Management of Heart Failure in the Elderly: New Data, New Guidelines, New Challenges?

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Overview

Part 1
Diagnosis

Part 2
Prevention

Part 3
Treatment

Part 4
Co-morbidities
If something does not work out, it is time to re-invent yourself.
Cardiologist’s Practice
New Guidelines 2016

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)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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Diagnosis of Heart Failure

1. Apply a novel algorithm for the diagnosis of heart failure in the non-acute setting based on:
   i) Clinical probability of the disease (derived from medical history, physical examination and resting ECG),
   ii) The assessment of circulating natriuretic peptides, and
   iii) Transthoracic echocardiography.
PATIENT WITH SUSPECTED HF (non-acute onset)

ASSESSMENT OF HF PROBABILITY

1. Clinical history:
   - History of CAD (MI, revascularization)
   - History of arterial hypertension
   - Exposition to cardiotoxic drug/radiation
   - Use of diuretics
   - Orthopnoea / paroxysmal nocturnal dyspnoea

2. Physical examination:
   - Rales
   - Bilateral ankle oedema
   - Heart murmur
   - Jugular venous dilatation
   - Laterally displaced/broadened apical beat

3. ECG:
   - Any abnormality
ASSESSMENT OF HF PROBABILITY
1. Clinical history; 2. Physical examination; 3. ECG

≥1 present

NATRIURETIC PEPTIDES
• NT-proBNP ≥125 pg/mL
• BNP ≥35 pg/mL

If assessment of natriuretic peptides not routinely done in clinical practice

If HF confirmed (based on all available data), determine aetiology and start appropriate treatment.
2. Use transthoracic echocardiography in patients with suspected or established HF for the assessment of myocardial structure and function along with the measurement of LVEF to establish the diagnosis of HF - with reduced (HFrEF, LVEF<40%), - mid-range (HFmrEF, LVEF: 40-49%) - or preserved ejection fraction (HFpEF, LVEF≥50%).
## Diagnosis of Heart Failure

### Identifying HFmrEF as a separate group will stimulate research into underlying characteristics, pathophysiology and treatment of this population

<table>
<thead>
<tr>
<th></th>
<th>HFFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms ± Signs(^a)</td>
<td>Symptoms ± Signs(^a)</td>
<td>Symptoms ± Signs(^a)</td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
<td></td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>1. Elevated levels of natriuretic peptides(^b); 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).</td>
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<td>–</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.  
\(^b\) BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.
Risk Factors for HFpEF
Risk Factors for the Development of Heart Failure

HF with preserved ejection fraction
- Female gender;
- Advanced age;
- Diabetes mellitus;
- History of hypertension;
- History of atrial fibrillation;
- Obesity.

HF with reduced ejection fraction
- Male gender;
- Smoking;
- Dyslipidaemia;
- Myocardial necrosis, inflammation, infiltration.

Why Is HFpEF so Common in Elderly Women?


