.52 [2.75; 8.29]</td>
<td>100% z = 3.9059 P&lt;0.0001</td>
</tr>
<tr>
<td>Heterogeneity: I² = 0%, tau² = 0, p = 0.4364</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q = 0.61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PGA</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean difference</th>
<th>MD</th>
<th>95% CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Total Mean</td>
<td>SD</td>
<td>Total Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Okonko et al. 2008</td>
<td>20 1.50</td>
<td>1.20</td>
<td>10 -0.20</td>
<td>1.60</td>
<td>1.70 [0.58; 2.82]</td>
<td>10.4%</td>
</tr>
<tr>
<td>3. Anker et al. 2009</td>
<td>292 1.31</td>
<td>1.32</td>
<td>149 0.68</td>
<td>1.48</td>
<td>0.63 [0.35; 0.91]</td>
<td>53.0%</td>
</tr>
<tr>
<td>5. Ponikowski et al. 2015</td>
<td>127 0.46</td>
<td>1.85</td>
<td>119 -0.06</td>
<td>1.80</td>
<td>0.52 [0.06; 0.98]</td>
<td>36.6%</td>
</tr>
<tr>
<td>Random effects model</td>
<td>439 278</td>
<td></td>
<td></td>
<td></td>
<td>0.70 [0.31; 1.09]</td>
<td>100% z = 3.5223 P&lt;0.0004</td>
</tr>
<tr>
<td>Heterogeneity: I² = 45.8%, tau² = 0.0535, p = 0.1573</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q = 3.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MLHFQ score</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean difference</th>
<th>MD</th>
<th>95% CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Total Mean</td>
<td>SD</td>
<td>Total Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Teblli et al. 2007</td>
<td>20 -19</td>
<td>6</td>
<td>20 1</td>
<td>7</td>
<td>-20.00 [-24.04; -15.96]</td>
<td>92.5%</td>
</tr>
<tr>
<td>2. Okonko et al. 2008</td>
<td>20 -10</td>
<td>18</td>
<td>10 3</td>
<td>19</td>
<td>-13.00 [-27.17; 1.17]</td>
<td>7.5%</td>
</tr>
<tr>
<td>Random effects model</td>
<td>40 30</td>
<td></td>
<td></td>
<td></td>
<td>-19.47 [-23.36; -15.59]</td>
<td>100% z = -9.8226 P&lt;0.0001</td>
</tr>
<tr>
<td>Heterogeneity: I² = 0%, tau² = 0, p = 0.2515</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q = 0.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials

<table>
<thead>
<tr>
<th>All-cause death</th>
<th>Cardiovascular death</th>
<th>All-cause death or cardiovascular hospitalization</th>
<th>Cardiovascular death or hospitalization for worsening HF</th>
<th>HF hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Experimental Events Total</strong></td>
<td><strong>Control Events Total</strong></td>
<td><strong>Odds Ratio</strong></td>
<td><strong>OR 95%-CI W(random)</strong></td>
</tr>
<tr>
<td>1. Toblli et al. 2007</td>
<td>0 26</td>
<td>5 20</td>
<td>0.97 [0.80; 1.24]</td>
<td>3.7%</td>
</tr>
<tr>
<td>2. Okonko et al. 2008</td>
<td>2 24</td>
<td>0 11</td>
<td>1.47 [0.96; 1.89]</td>
<td>4.7%</td>
</tr>
<tr>
<td>3. Anker et al. 2009</td>
<td>4 305</td>
<td>4 154</td>
<td>0.50 [0.32; 0.82]</td>
<td>25.7%</td>
</tr>
<tr>
<td>4. Beck-da-Silva et al. 2013</td>
<td>2 10</td>
<td>1 5</td>
<td>1.25 [0.96; 1.65]</td>
<td>51.1%</td>
</tr>
<tr>
<td>5. Ponikowski et al. 2015</td>
<td>12 150</td>
<td>14 151</td>
<td>0.86 [0.38; 1.91]</td>
<td>69.7%</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2$-squared [%, $Q$-value, $p$-value]

Q = 0.39

Q = 0.67

Q = 0.59

Q = 0.41

Q = 0.36

Q = 0.36

Q = 0.02

Q = 1.3

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34

Q = 0.02

Q = 0.34
Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>ICD is recommended in patients:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction,</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>in order to prevent sudden death and prolong life..</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SGLT-2 inhibitors

