Heart Failure Guidelines 2016

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Dept. Cardiology
University Heart Center
Zurich/Switzerland
President-elect HFA
Heart Failure is Moving Center Stage

Fatal MI

Heart Failure

Herzbericht 2014, Statistisches Bundesamt
Heart Failure in Switzerland

8.08 Millions

HF=2.1% ≅ 175,000 Patients

- 35% NYHA I
  ≅ 60,000 Patients
- 35% NYHA II
  ≅ 60,000 Patients
- 25% NYHA III (10% in IIIB)
  ≅ 47,000 Patients
- 5% NYHA IV
  ≅ 8,000 Patients

Ruschitzka HFA 2016
mod. Miller and Guglin JACC 2013
Heart Failure is the Number One Cause for Hospitalisations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Men</th>
<th>Mean age</th>
<th>%</th>
<th>Women</th>
<th>Mean age</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>230307</td>
<td>75.5 ± 11.1</td>
<td>49%</td>
<td>235691</td>
<td>79.8 ± 10.2</td>
<td>51%</td>
</tr>
<tr>
<td>AMI</td>
<td>202286</td>
<td>70.0 ± 12.2</td>
<td>59%</td>
<td>140460</td>
<td>76.5 ± 10.9</td>
<td>41%</td>
</tr>
<tr>
<td>Lung Ca</td>
<td>32152</td>
<td>69.3 ± 10.6</td>
<td>60%</td>
<td>21434</td>
<td>67.8 ± 11.8</td>
<td>40%</td>
</tr>
<tr>
<td>Colorectal Ca</td>
<td>39848</td>
<td>71.1 ± 11.5</td>
<td>50%</td>
<td>39948</td>
<td>72.6 ± 12.2</td>
<td>50%</td>
</tr>
<tr>
<td>Prostate Ca</td>
<td>81667</td>
<td>73.4 ± 9.4</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder Ca</td>
<td>24377</td>
<td>71.4 ± 11.0</td>
<td>74%</td>
<td>8404</td>
<td>73.0 ± 11.9</td>
<td>26%</td>
</tr>
<tr>
<td>Breast Ca</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>88321</td>
<td>63.1 ± 14.0</td>
<td>100%</td>
</tr>
<tr>
<td>Ovarian Ca</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17415</td>
<td>63.5 ± 14.5</td>
<td>100%</td>
</tr>
</tbody>
</table>
Five-year survival following a first admission to for heart failure, myocardial infarction and cancer
The Success of ACE Inhibition in Heart Failure

CONSENSUS: NEJM 1987

SOLVD: NEJM 1991
Drugs in Systolic Heart Failure: From Mere Palliation to Saving Lives

SOLVD-T 1991

Death at 1 year (%)

ACE inhib
15.6

ACE inhib.
12.4

CIBIS + MERIT-HF 1999

ACE inhib. Beta-blocker
11.9

EMPHASIS-HF 2011

ACE inhib. Beta-blocker
7.8

ACE inhib. Beta-blocker MRA
7.06

ACE inhib. Beta-blocker MRA
6.09

McMurray EJHF 2011
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)
Suspected Heart Failure

ASSESSMENT OF HF PROBABILITY

1. **Clinical history:** History of CAD (MI, revascularization); History of arterial hypertension; Exposition to cardiotoxic drug/radiation; Use of diuretics; Orthopnea / paroxysmal nocturnal dyspnea
2. **Physical examination:** Rales; bilateral ankle edema, heart murmur; jugular venous dilatation; laterally displaced/broadened apical beat
3. **ECG:** any abnormality

Assessment of natriuretic peptides not routinely done in clinical practice

≥ 1 present

NATRIURETIC PEPTIDES

NT-proBNP ≥ 125 pg/ml
BNP ≥ 35 pg/ml

Yes

ECHOCARDIOGRAPHY

≥ 1 present

All absent

HF unlikely: consider other diagnosis

No

Normal

If HF confirmed (based on all available data): determine etiology and start appropriate treatment

Heart Failure Guidelines
EHJ / EJHF 2016
Heart Failure – More Than Just LV Systolic Function

Heart Failure

Heart Failure with preserved ejection fraction (HFpEF)
Heart Failure with mid-range ejection fraction (HFmrEF)
Heart Failure with reduced ejection fraction (HFrEF)