LV mass adjusted for BW after aortic banding

LV systolic pressure after aortic banding

female (concentric)
male (eccentric)
female
male

Prognosis of HFpEF

HF with reduced ejection fraction  

HF with preserved ejection fraction

Morbidity & Mortality in HFpEF vs. HFrEF

Overall Mortality

Heart Failure Hospitalization

Mode of Death in HFpEF

- **Blue font = Epidemiological studies**
- **Red font = Clinical trials**

**Adabag et al. (n=787)**
- Cardiovascular Deaths: 39%
- Non-Cardiovascular Deaths: 61%
- Unknown Deaths: 0%

**Henkel et al.**
- Cardiovascular Deaths: 51%
- Non-Cardiovascular Deaths: 49%
- Unknown Deaths: 0%

**Lee et al.**
- Cardiovascular Deaths: 57%
- Non-Cardiovascular Deaths: 32%
- Unknown Deaths: 11%

**Tribouilloy et al.**
- Cardiovascular Deaths: 59%
- Non-Cardiovascular Deaths: 41%
- Unknown Deaths: 0%

**JCARE-CARD (n=429)**
- Cardiovascular Deaths: 58%
- Non-Cardiovascular Deaths: 28%
- Unknown Deaths: 14%

**I-PRESERVE (n=4128)**
- Cardiovascular Deaths: 61%
- Non-Cardiovascular Deaths: 30%
- Unknown Deaths: 9%

**DIG-PEF (n=988)**
- Cardiovascular Deaths: 70%
- Non-Cardiovascular Deaths: 24%
- Unknown Deaths: 6%

**CHARM-Preserved (n=3023)**
- Cardiovascular Deaths: 71%
- Non-Cardiovascular Deaths: 29%
- Unknown Deaths: 0%

**PEP-CHF (n=846)**
- Cardiovascular Deaths: 72%
- Non-Cardiovascular Deaths: 28%
- Unknown Deaths: 0%

Diagnosis of HF in Older Adults

Multiple etiology:
- Age
- Smoking
- Obesity
- Physical inactivity
- Hypertension
- Hypotension
- Coronary artery disease
- Diabetes mellitus
- Atrial fibrillation
- Chronic kidney disease

Interacting pathogenesis:
- LV diastolic dysfunction
- LV systolic dysfunction
- LV hypertrophy
- Cardiomyopathy
- Valvular heart disease
- Arrhythmias
- Disease-disease interactions
- Disease-drug interactions

Common symptoms:
- Shortness of breath
- Fatigue
- Edema

Prevention

If I'd known I was going to live this long, I'd taken better care of myself.

Eubie Blake
3.

To prevent or delay onset of HF and to prolong life, the following is recommend:

(i) Treatment of arterial hypertension,

(ii) Use of statins in patients with or at high risk of coronary artery disease,

(iii) Use of ACE-I in patients with asymptomatic left ventricular dysfunction and

(iv) Use of beta-blockers in those with asymptomatic left ventricular dysfunction and a history of myocardial infarction are recommended.
## Preventing Heart Failure

<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>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>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>
</tbody>
</table>
Be realistic, always plan for a miracle.

Osho
4. Implement **life-saving pharmacotherapy** in patients with symptomatic HFrEF, containing a **combination** of an ACE-I (or ARB if ACE-I not tolerated), a β-blocker and a **MRA**.

If a patient still remains symptomatic **sacubitril/valsartan** is recommended to replace ACE-I.

**Use diuretics** in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.
Treatment of Heart Failure (HFrEF)

Patient with symptomatic\(^a\) HFrEF\(^b\)

- Therapy with ACE-I\(^c\) and beta-blocker (Up-titrate to maximum tolerated evidence-based doses)
  - Still symptomatic and LVEF ≤35%
    - Yes: Add MR antagonist\(^d,e\) (up-titrate to maximum tolerated evidence-based dose)
      - Yes:
        - Still symptomatic and LVEF ≤35%
          - Yes:
            - Able to tolerate ACEI (or ARB)\(^f,g\)
        - No:
          - Sinus rhythm, QRS duration ≥130 msec
            - Yes:
              - Sinus rhythm, HR ≥70 bpm
            - No:
              - No:

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

Diuretics to relieve symptoms and signs of congestion
Treatment of Heart Failure (HFrEF)

Patient with symptomatic\(^a\) HFrEF\(^b\)

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

Still symptomatic and LVEF \(\leq 35\%\)

Add MR antagonist\(^{d,e}\)
(to maximum tolerated evidence-based dose)

Still symptomatic and LVEF \(\leq 35\%\)

Class I A recommendation
ATLAS, CONSENSUS, SOLVD...

Captopril 50 mg tid
Enalapril 10-20 mg bd
Lisinopril 20-35 mg od
Ramipril 5 mg bd
Trandolapril 4 mg od

Diuretics to reduce signs of congestion
If NYHA IV, implant ICD

\(^a\) Class I
\(^b\) Class IIa
\(^c\) ATLAS, CONSENSUS, SOLVD
\(^d\) IDEAL, CONSENSUS
\(^e\) ATLAS, CONSENSUS, SOLVD
\(^f\) CONSENSUS
\(^g\) HFrEF, EF \(\leq 40\%\)
Treatment of Heart Failure (HFrEF)

- Patient with symptomatic\(^a\) HFrEF\(^b\)
  - Therapy with ACE-I\(^c\) and beta-blocker
    (Up-titrate to maximum tolerated evidence-based doses)
    - Still symptomatic and LVEF ≤35%
      - No
      - Yes
        - Add MR antagonist\(^d,e\)
          (to maximum tolerated evidence-based dose)
          - Yes
            - Still symptomatic and LVEF ≤35%
              - No
              - Yes
                - Class I A recommendation
                  CARM, ELITE, Val-HeFT

