State of the Art of Drug Therapy in Heart Failure

-What is still missing?

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ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC
Diuretics to relieve symptoms/signs of congestion

ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

ADD a MR antagonist

Still NYHA class II–IV!

Yes

LVEF ≤35%?

Yes

Sinus rhythm and HR ≥70 beats/min?

Yes

ADD ivabradine

Still NYHA class II–IV and LVEF ≤35%!

Yes

QRS duration ≥120 ms?

Yes

Consider CRT-P/CRT-D

Consider ICD

Still NYHA class II–IV?

Yes

Consider digoxin and/or H-1SDN

No further specific treatment

Continue in disease-management programme

No

No

No

No

No

No

No

No

No

No

No

No

No
Diuretics to relieve symptoms/signs of congestion

ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

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ADD a MR antagonist

Still NYHA class II–IV?

LVEF ≤35%?

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Sinus rhythm and HR ≥70 beats/min?

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Still NYHA class II–IV and LVEF ≤35%?

Yes

No

QRS duration ≥120 ms?

Yes

No

Consider CRT-P/CRT-D

Consider ICD

Still NYHA class II–IV?

Yes

No

No further specific treatment

Continue in disease-management programme

Consider digoxin and/or Hydralazine

if end stage, consider LVAD and/or transplantation
## Beta-blocker dose and heart rate reduction in chronic HF patients

23 trials in 19,209 HF patients with beta-blocker (mean EF=17%-36%)

Results of 13 univariable meta-regressions evaluating the effect of individual covariates on mortality benefits of beta-blockers in heart failure

<table>
<thead>
<tr>
<th>Potential Modifier</th>
<th>Trials, n</th>
<th>Patients, n</th>
<th>Ratio of Relative Risks (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of men</td>
<td>21</td>
<td>18,773</td>
<td>0.93 (0.79-1.10) per 10% increment</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean age</td>
<td>21</td>
<td>18,773</td>
<td>1.04 (0.86-1.24) per decade</td>
<td>0.69</td>
</tr>
<tr>
<td>Percentage with an Ischemic cause</td>
<td>21</td>
<td>18,773</td>
<td>0.99 (0.86-1.14) per 20% increment</td>
<td>0.88</td>
</tr>
<tr>
<td>Mean baseline LVEF</td>
<td>20</td>
<td>18,392</td>
<td>1.04 (0.92-1.18) per 5% increment</td>
<td>0.54</td>
</tr>
<tr>
<td>Percentage with NYHA class III or IV symptoms</td>
<td>21</td>
<td>18,773</td>
<td>1.00 (0.96-1.05) per 10% increment</td>
<td>0.84</td>
</tr>
<tr>
<td>Percentage with atrial fibrillation</td>
<td>8</td>
<td>8,915</td>
<td>1.00 (0.91-1.09) per 5% increment</td>
<td>0.95</td>
</tr>
<tr>
<td>Percentage of digoxin use</td>
<td>19</td>
<td>18,336</td>
<td>1.01 (0.96-1.06) per 10% increment</td>
<td>0.64</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>19</td>
<td>17,981</td>
<td>1.07 (0.88-1.32) per 5 beats/min</td>
<td>0.47</td>
</tr>
<tr>
<td>Heart rate reduction*</td>
<td>17</td>
<td>17,831</td>
<td>0.82 (0.71-0.94) per 5 beats/min</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>β-Blocker dose</strong></td>
<td>17</td>
<td>17,660</td>
<td>1.02 (0.93-1.10) per increment</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean Baseline SBP</td>
<td>17</td>
<td>17,516</td>
<td>1.00 (0.73-1.35) per 20 mm Hg</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean SBP reduction</td>
<td>10</td>
<td>5,462</td>
<td>1.02 (0.87-1.20) per 2 mm Hg</td>
<td>0.78</td>
</tr>
<tr>
<td>Agent</td>
<td>21</td>
<td>18,773</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>–</td>
<td>–</td>
<td>Reference</td>
<td>–</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>–</td>
<td>–</td>
<td>1.05 (0.82-1.35)</td>
<td>0.68</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>–</td>
<td>–</td>
<td>1.03 (0.77-1.38)</td>
<td>0.85</td>
</tr>
<tr>
<td>Atenolol</td>
<td>–</td>
<td>–</td>
<td>0.89 (0.29-2.76)</td>
<td>0.83</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>–</td>
<td>–</td>
<td>1.36 (1.09-1.69)</td>
<td>0.009</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>–</td>
<td>–</td>
<td>1.30 (0.99-1.71)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Beta-Blockers and Outcome in Heart Failure and Atrial Fibrillation
A Meta-Analysis

