Behandlungsalgorithmus bei Herzinsuffizienz mit reduzierter Auswurffraktion

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DISCLOSURE: Research Grant NOVARTIS, VIFOR, Abbott
Treatment Algorithm
Heart Failure with Reduced Ejection Fraction

Patient with symptomatic* HFrEF

Therapy with ACE-I and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)

Still symptomatic and LVEF ≤35%

Yes

Add MR antagonist++
(up-titrate to maximum tolerated evidence-based dose)

Still symptomatic and LVEF ≤35%

No

Yes

Able to tolerate ACEI (or ARB)‡

Sinus rhythm, QRS duration ≥130 msec

Sinus rhythm, HR ≥70 bpm

Evaluate need for CRT

ARNI to replace ACE-I

Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

Yes

Consider digoxin or H-ISDN or LVAD, or heart transplantation

No

No further action required

Consider reducing diuretic dose

High Dose vs Low Dose Lisinopril Treatment
Effect on Mortality and Morbidity in Chronic Heart Failure

N=3164 chronic HF pts in NYHA II-IV with LVEF ≤30%

Time to Death

HR=0.92 95% CI:0.82-1.03; p=0.128

Time to Death or Hospitalization for any reason

HR=0.88 95% CI:0.82-0.96; p=0.002

Low dose= 2.5-5 mg Lisinopril/d
High dose= 32.5-35 mg Lisinopril d

Packer et al. Circulation 1999;100:2312-2318
High Dose vs Low Dose Lisinopril Treatment
Effect on Mortality and Morbidity in Chronic Heart Failure

N=3164 chronic HF pts in NYHA II-IV with LVEF ≤30%

<table>
<thead>
<tr>
<th></th>
<th>Low-Dose</th>
<th>High-Dose</th>
<th>Percent Reduction in High-Dose Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations for any reason</td>
<td>4397</td>
<td>3819</td>
<td>13</td>
<td>0.021</td>
</tr>
<tr>
<td>Hospitalizations for cardiovascular reason</td>
<td>2923</td>
<td>2456</td>
<td>16</td>
<td>0.050</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>1576</td>
<td>1199</td>
<td>24</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for ischemic events</td>
<td>543</td>
<td>432</td>
<td>20</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Packer et al. Circulation 1999;100:2312-2318
## High Dose vs Low Dose Lisinopril Treatment on Mortality and Morbidity in Chronic Heart Failure

N=3164 chronic HF pts in NYHA II-IV with LVEF ≤30%

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Patients With Adverse Experience</th>
<th>Patients Requiring Withdrawal of Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-Dose (n=1596)</td>
<td>High-Dose (n=1568)</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>709 (44)</td>
<td>594 (38)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>193 (12)</td>
<td>297 (19)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>107 (7)</td>
<td>169 (11)</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>112 (7)</td>
<td>155 (10)</td>
</tr>
<tr>
<td>Cough</td>
<td>211 (13)</td>
<td>166 (11)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>56 (4)</td>
<td>100 (6)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>53 (3)</td>
<td>22 (1)</td>
</tr>
</tbody>
</table>

Values in parentheses indicate percentage.
The CHARM-Alternative trial: effects of candesartan in HFrEF patients intolerant to ACE-inhibition

N=2018 chronic HF pts in NYHA II-IV with LVEF ≤40%

Kaplan-Meier cumulative event curves for cardiovascular death and HHF

adjusted HR for cardiovascular death=0.8

Effects of high-dose versus low-dose losartan on clinical outcomes in patients with HFrEF (HEAAL)

N=3846 chronic HF pts in NYHA II-IV with LVEF ≤40%

Kaplan Meier event curve for ACM & HHF

Change in NYHA class

Effects of high-dose versus low-dose losartan on clinical outcomes in patients with HFrEF (HEAAL)