Acute „de novo“
acutely decompensated chronic HF
Chronic, stable
Advanced, refractory
## HFmrEF: The Middle Child in Heart Failure

<table>
<thead>
<tr>
<th>Criteria</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs</td>
<td>Symptoms ± Signs</td>
<td>Symptoms ± Signs</td>
</tr>
<tr>
<td>2</td>
<td>LVEF &lt; 40%</td>
<td>LVEF 40-49%</td>
<td>LVEV ≥ 50%</td>
</tr>
</tbody>
</table>
| 3        | 1. Elevated levels of natriuretic peptides  
2. At least one additional criterion:  
   a. relevant structural heart disease (LVH and/or LAE)  
   b. Diastolic dysfunction | 1. Elevated levels of natriuretic peptides  
2. At least one additional criterion:  
   a. relevant structural heart disease (LVH and/or LAE)  
   b. Diastolic dysfunction | 1. Elevated levels of natriuretic peptides  
2. At least one additional criterion:  
   a. relevant structural heart disease (LVH and/or LAE)  
   b. Diastolic dysfunction |
PATIENT WITH SYMPTOMATIC HFrEF

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

Still symptomatic and LVEV ≤ 35%

Add MR antagonist
(uptitrate to maximum tolerated evidence based dose)

No further action required
Consider reducing diuretic dose
### Therapy of HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ACE-I(^d) is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
<td>2, 163 - 165</td>
</tr>
<tr>
<td>A beta-blocker is recommended, in addition an ACE-I(^d), for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
<td>167 - 173</td>
</tr>
<tr>
<td>An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I(^d) and a beta-blocker, to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
<td>174, 175</td>
</tr>
</tbody>
</table>

**ACE-Inhibitor**

**Beta-Blocker**

**Mineralocorticoid-Antagonist**
PATIENT WITH SYMPTOMATIC HFrEF

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

Still symptomatic and LVEV ≤ 35%

Add MR antagonist
(uptitrate to maximum tolerated evidence based dose)

Still symptomatic and LVEV ≤ 35%

Able to tolerate ACEI (or ARB)

ARNI to replace ACE-I

Sinus rhythm, QRS duration ≥ 130ms

Evaluate need for CR

No further action required
Consider reducing diuretic dose

Sinus rhythm, QRS HR ≥ 70 bpm

Ivabradine

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

Diuretics to relieve symptoms and signs of congestion

No

Heart Failure Guidelines EHJ / EJHF 2016
PATIENT WITH SYMPTOMATIC HFrEF

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

- Still symptomatic and LVEV ≤ 35%
  - No
  - Yes

Add MR antagonist (uptitrate to maximum tolerated evidence based dose)

- Still symptomatic and LVEV ≤ 35%
  - No
  - Yes

Able to tolerate ACEI (or ARB)

- ARNI to replace ACE-I

Sinus rhythm, QRS duration ≥ 130ms

Evaluate need for CR T

Sinus rhythm, QRS HR ≥ 70 bpm

Ivabradine

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

Heart Failure Guidelines EHJ / EJHF 2016
LCZ696 simultaneously inhibits NEP (via LBQ657) and blocks the AT$_1$ receptor (via valsartan)

**Natriuretic and other vasoactive peptides**
- Vasorelaxation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone levels
- ↓ Fibrosis
- ↓ Hypertrophy
- ↑ Natriuresis/diuresis

**LCZ696**
- Sacubitril (AHU377; pro-drug)
- LBQ657 (NEP inhibitor)
- Valsartan

**Enhancing**
- Vasorelaxation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone levels
- ↓ Fibrosis
- ↓ Hypertrophy
- ↑ Natriuresis/diuresis

**RAAS**
- Angiotensinogen (liver secretion)
  - Ang I
  - Ang II

**Inhibiting**
- ↑ Blood pressure
- ↑ Sympathetic tone
- ↑ Aldosterone
- ↑ Fibrosis
- ↑ Hypertrophy
Valsartan/Sacubitril: PARADIGM-HF Trial

Primary End Point

Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001

Death from Any Cause

Hazard ratio, 0.84 (95% CI, 0.76–0.93)
P<0.001
Guidance on Valsartan/Sacubitril

• **Contraindications:**
  – Angioedema
  – eGFR <10ml/min/1.73m²
  – Pregnancy

• **Titration:**
  – Low prior ACEI/ARB (i.e. <10mg lisinopril): 50mg b.i.d.
  – Higher ACEI/ARB dose: 100mg b.i.d.
  – Increase every 2-4 weeks to target dose: 200mg b.i.d