Beta-Blocker: HR Reduction in Atrial Fibrillation and Sinus Rhythm

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Beta-Blocker Mean [bpm]</th>
<th>SD [bpm]</th>
<th>Total</th>
<th>Placebo Mean [bpm]</th>
<th>SD [bpm]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI [bpm]</th>
<th>Mean Difference IV, Fixed, 95% CI [bpm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>-8.8</td>
<td>21.5</td>
<td>257</td>
<td>-0.2</td>
<td>13.7</td>
<td>264</td>
<td>4.9%</td>
<td>-8.60 [-11.70, -5.50]</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>14.8</td>
<td>21.5</td>
<td>274</td>
<td>-4</td>
<td>23</td>
<td>282</td>
<td>3.4%</td>
<td>-10.80 [-14.50, -7.10]</td>
<td></td>
</tr>
<tr>
<td>SENIORS</td>
<td>11</td>
<td>21.5</td>
<td>327</td>
<td>2.8</td>
<td>22.98</td>
<td>337</td>
<td>4.1%</td>
<td>-8.20 [-11.58, -4.82]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>858</td>
<td></td>
<td></td>
<td>883</td>
<td>12.4%</td>
<td></td>
<td></td>
<td>-9.08 [-11.02, -7.13]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.18$, df = 2 (P = 0.55); $I^2 = 0$
Test for overall effect: $Z = 9.14$ (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Beta-Blocker Mean [bpm]</th>
<th>SD [bpm]</th>
<th>Total</th>
<th>Placebo Mean [bpm]</th>
<th>SD [bpm]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI [bpm]</th>
<th>Mean Difference IV, Fixed, 95% CI [bpm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</td>
<td>-10.6</td>
<td>12.4</td>
<td>1014</td>
<td>-0.2</td>
<td>13.7</td>
<td>1004</td>
<td>36.1%</td>
<td>-10.40 [-11.54, -9.26]</td>
<td></td>
</tr>
<tr>
<td>SR</td>
<td>13.7</td>
<td>15.8</td>
<td>1569</td>
<td>-2.4</td>
<td>16.5</td>
<td>1563</td>
<td>36.7%</td>
<td>-11.30 [-12.43, -10.17]</td>
<td></td>
</tr>
<tr>
<td>SENIORS</td>
<td>-10.9</td>
<td>15.8</td>
<td>638</td>
<td>-1.9</td>
<td>16.5</td>
<td>619</td>
<td>14.7%</td>
<td>-9.00 [-10.79, -7.21]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>3221</td>
<td></td>
<td></td>
<td>3186</td>
<td>87.6%</td>
<td></td>
<td></td>
<td>-10.54 [-11.27, -9.81]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 4.64$, df = 2 (P = 0.10); $I^2 = 57$
Test for overall effect: $Z = 28.20$ (P < 0.00001)

Total (95% CI) 4079 4069 100.0% -10.36 [-11.05, -9.67]

Heterogeneity: $\chi^2 = 7.74$, df = 5 (P = 0.17); $I^2 = 35$
Test for overall effect: $Z = 29.62$ (P < 0.00001)
Test for subgroup differences: $\chi^2 = 1.91$, df = 1 (P = 0.17), $I^2 = 47.6$
**Beta-Blockers and Outcome in Heart Failure and Atrial Fibrillation**

A Meta-Analysis

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### Beta-Blocker: Mortality in Atrial Fibrillation and Sinus Rhythm