Candesartan 32 mg od
Valsartan 160 mg bd
Losartan 150 mg od

\(^a\) Diuresics to relieve symptoms and signs of congestion despite OMT

\(^b\) Despite evidence of left ventricular dysfunction, systolic dysfunction, or a history of CHF

\(^c\) No ceiling; titrate to maximum tolerated dose

\(^d\) Losartan

\(^e\) No ceiling; titrate to maximum tolerated dose

\(^f\) ACEI

\(^g\) ARB
Treatment of Heart Failure (HFrEF)

Patient with symptomatic\(^a\) HFrEF\(^b\)

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

Still symptomatic and LVEF ≤35%

No

Yes

Add MR antagonist\(^d,e\) (to maximum tolerated evidence-based dose)

Still symptomatic and LVEF ≤35%

Yes

No

Class I A recommendation

CIBIS, COPERNICUS, MERIT-HF, SENIORS

Bisoprolol

10 mg od

Carvedilol

25-50 mg bd

Metoprolol

200 mg od

Nebivolol

10 mg od

Able to tolerate ACEI (or ARB)\(^f,g\)

Sinus rhythm

QRS duration ≥130 ms

Diuretics to resolve signs and symptoms of congestion despite OMT, specific VT/VF, implant ICD

www.escardio.org/guidelines
Treatment of Heart Failure (HFrEF)

Patient with symptomatic\(^a\) HFrEF\(^b\)

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

Still symptomatic
and LVEF ≤35%

Add MR antagonist\(^d,e\)
(up-titrate to maximum tolerated evidence-based dose)

Still symptomatic
and LVEF ≤35%

Able to tolerate
ACEI (or ARB)\(^f,g\)

Sinus rhythm
QRS duration ≥130 ms

Klasse IA Empfehlung
RALES, EMPHASIS

Eplerenone 50 mg 1x tgl.
Spironolactone 25-50 mg 1x tgl.

Diuretic
HFrEF ≤35% despite OMT
or a high-sodium intake
symptomatic VT/VF, implant ICD
Treatment of Heart Failure (HFrEF)

Diuretics to relieve symptoms and signs of congestion

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

Able to tolerate ACEI (or ARB)\textsuperscript{f,g}

Sinus rhythm, QRS duration ≥130 msec

Sinus rhythm,\textsuperscript{h} HR ≥70 bpm

ARNI to replace ACE-I

Evaluate need for CRT\textsuperscript{i,j}

Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

Yes

No

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

No further action required Consider reducing diuretic dose

www.escardio.org/guidelines
Treatment of Heart Failure (HFrEF)

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD
Diuretics to relieve symptoms and signs of congestion

- Able to tolerate ACEI (or ARB)\textsuperscript{f,g}
- Sinus rhythm, QRS duration ≥130 msec
- Sinus rhythm, HR ≥70 bpm

- ARNI to replace ACE-I
- Evaluate need for CRT\textsuperscript{ij}

- These above treatments may be combined if indicated

- Resistant symptoms

- Ivabradin 5-7.5 mg bd

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

- No further action required: Consider reducing diuretic dose

Class II B recommendation
SHIFT
Treatment of Heart Failure (HFrEF)

- Ivabradin 5-7.5 mg bd: Class II B recommendation

### Table 1. Pharmacokinetic parameters of digoxin in younger versus elderly patients.* Data are expressed as mean (SD), except as indicated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age &lt;65 Years</th>
<th>Age ≥65 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 6)</td>
<td>(n = 7)</td>
</tr>
<tr>
<td>Dose, mg</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; oral, h&lt;sup&gt;†&lt;/sup&gt;</td>
<td>36.8 (4.5)</td>
<td>69.6 (13.1)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; IV, h&lt;sup&gt;†&lt;/sup&gt;</td>
<td>38.2 (3.5)</td>
<td>68.8 (12.3)</td>
</tr>
<tr>
<td>AUC oral, mmol/mL/h</td>
<td>89.7 (9.0)</td>
<td>144.6 (39.8)</td>
</tr>
<tr>
<td>AUC IV, mmol/mL/h</td>
<td>109.8 (15.5)</td>
<td>171.8 (32.8)</td>
</tr>
<tr>
<td>% Absorbed</td>
<td>84.3 (6.5)</td>
<td>76.0 (10.0)</td>
</tr>
<tr>
<td>V&lt;sub&gt;d&lt;/sub&gt;, L/kg</td>
<td>5.3 (0.6)</td>
<td>4.1 (0.9)</td>
</tr>
<tr>
<td>CL/wt, mL/min/kg&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.7 (0.2)</td>
<td>0.8 (0.2)</td>
</tr>
</tbody>
</table>
Treatment of Heart Failure (HFrEF)