Inhibit proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower BP and reduce weight. Also renoprotective (in diabetes)?
The sodium-glucose cotransporter-2 (SGLT2) inhibitors in antidiabetic treatment

Thiazide diuretics

Loop diuretics

Increased urinary glucose and sodium excretion

Modified from Nikolaus Marx, and Darren K. McGuire Eur Heart J 2016;37:3192-3200
Empagliflozin, cardiovascular outcomes and mortality. EMPA-REG Outcome trial
Outcomes in patients with and without heart failure at baseline in EMPA-REG Outcome trial

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n with event/n</td>
<td>n with event/n</td>
<td></td>
</tr>
<tr>
<td>Heart failure hospitalization or cardiovascular death</td>
<td>265/4687                198/2333</td>
<td>0.66 (0.55–0.79)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>265/4687 5.7%</td>
<td>198/2333 8.5%</td>
<td></td>
</tr>
<tr>
<td>Heart failure at baseline</td>
<td>75/462 16.2%</td>
<td>49/244 20.1%</td>
<td>0.72 (0.50–1.04)</td>
</tr>
<tr>
<td>No</td>
<td>190/4225 4.5%</td>
<td>149/2089 7.1%</td>
<td>0.63 (0.51–0.78)</td>
</tr>
<tr>
<td>Yes</td>
<td>75/462 16.2%</td>
<td>49/244 20.1%</td>
<td>0.72 (0.50–1.04)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>126/4687 2.7%</td>
<td>95/2333 4.1%</td>
<td>0.65 (0.50–0.85)</td>
</tr>
<tr>
<td>All patients</td>
<td>126/4687 2.7%</td>
<td>95/2333 4.1%</td>
<td>0.65 (0.50–0.85)</td>
</tr>
<tr>
<td>Heart failure at baseline</td>
<td>78/4225 1.8%</td>
<td>65/2089 3.1%</td>
<td>0.59 (0.43–0.82)</td>
</tr>
<tr>
<td>No</td>
<td>78/4225 1.8%</td>
<td>65/2089 3.1%</td>
<td>0.59 (0.43–0.82)</td>
</tr>
<tr>
<td>Yes</td>
<td>48/462 10.4%</td>
<td>30/244 12.3%</td>
<td>0.75 (0.48–1.19)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>172/4687 3.7%</td>
<td>137/2333 5.9%</td>
<td>0.62 (0.49–0.77)</td>
</tr>
<tr>
<td>All patients</td>
<td>172/4687 3.7%</td>
<td>137/2333 5.9%</td>
<td>0.62 (0.49–0.77)</td>
</tr>
<tr>
<td>Heart failure at baseline</td>
<td>134/4225 3.2%</td>
<td>110/2089 5.3%</td>
<td>0.60 (0.47–0.77)</td>
</tr>
<tr>
<td>No</td>
<td>134/4225 3.2%</td>
<td>110/2089 5.3%</td>
<td>0.60 (0.47–0.77)</td>
</tr>
<tr>
<td>Yes</td>
<td>38/462 8.2%</td>
<td>27/244 11.1%</td>
<td>0.71 (0.43–1.16)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>269/4687 5.7%</td>
<td>194/2333 8.3%</td>
<td>0.68 (0.57–0.82)</td>
</tr>
<tr>
<td>All patients</td>
<td>269/4687 5.7%</td>
<td>194/2333 8.3%</td>
<td>0.68 (0.57–0.82)</td>
</tr>
<tr>
<td>Heart failure at baseline</td>
<td>213/4225 5.0%</td>
<td>159/2089 7.6%</td>
<td>0.66 (0.51–0.81)</td>
</tr>
<tr>
<td>No</td>
<td>213/4225 5.0%</td>
<td>159/2089 7.6%</td>
<td>0.66 (0.51–0.81)</td>
</tr>
<tr>
<td>Yes</td>
<td>56/462 12.1%</td>
<td>35/244 14.3%</td>
<td>0.79 (0.52–1.20)</td>
</tr>
</tbody>
</table>

David Fitchett et al. Eur Heart J 2016;37:1526-1534
Potential mechanisms involved in the reduction of CV events (cardiovascular death, total mortality, and HF hospitalization) observed in the EMPA-REG OUTCOME trial

SGLT2 inhibition (Empagliflozin)