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Beta-Blocker Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>42</td>
<td>257</td>
<td>43</td>
<td>264</td>
<td>6·9%</td>
<td>1·00 [0·63, 1·60]</td>
<td></td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>30</td>
<td>274</td>
<td>31</td>
<td>282</td>
<td>5·3%</td>
<td>1·00 [0·58, 1·69]</td>
<td></td>
</tr>
<tr>
<td>SENIORS</td>
<td>38</td>
<td>227</td>
<td>51</td>
<td>237</td>
<td>8·1%</td>
<td>0·73 [0·46, 1·17]</td>
<td></td>
</tr>
<tr>
<td>US-Carvedilol</td>
<td>4</td>
<td>84</td>
<td>6</td>
<td>52</td>
<td>1·4%</td>
<td>0·38 [0·10, 1·43]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>842</td>
<td></td>
<td>835</td>
<td></td>
<td>21·6%</td>
<td>0·86 [0·66, 1·13]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>114</td>
<td></td>
<td>131</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 2·61, df = 3</td>
<td></td>
<td><strong>I² = 0%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z = 1·07 (P = 0·28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>105</td>
<td>1014</td>
<td>170</td>
<td>1004</td>
<td>29·7%</td>
<td>0·57 [0·44, 0·74]</td>
<td></td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>102</td>
<td>1563</td>
<td>160</td>
<td>1569</td>
<td>29·0%</td>
<td>0·61 [0·47, 0·80]</td>
<td></td>
</tr>
<tr>
<td>SENIORS</td>
<td>77</td>
<td>451</td>
<td>84</td>
<td>444</td>
<td>13·6%</td>
<td>0·88 [0·63, 1·24]</td>
<td></td>
</tr>
<tr>
<td>US-Carvedilol</td>
<td>18</td>
<td>612</td>
<td>25</td>
<td>346</td>
<td>6·0%</td>
<td>0·39 [0·21, 0·72]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>3640</td>
<td></td>
<td>3363</td>
<td></td>
<td>78·4%</td>
<td>0·63 [0·54, 0·73]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>302</td>
<td></td>
<td>439</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 6·71, df = 3</td>
<td></td>
<td><strong>I² = 55%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z = 5·88 (P &lt; 0·00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>4482</td>
<td></td>
<td>4198</td>
<td></td>
<td>100·0%</td>
<td>0·68 [0·59, 0·77]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>416</td>
<td></td>
<td>570</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 13·30, df = 7</td>
<td></td>
<td><strong>I² = 47%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z = 5·66 (P &lt; 0·00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences:</td>
<td>Chi² = 3·97, df = 1 (P = 0·046), I² = 74·8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Rienstra et al, JACC Heart Failure 1 (2013): 21-28
Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis

Dipak Kotecha, Jane Holmes, Henry Krum, Douglas G Altman, Luis Manzano, John G F Cleland, Gregory Y H Lip, Andrew J S Coats, Bert Andersson, Paulus Kirchhof, Thomas G von Lueder, Hans Wedel, Giuseppe Rosano, Marcelo C Shibata, Alan Rigby, Marcus D Flather, on behalf of the Beta-Blockers in Heart Failure Collaborative Group

**Survival**

![Graph A](image1)

- **β-blocker group**
- **Placebo group**

**HR 0.73 (95% CI 0.67–0.80); p<0.001**

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blocker group</td>
<td>7123</td>
</tr>
<tr>
<td>Placebo group</td>
<td>6819</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blocker group</td>
<td>5014 1798 722 1521 997 331 113</td>
</tr>
<tr>
<td>Placebo group</td>
<td>4604 1530 561 1542 1020 346 115</td>
</tr>
</tbody>
</table>

**HR 0.97 (95% CI 0.83–1.14); p=0.73**

Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis

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Survival

![Graph A](image1)

**Graph A**

- **β-blocker group**
- **Placebo group**

Survivors (%)

- **HR 0.73 (95% CI 0.67–0.80); p<0.001**

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<th>Time (years)</th>
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</tr>
<tr>
<td><strong>Placebo group</strong></td>
<td>6819</td>
</tr>
</tbody>
</table>

![Graph B](image2)