Table I. Pharmacokinetic parameters of digoxin in patients with and without sinus rhythm

| Parameter | Sinus rhythm | Sinus rhythm
<table>
<thead>
<tr>
<th></th>
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</tr>
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<tbody>
<tr>
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<tr>
<td>$V_d$ L/kg</td>
<td>5.3 (0.6)</td>
<td>4.1 (0.9)</td>
</tr>
<tr>
<td>$CL/wt$, mL/min/kg$^\dagger$</td>
<td>1.7 (0.2)</td>
<td>0.8 (0.2)</td>
</tr>
</tbody>
</table>

Table II. Important drug–drug interactions with digoxin.

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Recommendations for Minimizing Risk of Digoxin Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Initiating digoxin: 0.125 mg/d PO for normal renal function, 0.125 mg PO every other day for renal dysfunction (creatinine clearance &lt;30 mL/min). Already taking digoxin: reduce dose by 50%.</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Decrease digoxin dose by 50%.</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Decrease digoxin dose by 50%.</td>
</tr>
<tr>
<td>Clarithromycin, cyclosporine, diltiazem, erythromycin, itraconazole, ketoconazole, propafenone</td>
<td>Monitor digoxin serum concentrations closely and adjust dose accordingly.</td>
</tr>
</tbody>
</table>
Angiotensin-Receptor-Neprilysin-Inhibitor (ARNI)

- ANP, BNP, CNP, andere vasoaktive Peptide
- Angiotensin-Rezeptor-Neprilysin-Inhibitor (ARNI) Sacubitril/Valsartan
- RAAS
  - Angiotensinogen (Lebersekretion)
    - Ang I
    - Ang II
  - AT₁-Rezeptor

- Neprilysin
  - Inaktive Fragmente

- Verstärkung NP-vermittelter Effekte
  - Vasodilatation
  - Natriuresis und Diuresis
  - Proliferation
  - Hypertrophie
  - SNS-Aktivität/Sympathikotonus
  - Aldosteronsekretion
  - Nachteiliges vaskuläres Remodeling

- Abschwächung RAAS-vermittelter Effekte
  - Vasokonstriktion
  - Natrium- und Wasserretention
  - Hypertrophie/Remodeling
  - Aldosteronsekretion
  - Kardiale Fibrose
  - Sympathikotonus
  - Systemischer Gefäßwiderstand

Angiotensin-Rezeptor-Nepriylisyn-Inhibitor (ARNI)

ANP, BNP, CNP, andere vasoaktive Peptide

Angiotensin-Rezeptor-Nepriylisyn-Inhibitor (ARNI) Sacubitril/Valsartan

Sacubitril (AHU377; Predrug)

- ANP, BNP, CNP
- Angiotensin
- Endothelin 1
- Adrenomedullin
- Opioid
- Bradykinin
- Beta-Amyloid
- Substance P
- Glukagon

Neprilysin

Inaktive Fragmente

Verstärkung NP-vermittelte Effekte
- Vasodilatation
- Natriuresis und Diurese
- Proliferation
- Hypertrophie
- SNS-Aktivität/Sympathikotonus
- Aldosteronsekretion
- Nachteiliges vaskuläres Remodelling

Abschwächen RAAS-vermittelte Effekte
- Vasokonstriktion
- Natrium- und Wasserretention
- Hypertrophie/Remodelling
- Aldosteronsekretion
- Kardiale Fibrose
- Sympathikotonus
- Systemischer Gefäßwiderstand

RAAS

Angiotensinogen (Lebersekretion)
- Ang I
- Ang II

AT1-Rezeptor

PARADIGM-HF Trial: Study Design

**Single-blind period**
- Enalapril 10 mg bid
- LCZ 100 mg bid
- LCZ 200 mg bid

**Double-blind period**
- LCZ696 200 mg BID
- N = 7980 (1:1 randomization)
- Enalapril 10 mg BID

Outcomes driven (estimated mean f/u = 32 months)

Prior ACEI/ARB use discontinued
PARADIGM-HF: CV Death or HF Hospitalization


Cumulative Probability (%)