• **Precautions:**
  – Discontinue ACEI at least 36h before starting valsartan/sacubitril
  – Do not combine with ACEI, aliskiren or ARB
  – Hyperkalemia, Systolic blood pressure <100mmHg
  – eGFR 10-30ml/min/1.73m²

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Side effects more common with valsartan/sacubitril

- Symptomatic hypotension
- SBP <90mmHg
- Angioedema*

Side effects more common with enalapril

- Creatinine >2.5mg/dl
- Potassium >6mmol/l
- Cough

SwissMedic 25.09.2016
# Treatment of HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.</td>
<td>I</td>
<td>B</td>
<td>178, 179</td>
</tr>
<tr>
<td>Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.</td>
<td>IIa</td>
<td>B</td>
<td>178, 179</td>
</tr>
<tr>
<td><strong>Angiotensin receptor nephrilysin inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA.</td>
<td>I</td>
<td>B</td>
<td>162</td>
</tr>
<tr>
<td><strong>If-channel inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).</td>
<td>IIa</td>
<td>B</td>
<td>180</td>
</tr>
<tr>
<td>Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).</td>
<td>IIa</td>
<td>C</td>
<td>181</td>
</tr>
</tbody>
</table>
# Treatment of HFrEF

<table>
<thead>
<tr>
<th>ARB</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).</td>
<td>I</td>
<td>B</td>
<td>182</td>
</tr>
<tr>
<td>An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.</td>
<td>IIb</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hydralazine and isosorbide dinitrate</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF &lt;45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.</td>
<td>IIa</td>
<td>B</td>
<td>183</td>
</tr>
<tr>
<td>Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.</td>
<td>IIb</td>
<td>B</td>
<td>184</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other treatments with less-certain benefits</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Digoxin</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).</td>
<td>IIb</td>
<td>B</td>
<td>185</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N-3 PUFA</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>An n-3 PUFA preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalization and cardiovascular death.</td>
<td>IIb</td>
<td>B</td>
<td>186</td>
</tr>
</tbody>
</table>
Therapy with ACE-Inhibitor and beta-Blocker
(Up-titrate to maximum tolerated evidence-based doses)

Still symptomatic and LVEV ≤ 35%

Yes

Add MR antagonist
(uptitrate to maximum tolerated evidence based dose)

Still symptomatic and LVEV ≤ 35%

No

No

No further action required
Consider reducing diuretic dose

Able to tolerate ACEI (or ARB)

ARNI to replace ACE-I

Sinus rhythm, QRS duration ≥ 130ms

Evaluate need for CR

Ivabradine

Sinus rhythm, QRS HR ≥ 70 bpm

Diuretics to relieve symptoms and signs of congestion

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

Heart Failure Guidelines EHJ / EJHF 2016
CRT: Live Saving Therapy in Wide but not in Narrow QRS

CARE-HF

EchoCRT

No. at Risk
Cardiac resynchronization 409 323 273 166 68 7
Medical therapy 404 292 232 118 48 3

No. at Risk
CRT 404 297 223 155 103 65 42 19
Control 405 302 236 166 119 71 44 15

P=0.15

Cleveland J, et al. NEJM 2005

Ruschitzka F., et al. NEJM 2013
The Do`s and Don`ts of CRT

Mortality endpoint

- Smoothed estimate
- 95% bootstrap confidence bounds

Hazard ratio for CRT

QRS duration

LBBB Morphology
NON-LBBB Morphology

NO
Yes
### Implantable cardioverter-defibrillator (ICD)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary prevention:</strong> to reduce risk of sudden death and all-cause mortality</td>
<td>I A</td>
</tr>
<tr>
<td><strong>Primary prevention:</strong></td>
<td></td>
</tr>
<tr>
<td>In symptomatic HF (NYHA II-III) and EF &lt;35% despite &gt;3month of OMT in ischemic heart disease unless MI in the prior 40 days</td>
<td>I A</td>
</tr>
<tr>
<td>In symptomatic HF (NYHA II-III) and EF &lt;35% despite &gt;3month of OMT in dilated cardiomyopathy</td>
<td>I B</td>
</tr>
<tr>
<td>Wearable ICD in patients at risk of sudden cardiac death for a limited period or as bridge to an implanted device</td>
<td>IIb C</td>
</tr>
</tbody>
</table>
Treatment Algorithm of Patients with symptomatic HFrEF