**Graph B**

- **HR 0.97 (95% CI 0.83–1.14); p=0.73**

Relationship between heart rate and mortality and morbidity in the irbesartan patients with heart failure and preserved systolic function trial (I-Preserve)

Michael Bohm1,*,†, Ana-Cristina Perez2,*,‡, Pardeep S. Jhund3, Jan C. Roll†,
Michel Komajda3, Michael R. Zilo4, Robert S. McKelvie3, Indor S Anand6,
Barry M. Massie5, Peter E. Carson6, and John J. V. McMurray5, on behalf of the
I-Preserve Committees and Investigators

Composite of cardiovascular death or heart failure hospitalization

Sinus Rhythm

Atrial Fibrillation

T1:38-61, T2:62-72, T3:73-124

T1:40-72, T2:73-85, T3:86-155

Böhm et al., Eur J Heart Fail, 2014
Chronic Heart Failure
- What is missing?

- Prospective Study in AFib
- Most likely not applicable!
Diuretics to relieve symptoms/signs of congestion

ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

ADD a MR antagonist

Still NYHA class II–IV?

Yes

LVEF ≤35%?

Yes

Sinus rhythm and HR ≥70 beats/min

Yes

ADD ivabradine

Still NYHA class II–IV and LVEF ≤35%?

Yes

QRS duration ≥120 ms?

Yes

Consider CRT-P/CRT-D

Still NYHA class II–IV?

Yes

Consider ICD

No

No further specific treatment
Continue in disease-management programme

Consider digoxin and/or H1SDN
If end stage, consider LVAD and/or transplantation
Finerenone, a Novel Selective Nonsteroidal Mineralocorticoid Receptor Antagonist Protects From Rat Cardiorenal Injury

Peter Kolkhof, PhD,* Martina Delbeck, PhD,* Axel Kreisscher, PhD,† Wolfram Steinke, PhD,‡ Elke Hartmann, PhD,§ Lars Bürfacker, PhD,¶ Frank Eimer, MD,* Barbara Albrecht-Küpper, PhD,* and Stefan Schöfer, MD†

**Graph A**

Heart Weight g/100 g BW

- Control Placebo
- 0.1 Finerenone
- 1 Finerenone
- 10 Finerenone
- 30 Finerenone
- 100 Finerenone
- Eplerenone

**Graph B**

DOCA

**Graph C**

proBNP pg/100μl

- Control Placebo
- 0.1 Finerenone
- 1 Finerenone
- 10 Finerenone
- 30 Finerenone
- 100 Finerenone
- Eplerenone

**Images E and F**

DOCA

DOCA+Fin
Results of ARTS-HF:
finerenone versus eplerenone in patients with worsening chronic heart failure and diabetes and/or chronic kidney disease

Gerasimos Filippatos, Stefan D Anker, Michael Böhm, Mihai Gheorghiade, Lars Kober, Henry Krum, Aldo P Maggioni, Piotr Ponikowski, Adriaan A Voors, Faiez Zannad, So-Young Kim, Christina Nowack, Giovanni Palombo, Peter Kolkhof, Nina Kimmeskamp-Kirschbaum, Alexander Pieper and Bertram Pitt,
for the MinerAlocorticoid Receptor AnTagonist Study In Heart Failure (ARTS-HF) Committees and Investigators
Incidence, Predictors, and Outcomes Related to Hypo- and Hyperkalemia in Patients With Severe Heart Failure Treated With a Mineralocorticoid Receptor Antagonist

Orly Vardeny, PharmD, MS; Brian Claggett, PhD; Inder Anand, MD; Patrick Rossignol, MD, PhD; Akshay S. Desai, MD, MPH; Faiez Zannad, MD, PhD; Bertram Pitt, MD; Scott D. Solomon, MD;
for the Randomized Aldactone Evaluation Study (RALES) Investigators
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

Time to First Recurrence of Hyperkalemia during the Randomized Withdrawal Phase

A  Time to First Serum Potassium Level ≥5.5 mmol/liter

B  Time to First Serum Potassium Level ≥5.1 mmol/liter

No. at Risk
Placebo 52 46 38 31 29 25 25 23 15
Patiromer 55 53 49 48 45 43 42 42 32

No. at Risk
Placebo 52 37 24 16 10 8 8 7 1
Patiromer 55 47 42 36 34 30 29 29 23
Chronic Heart Failure
- What is missing?