N=3846 chronic HF pts in NYHA II-IV with LVEF ≤40%

<table>
<thead>
<tr>
<th>Adverse event*</th>
<th>Losartan 150 mg</th>
<th>Losartan 50 mg</th>
<th>p value†</th>
<th>Adverse event* with discontinuation‡</th>
<th>Losartan 150 mg</th>
<th>Losartan 50 mg</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with event</td>
<td>195</td>
<td>131</td>
<td>0.0004</td>
<td>Number with event</td>
<td>9</td>
<td>4</td>
<td>0.20</td>
</tr>
<tr>
<td>Rate§</td>
<td>2.79</td>
<td>1.87</td>
<td></td>
<td>Rate§</td>
<td>0.12</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Hypokalaemia (or increased potassium)</td>
<td>203</td>
<td>145</td>
<td>0.002</td>
<td>19</td>
<td>16</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>7.12</td>
<td>4.73</td>
<td>&lt;0.0001</td>
<td>65</td>
<td>49</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Renal impairment¶ (or increased creatinine)</td>
<td>454</td>
<td>317</td>
<td></td>
<td>48</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioedema</td>
<td>6</td>
<td>0.00</td>
<td></td>
<td>4</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total adverse events with discontinuation‡</td>
<td>148</td>
<td>133</td>
<td></td>
<td>1.99</td>
<td>1.83</td>
<td>0.44</td>
<td></td>
</tr>
</tbody>
</table>

β-blocker or ACE-inhibitor first?  
The CIBIS III - Study design

**Bisoprolol-first (o.d.)**

- First up-titration
- Maintenance period
- Second up-titration
- Second maintenance period

* = visits

**Enalapril-first (b.i.d.)**

- First up-titration
- Maintenance period
- Second up-titration
- Second maintenance period

* = visits

Willlenheimer et al. Circulation 2005;112:2426-2435
β-blocker or ACE-inhibitor first?
-all cause mortality in CIBIS III

n=1010 pts with stable HF on diuretic treatment; ≥65 y, LVEF ≤35%

B/E vs E/B
65 vs 73 deaths
HR 0.88 (95% CI 0.63-1.22)

12% risk reduction
p=0.44 (difference)

Willlenheimer et al. Circulation 2005;112:2426-2435
Is there a target resting heart rate in CHF?

-an analysis from COMET

COMET: Metoprolol tartrate vs. Carvedilol in 3029 CHF with LVEF < 30%

<table>
<thead>
<tr>
<th>Heart rate</th>
<th>Number of deaths / patients</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (all) &gt;80 vs. ≤80 b.p.m.</td>
<td>496/1312 vs. 613/1713</td>
<td>1.106 (0.971, 1.26)</td>
<td>0.1274</td>
</tr>
<tr>
<td>Baseline (on treatment at 4 months) &gt;80 vs. ≤80 b.p.m.</td>
<td>369/1136 vs. 435/1443</td>
<td>1.142 (0.981, 1.329)</td>
<td>0.0864</td>
</tr>
<tr>
<td>Change from baseline &gt;-12 vs. ≤-12 b.p.m.</td>
<td>382/1225 vs. 422/1354</td>
<td>1.078 (0.927, 1.254)</td>
<td>0.3282</td>
</tr>
<tr>
<td>4 months &gt;68 vs. ≤68 b.p.m.</td>
<td>388/1160 vs. 418/1422</td>
<td>1.357 (1.166, 1.58)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Metra et al. Eur Heart J 2005;26:2269-68
Is there a target dose of β-blockade in CHF?  
*an analysis from MERIT-HF*

MERIT-HF: 3991 CHF-patients, NYHA II-IV, LVEF<40%

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Wikstrand et al. J Am Coll Cardiol 2002;40:491-8
Treatment Algorithm
Heart Failure with Reduced Ejection Fraction

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Therapy with ACE-I and beta-blocker
(up-titrate to maximum tolerated evidence-based doses)

Still symptomatic and LVEF ≤35%

No

Add MR antagonist**
(up-titrate to maximum tolerated evidence-based dose)

Yes

Still symptomatic and LVEF ≤35%

No

Able to tolerate ACEI (or ARB)²

Sinus rhythm, QRS duration ≥130 msec

Sinus rhythm, HR ≥70 bpm

ARNI to replace ACE-I

Evaluate need for CRT-

Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

Yes

Consider digoxin or H-ISDN or LVAD, or heart transplantation

No further action required

Consider reducing diuretic dose
RALES
The effect of spironolactone on morbidity and mortality in patients with severe HFrEF