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

  - Still symptomatic and LVEV ≤ 35%
    - No
    - Yes
      - Add MR antagonist (uptitrate to maximum tolerated evidence-based dose)

  - Still symptomatic and LVEV ≤ 35%
    - No
    - Yes
      - Able to tolerate ACEI (or ARB)
      - Sinus rhythm, QRS duration ≥ 130ms
      - Sinus rhythm, QRS HR ≥ 70 bpm

  - These above treatments may be combined if indicated

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

  - Still symptomatic and LVEV ≤ 35%
    - No
    - Yes
      - Consider digoxin or H-ISDN or LVAD, or heart transplantation

  - No further action required
    - Consider reducing diuretic dose

- Diuretics to relieve symptoms and signs of congestion

- No further action required

- Class I

- Class IIa

- University Hospital Zurich
# Treatment in selected patients with HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine and isosorbide dinitrate (H-ISDN) in self-identified black patients with LVEF &lt; 35% or with LVEF &lt; 45% combined with dilated LV (NYHA III-IV) <strong>despite treatment with ACEI, BB and MRA to reduce risk of hosp. and death</strong></td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td><strong>H-ISDN</strong> in patients with HFrEF <strong>not tolerating ACEI nor ARB</strong> to reduce risk of death</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td><strong>Digoxin</strong> in symptomatic patients ins SR despite ACE, BB and MRA to reduce risk of hospitalization</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td><strong>N-3 PUFA</strong> in symptomatic HF patients to reduce the risk of CV hospitalization and CV death</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>
Drugs *not recommended*

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Thiazolidinediones (glitazones)</td>
<td>III</td>
<td>A</td>
</tr>
<tr>
<td>No NSAID’s or COX-2 inhibitors</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>No Diltiazem or Verapamil</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>No addition of an ARB (or renin inhibitor) to the combination of ACEI or MRA</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
## Comorbidities in HF

- **Iron deficiency:** Treat iron deficiency.
- **Metformin:** Metformin as first-line treatment in diabetes and HF.
- **Hypertension:** Addition of diuretics, Amlodipine or Felodipine in addition to OMT for HFrEF.

### Recommendations

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Treatment</th>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iron deficiency:</strong></td>
<td>IV ferric carboxymaltose in symptomatic patients with HFrEF and iron deficiency (ferritin &lt; 100 ug/L or ferritin 100-299 ug/L and transferrin saturation &lt; 20%) to alleviate symptoms, improve exercise capacity and QOL</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td><strong>Diabetes:</strong></td>
<td>Metformin as first-line treatment of glycaemic control in patients with DM and HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td><strong>Hypertension:</strong></td>
<td>Step 1: ACI, BB and/or MRA in HFrEF (also safe in HFpEF)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Step 2: Thiazide diuretic (or switching to loop diuretic when already on thiazide) when still hypertensive</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Step 3: Amlodipine or hydralazine if step 1 and 2 are not enough</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Step 3: Felodipine</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

*University Hospital Zurich*

*Heart Failure Guidelines EHJ / EJHF 2016*
Treatments *Not Recommended* in HF Patients with Comorbidities

Recommendations

**Central Sleep apnea: adaptive servo-ventilation** in HFrEF because increase in mortality

**Hypertension: Alpha-adrenoreceptor antagonists** (neurohormonal activation, fluid retention, worsening HF)

**Hypertension: Moxonidine** (increase mortality)
"No treatment has yet been shown, convicingly, to reduce morbidity or mortality in patients with HFpEF or HFmrEF."