Study duration (months)

Enalapril (n=4187)

Sacubitril/valsartan (n=4187)

p < 0.0001
HR: 0.80
(95% CI: 0.73; 0.87)
ARR: 4.7%
PARADIGM-HF: Selected Endpoints

Cardiovascular Death

Enalapril (n=4187)
- p < 0.001
- HR: 0.80
- (95% CI: 0.71; 0.89)
- ARR: 3.2%

Hospitalization for Heart Failure

Sacubitril/Valsartan (n=4187)
- p < 0.001
- HR: 0.79
- (95% CI: 0.71; 0.89)
- ARR: 2.8%

PARADIGM-HF: Selected Endpoints

Cardiovascular Death

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>2111</td>
<td>2168</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>2076</td>
<td>2044</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yr</td>
<td>3403</td>
<td>3433</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>784</td>
<td>779</td>
</tr>
</tbody>
</table>

Primary End Point

- LCZ696 vs Enalapril (Hazard Ratio (95% CI): 0.47, P value for interaction: 0.70)

Hospitalization for Heart Failure

- (95% CI: 0.71; 0.89, ARR: 3.2%)

Death from Cardiovascular Causes

- (95% CI: 0.71; 0.89, ARR: 2.8%)

Reduction in Mortality via Use of HF Medication

- ACE Inhibitor
- ARB
- Beta-Blocker
- MRA

Reduction in Mortality [%]
5.

Ensure an **ICD implantation in HF patients** who either have **recovered from a ventricular arrhythmia** causing haemodynamic instability or in those with **symptomatic HF, LVEF ≤35%** (despite at least 3 months of OMT), in order to reduce the risk of sudden death and all-cause mortality. **ICD implantation is not recommended within 40 days of an MI** as implantation at this time does not improve prognosis.
6.

Implant a **cardiac resynchronization therapy** in symptomatic patients with HF, LVEF ≤35% (despite at least 3 months of OMT), in **sinus rhythm** with a **QRS duration ≥130 msec** and **LBBB QRS morphology**, and in patients with a **QRS duration ≥150 msec** in order to improve symptoms and reduce morbidity and mortality. **CRT is contra-indicated** in patients with a **QRS duration < 130 msec**.
7. Manage HF co-morbidities in all heart failure patients. In HFpEF, this is the only evidence based treatment approach.
7. **Manage HF co-morbidities** in all heart failure patients. In HFP EF, this is the only evidence based treatment approach.

No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFP EF or HFmr EF. However, since these patients are often elderly and highly symptomatic, and often have a poor quality of life, an important aim of therapy may be to alleviate symptoms and improve well-being.
7. **Manage HF co-morbidities** in all heart failure patients. In HFpEF, this is the only evidence based treatment approach.

<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>
However beautiful the strategy, you should occasionally look at the results.

Winston Churchill
Relevant Co-morbidities of Heart Failure

- CAD / ischemia & Hypertension
- Diabetes mellitus & Metabolic syndrome
- Sleep apnoea
- Depression & Stroke
- Anemia and iron deficiency
- Renal dysfunction and kidney injury
- COPD
- Liver & bowel dysfunction
- Cachexia & muscle wasting/sarcopenia
## Co-morbidities

### Iron deficiency

Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 μg/L, or ferritin between 100–299 μg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class a</th>
<th>Level b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iron deficiency</strong></td>
<td>IIa</td>
<td>A</td>
</tr>
</tbody>
</table>

=> recommendation based on FAIR-HF & CONFIRM-HF trials

### Diabetes

Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class a</th>
<th>Level b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

=> should be treatment of choice, except in severe renal or hepatic impairment
Prevalence of Iron Deficiency in HF in Germany