Prospective Randomized Studies!

- GFR 15-45 ml/min below 30 ml/min!
- Planned with Patiromir (SAPPHIRE; DIAMOND)
- Spiro plus Patiromir vs. Standard treatment
Baseline heart rate is a predictor of endpoints on placebo

Stable CHF, SR > 70 bpm

Patients with primary composite endpoint (%)

Primary composite endpoint: risk increases by 2.9% per 1-bpm increase, and by 15.6% per 5-bpm increase

Prediction of Outcome by Discharge Heart Rate - One Year Mortality -

Patients at high HR at Discharge had 41% Increase in Mortality

Logeart D et al. Eur J Heart Failure 2012
Primary composite endpoint
NYHA II-IV, SR > 70 bpm

Ivabradine n=793 (14.5%PY) Placebo n=937 (17.7%PY)

HR = 0.82  \( p<0.0001 \)

NNT=26 (annualized)

Pre-Discharge Management: Targeting the Vulnerable Patient
Estimated Treatment Effects of Ivabradine and Associated Numbers Needed to Treat (NNT) for SHIFT Outcomes

### Estimated Treatment Effects of Ivabradine and Associated Numbers Needed to Treat (NNT) for SHIFT Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>P-Value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>&lt;0.0001</td>
<td>26</td>
</tr>
<tr>
<td>1st HF Hospitalization</td>
<td>&lt;0.0001</td>
<td>27</td>
</tr>
<tr>
<td>Recurrent HF Hospitalization</td>
<td>&lt;0.0001</td>
<td>14</td>
</tr>
<tr>
<td>1st All-cause Hospitalization</td>
<td>0.0036</td>
<td>37</td>
</tr>
<tr>
<td>Recurrent All-Cause Hospitalization</td>
<td>&lt;0.0001</td>
<td>10</td>
</tr>
</tbody>
</table>
Chronic Heart Failure
- What is missing?
- Once a day compound!
- EDIfY – Proof of concept in HFPEF
- Trial in Post Discharge Patients
Regulation of Natriuretic Peptides, Bradykinin, and Angiotensin II

- **Angiotensin I** → **ACE** → **Angiotensin II**
- **Bradykinin** → **NEP** → Inactive products
- Natriuretic peptides (ANP, BNP, CNP)

- **Heart**:
  - Cardioprotection
  - Hypertrophy

- **Blood vessels**:
  - Vasodilation
  - Vasoconstriction

- **Kidney**:
  - Sodium excretion
  - Sodium retention
Concept of ARNIs: Pharmacologic Actions

- Angiotensin I
  - ACE Inhibition
  - Angiotensin II
  - Inactive products

- Bradykinin
  - NEP Inhibition
  - Inactive products

- Natriuretic peptides (ANP, BNP, CNP)

Heart:
- Cardioprotection
- Hypertrophy

Blood vessels:
- Vasodilation
- Vasoconstriction

Kidney:
- Sodium excretion
- Sodium Retention
What is new? Molecular structure of LCZ696
Angiotensin Receptor Neprilysin Inhibitor (ARNI)

- The LCZ696 molecular structure comprises molecular moieties of the NEP inhibitor pro-drug AHU377 and the AT-1 receptor blocker valsartan
- LCZ696 belongs to the novel ARNI class of compounds (Angiotensin Receptor Neprilysin Inhibitors)
Similar valsartan exposures follow dosing of LCZ696 and corresponding doses of Diovan®

Concentration time profiles for valsartan

Parameter | Geometric mean ratio (90% CI)
--- | ---
$C_{\text{max}}$ (ng/mL) | 0.98 (0.87–1.10)
$AUC_{0-\infty}$ (ng⋅h/mL) | 0.90 (0.82–0.99)

PARADIGM-HF: Primary outcome

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

At risk

Enalapril: 4212 3883 3579 2922 2123 1488 853 236
LCZ696: 4187 3922 3663 3018 2257 1544 896 249