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.</td>
<td>I</td>
<td>B</td>
<td>178, 179</td>
</tr>
</tbody>
</table>

Important comorbidities:
- Hypertension
- Atrial fibrillation
- Diabetes
- Ischemia

Exercise training
## Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitoring of pulmonary artery pressures</strong> using wireless implantable hemodynamic monitoring in HF patients with previous hospitalization to reduce recurrent HF hospitalization</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Multiparameter monitoring based on ICD in symptomatic patients (LVEF &lt; 35%) to improve clinical outcome</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Regular <strong>aerobic exercise</strong> to improve functional capacity, symptoms and risk of HF hospitalization</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>Multidisciplinary care management</strong> program to reduce the risk of HF hospitalization and mortality</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
Acute Heart Failure: the New Frontier

Onset of CHF  Sudden Death  Decompensations  Pump Failure

Clinical Course  Chronic  Acute

Quality of Life

Acute heart failure: Initial Assessment

### Hypoperfusion
(e.g. cold extremities, oliguria, confusion, dizziness, narrow pulse pressure, elevated lactate)

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm and Dry</td>
<td>Warm and Wet</td>
</tr>
<tr>
<td>Cold and Dry</td>
<td>Cold and Wet</td>
</tr>
</tbody>
</table>
Acute heart failure: Algorithms

- **PATIENT WITH ACUTE HEART FAILURE**
  - Bedside assessment to identify *haemodynamic profiles*

- **PRESENCE OF CONGESTION?**
  - **YES** (95% of all AHF patients)
    - ‘Wet’ patient
  - **NO** (5% of all AHF patients)
    - ‘Dry’ patient

- **ADEQUATE PERIPHERAL PERFUSION?**
  - **YES**
  - **NO**
Acute heart failure: Algorithms

1. 'Wet and Warm' patient (typically elevated or normal systolic blood pressure)
   - Vascular type – fluid redistribution
     - Hypertension predominates
     - Vasodilator
     - Diuretic
   - Cardiac type – fluid accumulation
     - Congestion predominates
     - Diuretic
     - Vasodilator
     - Ultrafiltration (consider if diuretic resistance)

2. 'Wet and Cold' patient
   - Systolic blood pressure <90 mm Hg
     - Inotropic agent
     - Consider vasopressor in refractory cases
     - Diuretic (when perfusion corrected)
     - Consider mechanical circulatory support if no response to drugs
     - Vasodilators
     - Diuretics
     - Consider inotropic agent in refractory cases

3. 'Dry and warm'
   - Adequately perfused
     - Compensated
     - Adjust oral therapy

4. 'Dry and cold'
   - Hypoperfused, Hypovolemic
     - Consider fluid challenge
     - Consider inotropic agent if still hypoperfused
### Acute heart failure: Treatment

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of i.v. diuretics.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20–40 mg i.v. furosemide (or equivalent); for those on chronic diuretic therapy, initial i.v. dose should be at least equivalent to oral dose.</td>
<td>I</td>
<td>B</td>
<td>540, 548</td>
</tr>
<tr>
<td>It is recommended to give diuretics either as intermittent boluses or as a continuous infusion, and the dose and duration should be adjusted according to patients’ symptoms and clinical status.</td>
<td>I</td>
<td>B</td>
<td>548</td>
</tr>
<tr>
<td>Combination of loop diuretic with either thiazide-type diuretic or spironolactone may be considered in patients with resistant oedema or insufficient symptomatic response.</td>
<td>IIb</td>
<td>C</td>
<td>549</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.v. vasodilators should be considered for symptomatic relief in AHF with SBP &gt;90 mmHg (and without symptomatic hypotension). Symptoms and blood pressure should be monitored frequently during administration of i.v. vasodilators.</td>
<td>IIa</td>
<td>B</td>
<td>537, 550–555</td>
</tr>
<tr>
<td>In patients with hypertensive AHF, i.v. vasodilators should be considered as initial therapy to improve symptoms and reduce congestion.</td>
<td>IIa</td>
<td>B</td>
<td>537, 551–554</td>
</tr>
</tbody>
</table>
## Acute heart failure: Treatment

### Inotropic agents – dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors

<table>
<thead>
<tr>
<th>Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP &lt;90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function.</th>
<th>IIb</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Inotrophic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

### Vasopressors

| A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and vital organ perfusion. | IIb | B | 558 |
| It is recommended to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischaemia, and in the case of levosimendan and PDE III inhibitors also hypotension. | I | C | 540, 559–563 |
| In such cases intra-arterial blood pressure measurement may be considered. | IIb | C |