42 Cardiology practices in Germany
1198 patients with heart failure

Prevalence of iron deficiency: 42.5%

# Predictors of Low Exercise Capacity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariable models</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (1 year increase)</td>
<td>1.085 (1.071-1.100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>3.788 (2.830-5.072)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP (1 mmHg increase)</td>
<td>0.992 (0.986-0.998)</td>
<td>0.007</td>
</tr>
<tr>
<td>Diastolic BP (1 mmHg increase)</td>
<td>0.973 (0.962-0.983)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischaemic heart disease (present)</td>
<td>1.143 (0.904-1.445)</td>
<td>0.27</td>
</tr>
<tr>
<td>NYHA class (1 class increase)</td>
<td>3.246 (2.547-4.136)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF (1 unit increase)</td>
<td>0.968 (0.953-0.984)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Oedema (present)</td>
<td>2.254 (1.699-2.989)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron deficiency (present)</td>
<td>1.547 (1.227-1.950)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Haemoglobin (1 g/dl increase)</td>
<td>0.693 (0.640-0.751)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current anaemia (present)</td>
<td>2.361 (1.732-3.219)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of anaemia (present)</td>
<td>2.597 (1.424-4.736)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ferritin (10 µg/l increase)</td>
<td>0.991 (0.985-0.998)</td>
<td>0.007</td>
</tr>
<tr>
<td>log serum ferritin (1 SD increase)</td>
<td>0.789 (0.702-0.887)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TSAT (1 unit increase)</td>
<td>0.985 (0.970-0.999)</td>
<td>0.04</td>
</tr>
<tr>
<td>BNP/NT-proBNP above diagnostic cutoff for non-acute HF (present)</td>
<td>2.379 (1.622-3.492)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>log serum creatinine (1 SD increase)</td>
<td>1.323 (1.172-1.493)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>log C-reactive protein (1 SD increase)</td>
<td>1.208 (1.076-1.355)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of diabetes mellitus (present)</td>
<td>1.155 (0.901-1.481)</td>
<td>0.26</td>
</tr>
<tr>
<td>History of COPD (present)</td>
<td>1.150 (0.771-1.715)</td>
<td>0.49</td>
</tr>
<tr>
<td>History of renal dysfunction (present)</td>
<td>2.461 (1.844-3.285)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Multivariable models</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron deficiency (present)*</td>
<td>1.323 (1.009-1.735)</td>
<td>0.04</td>
</tr>
<tr>
<td>Anaemia (present)*</td>
<td>1.939 (1.356-2.773)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, log serum creatinine, log C-reactive protein, LVEF, and BNP/NT-proBNP above diagnostic cutoff for non-acute HF plus current anaemia or current iron deficiency*
## Patients’ Demographics

<table>
<thead>
<tr>
<th></th>
<th>FCM (N=304)</th>
<th>Placebo (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>NYHA class III, n (%)</td>
<td>251 (82.6)</td>
<td>126 (81.3)</td>
</tr>
<tr>
<td>6-min walk test distance (m)*</td>
<td>274 ± 105</td>
<td>269 ± 109</td>
</tr>
<tr>
<td>Ischemic etiology (%)</td>
<td>81</td>
<td>79</td>
</tr>
<tr>
<td>Estimated GFR (mL/min/1.73m²)*</td>
<td>64 ± 21</td>
<td>65 ± 25</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>Hb (g/L)*</td>
<td>119 ± 13</td>
<td>119 ± 14</td>
</tr>
<tr>
<td>Serum ferritin (µg/L)*</td>
<td>53 ± 55</td>
<td>60 ± 67</td>
</tr>
<tr>
<td>ACEi/ARB (%)</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>Beta-Blocker (%)</td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>92</td>
<td>90</td>
</tr>
</tbody>
</table>
FCM improved self-reported PGA scores at week 24
Odds ratio for better rank: 2.51 (95% CI 1.75,3.61), P<0.0001

**Secondary Endpoint: 6-Minute Walk Distance**

**FCM**
- No. of patients: 303, 284, 280, 268
- Distance (mean ± SE): 274 ± 6, 294 ± 7, 312 ± 6, 313 ± 7

**Placebo**
- No. of patients: 155, 144, 141, 134
- Distance (mean ± SE): 269 ± 9, 269 ± 10, 272 ± 10, 277 ± 10
- Treatment effect (mean ± SE): 21 ± 6, 37 ± 7, 35 ± 8