EMPA-REG OUTCOME

Nikolaus Marx, and Darren K. McGuire Eur Heart J 2016;37:3192-3200
Impact of glucose-lowering drugs on HF hospitalizations

Fitchett, Udell, Inzucchi Eur J Heart Fail 2016. doi:10.1002/ejhf.633
Comparison of all-cause mortality reductions in HF trials and in CV outcomes trials in diabetics

Fitchett, Udell, Inzucchi Eur J Heart Fail 2016. doi:10.1002/ejhf.633
<table>
<thead>
<tr>
<th>Drug</th>
<th>Cohort</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin*</td>
<td>Chronic HF</td>
<td>Change from baseline aerobic exercise capacity at 12 weeks&lt;br&gt;Change from baseline ventilator efficiency at 12 weeks</td>
</tr>
<tr>
<td>Dapagliflozin*</td>
<td>Chronic HF</td>
<td>Time to first occurrence of CV death or hospitalization for HF or urgent HF visit&lt;br&gt;Time to first occurrence of ≥50% sustained decline in eGFR or reaching ESRD or CV death or renal death</td>
</tr>
<tr>
<td>Empagliflozin*</td>
<td>HFrEF  &lt;br&gt; HFrEF</td>
<td>Time to first adjudicated CV death or adjudicated hospitalization for HF</td>
</tr>
<tr>
<td>Luseogliflozin</td>
<td>HFrEF</td>
<td>Change in BNP at 12 weeks</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Sotagliflozin</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

* Currently approved by Food and Drug Administration and European Medicines Agency
Thromboembolic risk stratification of patients hospitalized with heart failure in sinus rhythm: a nationwide cohort study

Emil Wolsk1*, Morten Lamberts1, Morten L. Hansen1, Paul Blanche2, Lars Køber3, Christian Torp-Pedersen4, Gregory Y. H. Lip5,†, and Gunnar Gislason1,6,‡

1Department of Cardiology, Gentofte Hospital, University of Copenhagen, Gentofte, Denmark; 2Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark; 3The Heart Centre, Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; 4Institute of Health, Science and Technology, Aalborg University, Aalborg, Denmark; 5University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; and 6The National Institute of Public Health, University of Southern Denmark, Odense, Denmark.

Received 7 January 2015; revised 25 February 2015; accepted 20 May 2015; online publish-ahead-of-print 2 July 2015.

Aims
Patients with heart failure in sinus rhythm are at an increased risk of thromboembolic complications. So far, validated risk stratification tools are lacking for such patients, which makes the decision to initiate anti-thrombotic treatment difficult.

Methods and results
We included 136 545 patients admitted with heart failure in sinus rhythm from national registries from 1999 to 2012. Patients receiving oral anticoagulants were omitted from the study. First, we investigated if the CHA2DS2-VASc
Thromboembolism according to CHA$_2$DS$_2$-VASc classification. Data from 136 545 patients admitted with HF in sinus rhythm from national registries, 1999 to 2012.

In patients with all CHA2DS2-VASc risk factors, vs. with the others:
Risk of TE events > 9-fold (HR 9.2, 6.8–12.5)
The rates of TE events of 6.0 (95%CI, 5.98–6.02) per 100 patient years in the 1st year after diagnosis

Wolsk et al. Eur J Heart Fail 2015; 17: 828-836,
Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial

Faiez Zannad¹, Barry Greenberg², John G.F. Cleland³, Mihai Gheorghiade⁴, Dirk J. van Veldhuisen⁵, Mandeep R. Mehra⁶, William M. Byra⁷, Min Fu⁷, and Roger M. Mills⁷*
Two new potassium binders (patiromer and sodium zirconium cyclosilicate) are currently under consideration for regulatory approval.\textsuperscript{453,454} Initial results from patients with HF are available and confirm the efficacy of these therapies in reducing serum potassium\textsuperscript{455} and preventing recurrent hyperkalaemia in patients with HF and CKD in the context of treatment with RAAS inhibitors.\textsuperscript{456}
Sodium Zirconium Cyclosilicate in Hyperkalemia

David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.

K+ = potassium, Z = zirconium, S = silicon

This article was published on November 21, 2014, at NEJM.org.