### Other drugs

<table>
<thead>
<tr>
<th>For acute control of the ventricular rate in patients with atrial fibrillation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. digoxin and/or beta-blockers should be considered as the first-line therapy.</td>
</tr>
<tr>
<td>b. amiodarone may be considered.</td>
</tr>
<tr>
<td>IIb</td>
</tr>
<tr>
<td>Opiates may be considered for cautious use to relieve dyspnoea and anxiety in patients with severe dyspnoea but nausea and hypopnea may occur.</td>
</tr>
</tbody>
</table>
# Recommendations for Mechanical Circulatory Support in Patients with Refractory HF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>An LVAD should be considered in patients who have end-stage HFrEF despite optimal medical and device therapy and who are eligible for heart transplantation in order to improve symptoms, reduce the risk of HF hospitalization and the risk of premature death (Bridge to transplant indication).</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>An LVAD should be considered in patients who have end-stage HFrEF despite optimal medical and device therapy and who are not eligible for heart transplantation to, reduce the risk of premature death.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
15. Gaps in evidence

Clinicians responsible for managing patients with HF must frequently make treatment decisions without adequate evidence or a consensus of expert opinion. The following is a short list of selected, common issues that deserve to be addressed in future clinical research.

- Indications for ICDs in specific subgroups (e.g. ARVC and HFmrEF/HFpEF) and optimal selection of ICD candidates
- QRS morphology or duration as a predictor of response to CRT
- CRT in patients with AF
- Efficacy of PV ablation as a rhythm-control strategy in patients with AF
- Interventional approach to recurrent, life-threatening ventricular tachyarrhythmias
- The role of remote monitoring strategies in HF
- Non-surgical (percutaneous) correction of functional mitral and tricuspid regurgitations
- Identification of indications for coronary angiography/revascularization in patients with HF and chronic stable CAD
- Effects of novel LVADs as destination therapy and bridge to transplantation

Ponikowski et al., EHJ and EJHF 2016 (in press)
Merci

Frank Ruschitzka, MD, FRCP
Professor and Co-Head of Cardiology
University Heart Center
Zürich, Switzerland
President ESC-HFA
E-mail: frank.ruschitzka@usz.ch
**Recommendations for multidisciplinary management and monitoring of patients with heart failure**

| Monitoring of pulmonary artery pressures using a wireless implantable haemodynamic monitoring system (CardioMems) may be considered in symptomatic patients with HF with previous HF hospitalization in order to reduce the risk of recurrent HF hospitalization. | IIb | B | 628,629 |
| Multiparameter monitoring based on ICD (IN-TIME approach) may be considered in symptomatic patients with HFrEF (LVEF ≤35%) in order to improve clinical outcomes. | IIb | B | 630 |

Ponikowski et al., EHJ and EJHF 2016 (in press)
Conclusion: (R)evolution of heart failure treatment

- **Palliative Drugs**
  - Pre-1980
  - 1980s
  - 1990s
  - 2000s
  - 2010s
  - 2016

- **Neurohormonal Drugs**
  - Pre-1980
  - 1980s
  - 1990s
  - 2000s
  - 2010s
  - 2016

- **Devices**
  - Pre-1980
  - 1980s
  - 1990s
  - 2000s
  - 2010s
  - 2016

- **ARNI**
  - Pre-1980
  - 1980s
  - 1990s
  - 2000s
  - 2010s
  - 2016

- **Digitalis**
- **Diuretics**
- **ACE-I**
- **β-Blockers**
- **ICDs**
- **CRT, CRT-D**
- **MR-Antagonists**
- **Ivabradine**
- **LVAD**
- **Transplantation**
- **Sensing Devices**

**TABLE:**

<table>
<thead>
<tr>
<th>Period</th>
<th>Palliative Drugs</th>
<th>Neurohormonal Drugs</th>
<th>Devices</th>
<th>ARNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1980</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980s</td>
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</tr>
<tr>
<td>1990s</td>
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<tr>
<td>2000s</td>
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</tr>
<tr>
<td>2010s</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**REFERENCES:**

- University Hospital Zurich
- Courtesy of Ruschitzka F
PARADIGM-HF: Study Design

Double-blind randomized treatment

Single-blind run-in

- Enalapril 10 mg bid
- LCZ696 100 mg bid
- LCZ696 200 mg bid

Testing tolerability to target doses of enalapril and LCZ696

- 2 weeks
- 1–2 weeks
- 2–4 weeks

LCZ696 200 mg bid

N = 7,980 patients

Enalapril 10 mg bid

On top of standard heart failure therapy (excluding ACEIs and ARBs)