Cumulative Proportion of Patients with Primary End Point (%)

Days after Randomization

HR: 0.80 (0.73, 0.87)
p = 0.0000002
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Death from CV causes 20% risk reduction

HF hospitalization 21% risk reduction

McMurray, Packer et al. NEJM 2014
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Death from any cause
16% risk reduction

HR: 0.84 (0.76, 0.93)
p < 0.0001
## PARADIGM-HF: Safety

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>symptoms</td>
<td>14.0</td>
<td>9.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>symptoms and SBP &lt; 90 mmHg</td>
<td>2.7</td>
<td>1.4</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Renal impairment (%)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cr ≥ 2.5 mg/dl</td>
<td>3.3</td>
<td>4.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Cr ≥ 3.0 mg/dl</td>
<td>1.5</td>
<td>2.0</td>
<td>0.10</td>
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<tr>
<td><strong>Hyperkalaemia (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>K⁺ &gt; 5.5 mmol/l</td>
<td>16.2</td>
<td>17.4</td>
<td>0.15</td>
</tr>
<tr>
<td>K⁺ &gt; 6.0 mmol/l</td>
<td>4.3</td>
<td>5.6</td>
<td>0.007</td>
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<tr>
<td><strong>Cough (%)</strong></td>
<td>11.3</td>
<td>14.3</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Effect of the angiotensin receptor neprylisin inhibitor LCZ696 compared with enalapril according to age in PARADIGM-HF

John JV McMurray MD, Pardeep S Jhund MBChB, PhD, Michael Fu MD, Tzvetana Katova MD, Jean Rouleau MD, Scott D Solomon MD, Kari Swedberg MD, Michael R Zile MD, Thomas Salko BA, Milton Packer MD

CV death/HF hosp

enalapril better

LCZ696 better

Age (years)
Comparing LCZ696 With Enalapril According to Baseline Risk Using the MAGGIC and EMPHASIS-HF Risk Scores
An Analysis of Mortality and Morbidity in PARADIGM-HF

**Figure 1.** Distribution of Risk Scores and Probability of Reaching Primary Composite Endpoint.
What can the Guideline Committee Do?

Class I:
Evidence and/or general agreement that a given treatment is beneficial, useful and effective.

Evidence A:
Data derived from multiple randomised clinical trials or meta-analyses.

Evidence B:
Data derived from a single randomised trial or multiple non-randomized studies ("registry trials") or a single meta-analysis.
<table>
<thead>
<tr>
<th>Number of trials with P &lt; 0.05 showing efficacy</th>
<th>P value required in a single trial to provide same strength of evidence</th>
<th>PARADIGM-HF Effect on primary endpoint</th>
<th>PARADIGM-HF Effect on cardiovascular death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.00125</td>
<td></td>
<td>0.00008</td>
</tr>
<tr>
<td>3</td>
<td>0.00003125</td>
<td></td>
<td>0.000004</td>
</tr>
<tr>
<td>4</td>
<td>0.00000078</td>
<td></td>
<td>0.0000004</td>
</tr>
<tr>
<td>5</td>
<td>0.0000000195</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on formula \((0.025)^n \times 2\) (personal communication Stuart Pocock)

McMurray et al., EHFA 2015
Chronic Heart Failure
- What is missing?

- PARAGON in HFPEF Patients!

- New indications like resistant hypertension, CKD

- Once daily drug
15. Gaps in evidence

15.2 Co-morbidity

The long-term safety and efficacy of many treatments for co-morbidities are unknown, but are of great interest and importance.