DOI: 10.1056/NEJMoal411487
Mean serum potassium after randomization

Anker et al. Eur J Heart Fail; 16 JUN 2015 DOI: 10.1002/ejhf.300
Serum potassium levels over time in OPAL-HK Trial

Pitt et al. Eur J Heart Fail; doi:10.1002/ejhf.402
A propitious time for initiating clinical trials in patients with heart failure with reduced ejection fraction and an estimated glomerular filtration rate <30 mL/min with an mineralocorticoid receptor antagonist and a K⁺ binder: ‘the forbidden fruit’

Murray Epstein¹ and Bertram C. Pitt²
Inotropic agents for the treatment of heart failure

- Sympathomimetic agents
- PDE-3 Inhibitors
- Levosimendan
  - Intermittent administration
- SERCA Activators, istoroxime
- Myosin activators, omecamtv mecarbil
- Mitochondrial targeted peptides, elamipretide
- Recombinant neoregulin
Omecamtiv mecarbil: A small molecule selective cardiac myosin activator

**Mechanochemical Cycle of Myosin**

OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin

“More hands pulling on the rope”

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in $dP/dt_{max}$
- No increase in $MVO_2$

CONCLUSIONS  In patients with AHF, intravenous OM did not meet the primary endpoint of dyspnea improvement, but it was generally well tolerated, it increased systolic ejection time, and it may have improved dyspnea in the high-dose group. (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure [ATOMIC-AHF]; NCT01300013) (J Am Coll Cardiol 2016;67:1444-55) © 2016 by the American College of Cardiology Foundation.
Left Ventricular Systolic Ejection Time versus plasma omecamtiv mecarbil concentrations in ATOMIC-AHF

John R. Teerlink et al. JACC 2016;67:1444-1455
Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial


Findings From March 17, 2014, to March 5, 2015, we enrolled 150 patients in the fixed-dose omecamtiv mecarbil group and 149 in the pharmacokinetic-titration and placebo groups. Mean maximum concentration of omecamtiv mecarbil at 12 weeks was 200 (SD 71) ng/mL in the fixed-dose group and 318 (129) ng/mL in the pharmacokinetic-titration group. For the pharmacokinetic-titration group versus placebo group at 20 weeks, least square mean differences were as follows: systolic ejection time 25 ms (95% CI 18–32, p<0·0001), stroke volume 3·6 mL (0·5–6·7, p=0·0217), left ventricular end-systolic diameter −1·8 mm (−2·9 to −0·6, p=0·0027), left ventricular end-diastolic diameter −1·3 mm, (−2·3 to 0·3, p=0·0128), heart rate −3·0 beats per min (−5·1 to −0·8, p=0·0070), and N-terminal pro B-type natriuretic peptide concentration in plasma −970 pg/mL (−1672 to −268, p=0·0069). The frequency of adverse clinical events did not differ between groups.

Interpretation Omecamtiv mecarbil dosing guided by pharmacokinetics achieved plasma concentrations associated with improved cardiac function and decreased ventricular diameter.
Omecamtiv mecarbil in HFrEF: COSMIC-HF
Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction

Amgen Protocol Number (Omecamtiv Mecarbil [AMG 423]) 20110203

EudraCT number 2016-002299-28

GALACTIC-HF

Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure

Study Design and Treatment Schema

2 years enrollment, approx. 4 years total follow-up/study period

Subject source

Chronic HFpEF patients currently hospitalized for a primary reason of HF or with history of hospitalization or ER/ED admission for a primary reason of HF within 1 year.

Screening

Randomization 1:1

Blinded by randomization and region

Omecamtiv mecarbil + SoC

Starting dose: 25 mg PO BID

Placebo + SoC

Follow the same study procedures as OM group to ensure blinding

Study Visits:

PK assessment for dose adjustment

PK assessment
Quali novità nel trattamento dell’insufficienza cardiaca

- Sacubitril/ valsartan
- Iron
- SGLT-2 Inhibitors
- K binders
- Inotropic agents
- Guanilate cyclase activators
- Metabolic agents
Soluble guanylyl cyclase (sGC) stimulation to increase cGMP
Original Investigation

Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction

The SOCRATES-REDUCED Randomized Trial

Mihai Gheorghiade, MD; Stephen J. Greene, MD; Javed Butler, MD, MPH, MBA; Gerasimos Filippatos, MD; Carolyn S. P. Lam, MBBS, Aldo P. Maggioni, MD; Piotr Ponikowski, MD; Sanjiv J. Shah, MD; Scott D. Solomon, MD; Elisabeth Kraigher-Krainer, MD; Eliana T. Samano, MD; Katharina Müller, DiplStat; Lothar Roessig, MD; Burkert Pieske, MD; for the SOCRATES-REDUCED Investigators and Coordinators