~ 21 to 43 months (event-driven)

Primary outcome: CV death or heart failure hospitalization (event driven: 2,410 patients with primary events)

† Enalapril 5 mg bid for 1–2 weeks followed by enalapril 10 mg bid as an optional starting run-in dose for those pts who are treated with ARBs or with low dose of ACEI

### PARADIGM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td><strong>Women (%)</strong></td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy (%)</strong></td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td><strong>LV ejection fraction (%)</strong></td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td><strong>NYHA functional class II / III (%)</strong></td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td><strong>N-terminal pro-BNP (pg/ml)</strong></td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td><strong>B-type natriuretic peptide (pg/ml)</strong></td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Digitalis</strong></td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td><strong>Beta-adrenergic blockers</strong></td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td><strong>Mineralocorticoid antagonists</strong></td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
</tbody>
</table>
**PARADIGM-HF**: Cardiovascular Death or Heart Failure Hospitalization

- **Enalapril** (n=4212)
  - Kaplan-Meier Estimate of Cumulative Rates (%)
  - Days After Randomization
  - HR = 0.80 (0.73-0.87)
  - P = 0.0000004
  - Number needed to treat = 21

- **LCZ696 (Entresto®)** (n=4187)
  - Kaplan-Meier Estimate of Cumulative Rates (%)
  - Days After Randomization
  - HR = 0.80 (0.73-0.87)
  - P = 0.0000004
  - Number needed to treat = 21

McMurray NEJM 2014
PARADIGM-HF

**A Primary End Point**

Hazard ratio, 0.80 (95% CI, 0.73–0.87)

\[ P < 0.001 \]

**B Death from Cardiovascular Causes**

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

\[ P < 0.001 \]

**C Hospitalization for Heart Failure**

Hazard ratio, 0.79 (95% CI, 0.71–0.89)

\[ P < 0.001 \]

**D Death from Any Cause**

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

\[ P < 0.001 \]
## PARADIGM: $1^0$ and $2^0$ Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite outcome — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary outcomes — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo$^+$</td>
<td>-2.99±0.36</td>
<td>-4.63±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation$^{++}$</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function$^{++}$</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

McMurray NEJM 2014
# PARADIGM: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with systolic blood pressure &lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 2.5 ) mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>( \geq 3.0 ) mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

*McMurray NEJM 2014*
PARADIGM-HF: Adverse events leading to permanent study drug discontinuation

- Any adverse event: p = 0.03
- Hypotension: p = 0.38
- Renal reasons: p = 0.002
- Hyperkalaemia: p = 0.56
## PARADIGM-HF: Angioedema

<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>Not hospitalized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment/antihistamines n, (%)</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19  0.52</td>
</tr>
<tr>
<td>Catecholamines/corticosteroids n, (%)</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No airway compromise n, (%)</td>
<td>3 (0.1)</td>
<td>1 (0.0)</td>
<td>0.31  -</td>
</tr>
<tr>
<td>Airway compromise n, (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>
PARADIGM-HF: Mode of Death

Sudden Death

Death due to Worsening Heart Failure
A Putative Placebo Analysis of the Effects of LCZ696 on Clinical Outcomes in Heart Failure:
Baseline characteristics in trials compared

<table>
<thead>
<tr>
<th></th>
<th>SOLVD-T (n = 2569)</th>
<th>CHARM-Alternative (n = 2028)</th>
<th>PARADIGM-HF (n = 8399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61 (10)</td>
<td>67 (11)</td>
<td>64 (11)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>20</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td>57</td>
<td>48</td>
<td>70</td>
</tr>
<tr>
<td>III</td>
<td>30</td>
<td>49</td>
<td>24</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>History</td>
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</tr>
<tr>
<td>MI</td>
<td>66</td>
<td>61</td>
<td>43</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42</td>
<td>50</td>
<td>71</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>125 (18)</td>
<td>130 (19)</td>
<td>121 (19)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>25 (7)</td>
<td>30 (7.4)</td>
<td>29 (6.2)</td>
</tr>
<tr>
<td>Background therapy (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diuretic</td>
<td>85</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>Digoxin</td>
<td>67</td>
<td>45</td>
<td>30</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>8</td>
<td>55</td>
<td>93</td>
</tr>
<tr>
<td>MRA</td>
<td>NR</td>
<td>24</td>
<td>56</td>
</tr>
</tbody>
</table>