### Selected Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Self-Reported Patient Global Assessment</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ferric Carboxymaltose</td>
<td>Placebo</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120 (g/liter)</td>
<td>146</td>
<td>74</td>
</tr>
<tr>
<td>&gt;120 (g/liter)</td>
<td>146</td>
<td>75</td>
</tr>
<tr>
<td>Median ferritin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;39 (µg/liter)</td>
<td>153</td>
<td>72</td>
</tr>
<tr>
<td>&gt;39 (µg/liter)</td>
<td>139</td>
<td>77</td>
</tr>
<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 (ml/min/1.73 m² of body-surface area)</td>
<td>119</td>
<td>67</td>
</tr>
<tr>
<td>≥60 (ml/min/1.73 m² of body-surface area)</td>
<td>173</td>
<td>82</td>
</tr>
<tr>
<td>Median age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤69.7 yr</td>
<td>149</td>
<td>75</td>
</tr>
<tr>
<td>&gt;69.7 yr</td>
<td>143</td>
<td>74</td>
</tr>
</tbody>
</table>
What Is Sarcopenia?
What Is Sarcopenia?
What Is Sarcopenia?
## Sarcopenia in Chronic Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients without muscle wasting (n = 161)</th>
<th>Patients with muscle wasting (n = 39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m/f %)</td>
<td>79.5/20.5</td>
<td>75.8/24.2</td>
<td>94.9/5.1</td>
<td>0.007*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.9 ± 10.4</td>
<td>66.0 ± 10.6</td>
<td>70.8 ± 8.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.7 ± 16.9</td>
<td>89.2 ± 15.9</td>
<td>76.3 ± 17.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.8 ± 5.1</td>
<td>29.9 ± 4.7</td>
<td>24.5 ± 4.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cause of HF (ischaemic/non-ischaemic %)</td>
<td>50.5/49.5</td>
<td>45.9/54.1</td>
<td>69.2/30.8</td>
<td>0.02*</td>
</tr>
<tr>
<td>NYHA—class</td>
<td>2.3 ± 0.5</td>
<td>2.3 ± 0.6</td>
<td>2.5 ± 0.8</td>
<td>0.16</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>38.9 ± 13.5</td>
<td>39.8 ± 13.8</td>
<td>35.0 ± 11.6</td>
<td>0.05</td>
</tr>
<tr>
<td>HFrEF/HFpEF (%)</td>
<td>68.8/31.2</td>
<td>65.1/34.9</td>
<td>83.8/16.2</td>
<td>0.03*</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>141.4 ± 3.5</td>
<td>141.6 ± 3.5</td>
<td>140.8 ± 3.3</td>
<td>0.23</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.5 ± 0.9</td>
<td>4.5 ± 0.6</td>
<td>4.3 ± 0.6</td>
<td>0.18</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2 ± 0.4</td>
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</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>176.6 ± 52.5</td>
<td>177.8 ± 52.2</td>
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<td>Haemoglobin (g/dL)</td>
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<td>13.2 ± 1.4</td>
<td>0.32</td>
</tr>
<tr>
<td>Leucocytes (/nl)</td>
<td>6.9 ± 1.9</td>
<td>6.9 ± 2.0</td>
<td>6.5 ± 1.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Interleukin-1B (pg/mL)</td>
<td>0.26 ± 0.71</td>
<td>0.28 ± 0.80</td>
<td>0.21 ± 0.30</td>
<td>0.43</td>
</tr>
<tr>
<td>Interleukin-6 (pg/mL)</td>
<td>3.0 ± 4.4</td>
<td>2.6 ± 4.0</td>
<td>4.4 ± 5.4</td>
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</tr>
<tr>
<td>Tumour necrosis factor-α (pg/mL)</td>
<td>8.2 ± 22.9</td>
<td>9.3 ± 25.5</td>
<td>4.0 ± 4.4</td>
<td>0.90</td>
</tr>
</tbody>
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Prevalence 39/200 = 19.5%

Sarcopenia in Chronic Heart Failure

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<td>141.6 ± 3.5</td>
<td>140.8 ± 3.3</td>
<td>0.23</td>
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<td>4.3 ± 0.6</td>
<td>0.18</td>
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<td>0.78</td>
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<td>171.4 ± 54.1</td>
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</tr>
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<td>13.2 ± 1.4</td>
<td>0.32</td>
</tr>
<tr>
<td>Leucocytes (/nL)</td>
<td>6.9 ± 1.9</td>
<td>6.9 ± 2.0</td>
<td>6.5 ± 1.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Interleukin-1β (pg/mL)</td>
<td>0.26 ± 0.71</td>
<td>0.28 ± 0.8</td>
<td>0.21 ± 0.30</td>
<td>0.43</td>
</tr>
<tr>
<td>Interleukin-6 (pg/mL)</td>
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<td>2.6 ± 4.0</td>
<td>4.4 ± 5.4</td>
<td>0.001</td>
</tr>
<tr>
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<td>9.3 ± 25.5</td>
<td>4.0 ± 4.4</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Prevalence 39/200 = 19.5%