**Anaemia**—erythropoiesis-stimulating agents, iron?

**Depression**—selective serotonin reuptake inhibitors, cognitive therapy?

**Diabetes**—metformin, GLP-1 agonists/analogues, DPP IV inhibitors, SGLT-2 inhibitors?

**Sleep-disordered breathing**—positive airways pressure therapies?
Functional Class in Patients with Heart Failure Is Associated with the Development of Diabetes

Alexander Tenenbaum, MD, PhD, Michael Motro, MD, Enrique Z. Fisman, MD, Jonathan Leor, MD, Dov Freimark, MD, Valentina Boyko, MS, Lori Mandelzweig, MPH, Yehuda Adler, MD, Yaniv Sherer, MD, Solomon Behar, MD

Risk of Diabetes Development in CHF
Outcome: Advanced CHF

Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure

Stephanie Smooke, MD, Tamara B. Horwich, MD, and Gregg C. Fonarow, MD, FACC  Los Angeles, Calif
Glucose Filtration in Health and Disease

Normal plasma glucose

Plasma glucose (mg/dL) vs. Glucose filtration (mg/min)

Normal plasma glucose: 70-110 mg/dL

Glucose Filtration in Health and Disease

Plasma glucose (mg/dL)

Tubular reabsorption

Normal plasma glucose

Glucose (mg/min)

TmG Transport Maximum

Threshold

0 70 110 200 400 600 800

Glucose Filtration in Health and Disease

- Normal plasma glucose
- Threshold
- Glucose in urine
- Tubular reabsorption
- Urine glucose
- \( T_mG \)

Plasma glucose (mg/dL)

<table>
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<tr>
<th>Glucose (mg/min)</th>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>400</td>
</tr>
<tr>
<td>600</td>
</tr>
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</table>

Glucose Filtration in Health and Disease

Glucose Filtration in Health and Disease

- Normal plasma glucose
- Elevated Plasma glucose
- Tubular reabsorption
- Urine Glucose
- Glucose in urine
- Threshold
- $T_mG$

![Graph showing glucose filtration in health and disease](image_url)
Glucose- Reabsorption Takes Place in the Proximal Tubule

- **S1 Segment of the proximal tubule**
  - ~90% Glucose reabsorbed
  - transport by SGLT2

- **Distal S3 Segment of the proximal tubule**
  - ~10% glucose reabsorbed
  - transport by SGLT1

SGLT: sodium glucose transporter

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

No. at Risk

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2294</td>
<td>2272</td>
<td>2188</td>
<td>2133</td>
<td>2113</td>
<td>2063</td>
<td>2008</td>
<td>1967</td>
<td>1741</td>
<td>1456</td>
<td>1241</td>
<td>1109</td>
<td>962</td>
<td>705</td>
<td>420</td>
</tr>
<tr>
<td>Empagliflozin 10 mg</td>
<td>2296</td>
<td>2272</td>
<td>2218</td>
<td>2150</td>
<td>2155</td>
<td>2108</td>
<td>2072</td>
<td>2058</td>
<td>1805</td>
<td>1520</td>
<td>1297</td>
<td>1164</td>
<td>1006</td>
<td>749</td>
<td>488</td>
</tr>
<tr>
<td>Empagliflozin 25 mg</td>
<td>2296</td>
<td>2280</td>
<td>2212</td>
<td>2152</td>
<td>2150</td>
<td>2115</td>
<td>2080</td>
<td>2044</td>
<td>1842</td>
<td>1540</td>
<td>1327</td>
<td>1190</td>
<td>1043</td>
<td>795</td>
<td>498</td>
</tr>
</tbody>
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Hospitalization for heart failure

<table>
<thead>
<tr>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 0.62</td>
<td>HR 0.68</td>
</tr>
<tr>
<td>(95% CI 0.45, 0.86)</td>
<td>(95% CI 0.50, 0.93)</td>
</tr>
<tr>
<td>p=0.004</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

No. of patients

- Empagliflozin 10 mg: 2345, 2306, 2256, 2204, 1981, 1473, 1240, 804, 188
- Empagliflozin 25 mg: 2342, 2308, 2267, 2223, 2007, 1477, 1247, 830, 207
- Placebo: 2333, 2271, 2226, 2173, 1932, 1424, 1202, 775, 168
Chronic Heart Failure
- What is missing?
- Prospective Randomized Studies!
- Heart Failure
  - in general
  - obese, diabetic CHF patients
  - HFPEF
    ??? !!!
Thank you!

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Universitätsklinikum des Saarlandes
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michael.boehm@uks.eu