McMurray EHJ 2015
A Putative Placebo Analysis of the Effects of LCZ696 on Clinical Outcomes in Heart Failure: Number of events and event rates (per 100 patient-years) in trials compared

<table>
<thead>
<tr>
<th>Outcome number (rate(^a))</th>
<th>SOLVD-T</th>
<th>CHARM-Alternative</th>
<th>PARADIGM-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo ((n = 1284))</td>
<td>Enalapril ((n = 1285))</td>
<td>Placebo ((n = 1015))</td>
</tr>
<tr>
<td>CV death or HF hospitalization</td>
<td>707 (26.2)</td>
<td>573 (18.5)</td>
<td>406 (18.2)</td>
</tr>
<tr>
<td>CV death</td>
<td>461 (13.7)</td>
<td>399 (11.2)</td>
<td>252 (9.8)</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>470 (17.2)</td>
<td>332 (10.9)</td>
<td>286 (12.8)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>510 (15.1)</td>
<td>452 (12.8)</td>
<td>296 (11.5)</td>
</tr>
</tbody>
</table>

McMurray NEJM 2014
A Putative Placebo Analysis of the Effects of LCZ696 on Clinical Outcomes in Heart Failure: Outcomes

| Outcome number (rate\(^a\)) | SOLVD-T | | CHARM-Alternative | | PARADIGM-HF |
|-----------------------------|---------|----------------|------------------|----------------|
|                             | Placebo (n = 1284) | Enalapril (n = 1285) | Placebo (n = 1015) | Candesartan (n = 1013) | Enalapril (n = 4212) | LCZ696 (n = 4187) |
| CV death or HF hospitalization | 707 (26.2) | 573 (18.5) | 406 (18.2) | 334 (13.8) | 1117 (13.2) | 914 (10.5) |
| CV death | 461 (13.7) | 399 (11.2) | 252 (9.8) | 219 (8.2) | 693 (7.5) | 558 (6.0) |
| HF hospitalization | 470 (17.2) | 332 (10.9) | 286 (12.8) | 207 (8.6) | 658 (7.7) | 537 (6.2) |
| All-cause mortality | 510 (15.1) | 452 (12.8) | 296 (11.5) | 265 (10.0) | 835 (9.0) | 711 (7.6) |

McMurray EHJ 2015
A Putative Placebo Analysis of the Effects of LCZ696 on Clinical Outcomes in Heart Failure

McMurray NEJM 2015
How Does Combined Angiotensin Receptor Antagonism and Neprolysin Inhibition Work?


Braunwald JACC-HF 2015
PARADIGM: What are the mechanisms?

Natriuretic peptides
- BK, ADM
- Subs-P, VIP, CGRP

- Vasodilation
- Natriuresis
- Diuresis
- Inhibition of pathologic growth/fibrosis

Angiotensin II

- Degradation products
- AT_1 Receptor
- Vasoconstriction
- Sodium/water retention
- Fibrosis/hypertrophy

LCZ696

sacubitril

valsartan

Neprilysin
PARADIGM: What are the mechanisms?

(A) N-terminal pro-BNP
(B) B-type Natriuretic Peptide
(C) Urinary Cyclic GMP

Legend:
- LCZ
- Control
The Road to Combined Angiotensin Receptor Antagonism and Neprolysin Inhibition

- angiotensin isolated (12,13)
- renin discovered (9)
- ACE isolated (16)
- NEP isolated (63)
- ANP discovered (34)
- NEPi characterized (69)
- First oral ACEi (20)
- HF mortality ↓ ACEi (24)
- First oral ARB (26)
- Omapatrilat synthesized (88)
- Patent for ARNi (97)
- PARADIGM-HF (6)
"There is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things."

Niccolo Machiavelli

The Prince. 1513
Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction.

Ponikowski et al., EHJ and EJHF 2016 (in press)
### PARADIGM-HF: Angioedema

<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>Not hospitalized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment/antihistamines n, (%)</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Catecholamines/corticosteroids n, (%)</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Hospitalized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No airway compromise n, (%)</td>
<td>3 (0.1)</td>
<td>1 (0.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise n, (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
</tbody>
</table>