N=1663 pts with and NYHA III/IV at enrollment and NYHA IV within the preceding 6 months

Pitt et al. NEJM 1999;341:709-717
EMPHASIS-HF
Effect of Eplerenone on Cardiovascular Mortality and HHF

N=2737 pts, >55y, NYHA II, LVEF ≤30%, on maximal HF treatment

Zannad et al. NEJM 2011;364:11-21
Effect of race on safety and efficacy of spironolactone in patients with severe HFrEF

n=120 afro-american pts vs. 1543 non-AA patients
Yancy et al. J Am Coll Cardiol 2018; 71:202-230
Determinants and clinical outcome of up-titration of ACE-I and beta blockers in HF

n=2516; LVEF ≤40% or NT-proBNP >2000 pg/m

Treatment Algorithm
Heart Failure with Reduced Ejection Fraction

N=6558 pts with stable CHF, optimal treatment and previous HHF <1y, and ≥70bpm

Swedberg et al. Lancet 2010;376:875-885
SHIFT
Heart rate reduction with ivabradine for improvement of clinical outcomes

Yancy et al. J Am Coll Cardiol 2018; 71:202-230
with an elevated plasma natriuretic peptide level
(BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL,
or if HF hospitalization within recent 12 months plasma
BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL.

In doses equivalent to enalapril 10 mg b.i.d.
PARADIGM-HF
Primary and Secondary Endpoints

A Primary End Point

<table>
<thead>
<tr>
<th>Days since Randomization</th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>900</td>
<td>1544</td>
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<tr>
<td>1080</td>
<td>896</td>
<td>853</td>
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<tr>
<td>1260</td>
<td>249</td>
<td>236</td>
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Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P < 0.001

B Death from Cardiovascular Causes

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Hazard ratio, 0.80 (95% CI, 0.71–0.89)
P < 0.001

C Hospitalization for Heart Failure

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</tbody>
</table>

Hazard ratio, 0.79 (95% CI, 0.71–0.89)
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D Death from Any Cause

<table>
<thead>
<tr>
<th>Days since Randomization</th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td></td>
</tr>
</tbody>
</table>

Hazard ratio, 0.84 (95% CI, 0.76–0.93)
P < 0.001

McMurray et al. NEJM 2014;2:663-670
Efficacy of LCZ696 vs. Enalapril when Drug Dose is Reduced In Heart Failure with Reduced Ejection Fraction

Vardeny et al. Eur J Heart Fail 2016;18:1228-1234
Efficacy of LCZ696 vs. Enalapril at Lower than Target Dose In Heart Failure with Reduced Ejection Fraction

HR of the Primary Outcome Measure by Time-updated Mean Post-Randomization

Vardeny et al. Eur J Heart Fail 2016;18:1228-1234
Dosage of Heart Failure Medication Improves Outcome Following Cardiac Resynchronisation Therapy

Schmidt et al. Eur Heart J 2014;35:1051-1060
ESC Heart Failure Guidelines 2016

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  - No
  - Yes, Add MR antagonist* (up-titrated to maximum tolerated evidence-based dose)

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  - Sinus rhythm, HR ≥70 bpm

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  - ARNI to replace ACE-I
  - Evaluate need for CRT

- These above treatments may be combined if indicated

- Resistant symptoms
  - Yes
    - Consider digoxin or H-ISDN or LVAD, or heart transplantation
  - No
    - No further action required; Consider reducing diuretic dose

Diuretics to relieve symptoms and signs of congestion

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

Impact of Carvedilol and Metoprolol on inappropriate implantable Cardioverter-Defibrillator Therapy

n=1790 pts of the MADIT-CRT 556; a total of 253 inappropriate treatments

Impact of Carvedilol and Metoprolol on VT/VF incidence in the MADIT-CRT study population

n=1790 pts of the MADIT-CRT

Kaplan-Meier estimates of ACM and HHF

Unadjusted P=0.003

p=0.003)

MERCI