CONCLUSIONS AND RELEVANCE Among patients with worsening chronic HF and reduced LVEF, compared with placebo, vericiguat did not have a statistically significant effect on change in NT-proBNP level at 12 weeks but was well-tolerated. Further clinical trials of vericiguat based on the dose-response relationship in this study are needed to determine the potential role of this drug for patients with worsening chronic HF.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01951625

JAMA. doi:10.1001/jama.2015.15734
Published online November 8, 2015.
SOCRATES Reduced (Exploratory analyses)

Placebo-corrected change in NT-proBNP from baseline (expressed as a ratio of geometric means)
SOCRATES Reduced

CV death or HF hospitalization

![Graph showing the proportion of patients experiencing the composite of CV death and HF hospitalization over time for different groups. The Placebo group shows the highest proportion of events, followed by the Vericiguat 2.5-10mg group, which shows a lower and more linear increase in events.]

- Placebo group
- Vericiguat 2.5-10mg group
HNO Enhances Contractility and Relaxation

**HNO enhances RyR activity**
- Open probability of RyR increased

**HNO enhances SERCa activity**
- Formation of disulfide bonds between Phospholamban monomers

**HNO enhances myofilament calcium sensitivity**
- Formation of disulfide bonds in Actin, Myosin light chain, and Tropomyosin

---

Ica, L-type calcium current; CONT, control; AS, Angeli’s Salt; SR, sarcoplasmic reticulum; NCX, Na-Ca exchanger; RyR, ryanodine receptor

References:
1. Kohr, et al., Front Biosci., 2009
4. Murray et al., JACC, 2009
5. Froehlich, et al., Biochem., 2008
A Phase 2a dose-escalation study of the safety, tolerability, pharmacokinetics and haemodynamic effects of BMS-986231 in hospitalized patients with heart failure with reduced ejection fraction

Cristina Tita¹, Edward M. Gilbert², Adrian B. Van Baelen³, Jacek Grzybowski⁴, Garrin J. Haas⁵, Mohammad Jarrah⁶, Stephanie H. Dunlap⁷, Stephen S. Gottlieb⁸, Marc Klapcho⁹, Parag C. Patel¹⁰, Roman Pfister¹¹, Tim Seidler¹², Kayur B. Shah¹³, Tomasz Zielinski¹⁴, Robert P. Vemuri¹⁵, Douglas Cowart¹⁶, Shi Yin Foo¹⁷, Alexander Vishnevsky¹⁸, and Veselin Mitrovic¹⁹

PAWP
Chronic Therapy With Elamipretide (MTP-131), a Novel Mitochondria-Targeting Peptide, Improves Left Ventricular and Mitochondrial Function in Dogs With Advanced Heart Failure

Hani N. Sabbah, PhD; Ramesh C. Gupta, PhD; Smita Kohli, MD; Mengjun Wang, MD; Souheila Hachem, BS; Kefei Zhang, MD

Background—Elamipretide (MTP-131), a novel mitochondria-targeting peptide, was shown to reduce infarct size in animals with myocardial infarction and improve renal function in pigs with acute and chronic kidney injury. This study examined the effects of chronic therapy with elamipretide on left ventricular (LV) and mitochondrial function in dogs with heart failure (HF).

Methods and Results—Fourteen dogs with microembolization-induced HF were randomized to 3 months monotherapy with subcutaneous injections of elamipretide (0.5 mg/kg once daily, HF+ELA, n=7) or saline (control, HF-CON, n=7). LV ejection fraction, plasma n-terminal pro-brain natriuretic peptide, tumor necrosis factor-α, and C-reactive protein were measured before (pretreatment) and 3 months after initiating therapy (post-treatment). Mitochondrial respiration, membrane potential (Δψm), maximum rate of ATP synthesis, and ATP/ADP ratio were measured in isolated LV cardiomyocytes obtained at post-treatment. In HF-CON dogs, ejection fraction decreased at post-treatment compared with pretreatment (29±1% versus 31±2%), whereas in HF+ELA dogs, ejection fraction significantly increased at post-treatment compared with pretreatment (36±2% versus 30±2%; P<0.05). In HF-CON, n-terminal pro-brain natriuretic peptide increased by 88±120 pg/mL during follow-up but decreased significantly by 774±85 pg/mL in HF+ELA dogs (P<0.001). Treatment with elamipretide also normalized plasma tumor necrosis factor-α and C-reactive protein and restored mitochondrial state-3 respiration, Δψm, rate of ATP synthesis, and ATP/ADP ratio (ATP/ADP: 0.38±0.04 HF-CON versus 1.16±0.15 HF+ELA; P<0.001).

Conclusions—Long-term therapy with elamipretide improves LV systolic function, normalizes plasma biomarkers, and reverses mitochondrial abnormalities in LV myocardium of dogs with advanced HF. The results support the development of elamipretide for the treatment of HF. (Circ Heart Fail. 2016;9:e002206. DOI: 10.1161/CIRCHEARTFAILURE.115.002206.)
Elamipretide on plasma neurohormones

2 Hours Intravenous Infusion

3 Months Subcutaneous Treatment

Treatment Effect, $\Delta$

- **EDV (ml)**
  - Saline Control Infusion
  - Elamipretide Infusion
  - $p=0.145$
  - $p=0.006$
  - $p=0.028$

- **ESV (ml)**
  - $p=0.012$

- **EF (%)**
  - $p=0.08$
  - $p=0.001$
  - $p=0.05$

- **SV (ml)**

- **EDV (ml)**
- **ESV (ml)**
- **EF (%)**
- **FAS (%)**
Elamipretide on plasma neurohormones
Clinical development plan for regenerative therapy in heart failure

Andre Terzic¹, Atta Behfar¹, and Gerasimos Filippatos²*

[Diagram showing process comparison between routine and recommended practices]
The quest for a successful cell-based therapeutic approach for heart failure

Ana Marie Landin¹ and Joshua M. Hare¹,²*

Table 1  Cell types under investigation in cell-based therapy trials for heart failure

<table>
<thead>
<tr>
<th>Cell types</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated BM-MNCs</td>
<td>Ischaemic heart failure and chronic heart failure</td>
</tr>
<tr>
<td>CD34⁺ stem cells</td>
<td>Chronic ischaemic failure</td>
</tr>
<tr>
<td>Mesenchymal precursor cells</td>
<td>Ischaemic heart failure</td>
</tr>
<tr>
<td>Adipose tissue derived MSCs</td>
<td>Ischaemic and non-ischaemic heart failure</td>
</tr>
<tr>
<td>Bone marrow-derived MSCs</td>
<td>Ischaemic and non-ischaemic heart failure</td>
</tr>
<tr>
<td>Cardiosphere-derived cells</td>
<td>Ischaemic heart failure</td>
</tr>
<tr>
<td>Cardiac c-Kit cells</td>
<td>Ischaemic heart failure</td>
</tr>
<tr>
<td>Cardiopoietic stem cells</td>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>Induced pluripotent cell-derived cardiomyocytes</td>
<td>Chronic heart failure</td>
</tr>
</tbody>
</table>

*Corresponding author.
Congestive Heart Failure Cardiopoiotic Regenerative Therapy (CHART-1) trial design

Cardiopoiotic cell therapy for advanced ischemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial.

Jozef Bartunek1, Beth Davison3, Warren Sherm, Timothy D. Henry5, Bernard Gersh6, Marco Me, Roger Hajjar9, Atta Behfar4, Christian Homsy3, Michal Tendera10, and Andre Terzic6

Benefit of cardiopoiotic mesenchymal stem cell therapy on left ventricular remodelling: results from the Congestive Heart Failure Cardiopoiotic Regenerative Therapy (CHART-1) study

CHART-1 Clinical Trial
Changes in LV EDV and LV ESV at 52 Weeks

LV volume reduction achieved on top of maximally tolerated standard-of-care
Extent of LV remodeling compares favorably to effects of established HF therapies

![Graph showing changes in LV EDV and ESV reduction over study weeks.](chart-1-clinical-trial.png)

CHART-1 Clinical Trial
Changes in LV EDV and LV ESV at 52 Weeks

Reversed remodeling inversely related to number of injections

P value as compared to control

Exploratory Analysis at 52 weeks
Hierarchical Outcome as a Function of Baseline LV EDV and Treatment Intensity