Sarcopenia in Chronic Heart Failure

A. Handgrip strength (kg)
   - No muscle wasting (n=147)
   - Muscle wasting (n=37)
   - P=0.006

B. Quadriceps strength (kg)
   - No muscle wasting (n=155)
   - Muscle wasting (n=37)
   - P=0.001

C. 4-m walk (s)
   - No muscle wasting (n=147)
   - Muscle wasting (n=37)
   - P=0.002

D. 6-minute walk (m)
   - No muscle wasting (n=149)
   - Muscle wasting (n=33)
   - P=0.005
Sarcopenia in Chronic Heart Failure

Figure A: LVEF (%)
- No muscle wasting (n=161)
- Muscle wasting (n=38)

Figure B: Absolute peak VO₂ (mL/min)
- No muscle wasting (n=121)
- Muscle wasting (n=26)

Figure C: Exercise time (min)
- No muscle wasting (n=115)
- Muscle wasting (n=26)
<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.07</td>
<td>1.03–1.12</td>
<td>0.00004</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Sex (female)</td>
<td>3.48</td>
<td>1.47–8.25</td>
<td>0.005</td>
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<td></td>
</tr>
<tr>
<td>BMI (per kg/m² increase)</td>
<td>0.86</td>
<td>0.79–0.93</td>
<td>0.0002</td>
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<tr>
<td>Overweight or obesity (present)</td>
<td>0.25</td>
<td>0.11–0.59</td>
<td>0.002</td>
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<td></td>
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</tr>
<tr>
<td>NYHA (per 1 class increase)</td>
<td>4.20</td>
<td>2.23–7.93</td>
<td>&lt;0.0001</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Atrial fibrillation (present)</td>
<td>1.37</td>
<td>0.65–2.86</td>
<td>0.41</td>
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<td></td>
</tr>
<tr>
<td>Hb (per 1 g/dL increase)</td>
<td>0.59</td>
<td>0.45–0.78</td>
<td>0.0002</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia (present)</td>
<td>3.79</td>
<td>1.82–7.92</td>
<td>0.0004</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>LVEF (per 1% increase)</td>
<td>0.98</td>
<td>0.95–1.00</td>
<td>0.039</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6-min walk test (per 10 m increase)</td>
<td>0.91</td>
<td>0.87–0.94</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean mass, legs (per 500 g increase)</td>
<td>0.81</td>
<td>0.75–0.87</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
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<tr>
<td>Appendicular lean mass (per 500 g increase)</td>
<td>0.85</td>
<td>0.80–0.90</td>
<td>&lt;0.0001</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Muscle wasting (present)</td>
<td>5.07</td>
<td>1.90–13.50</td>
<td>0.0012</td>
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</tr>
<tr>
<td>Coronary artery disease (present)</td>
<td>2.06</td>
<td>1.05–4.03</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (present)</td>
<td>0.93</td>
<td>0.45–1.94</td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (present)</td>
<td>2.55</td>
<td>0.83–7.88</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of co-morbidities (per 1 increase)²</td>
<td>1.41</td>
<td>1.02–1.95</td>
<td>0.04</td>
<td></td>
<td></td>
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</table>

### Multivariable Logistic Regression: Reduced PeakVO$_2$

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.07</td>
<td>1.03–1.12</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>3.48</td>
<td>1.47–8.25</td>
</tr>
<tr>
<td>BMI (per kg/m$^2$ increase)</td>
<td>0.86</td>
<td>0.79–0.93</td>
</tr>
<tr>
<td>Overweight or obesity (present)</td>
<td>0.25</td>
<td>0.11–0.59</td>
</tr>
<tr>
<td>NYHA (per 1 class increase)</td>
<td>4.20</td>
<td>2.23–7.93</td>
</tr>
<tr>
<td>Atrial fibrillation (present)</td>
<td>1.37</td>
<td>0.65–2.86</td>
</tr>
<tr>
<td>Hb (per 1 g/dL increase)</td>
<td>0.59</td>
<td>0.45–0.78</td>
</tr>
<tr>
<td>Anaemia (present)</td>
<td>3.79</td>
<td>1.82–7.92</td>
</tr>
<tr>
<td>LVEF (per 1% increase)</td>
<td>0.98</td>
<td>0.95–1.00</td>
</tr>
<tr>
<td>6-min walk test (per 10 m increase)</td>
<td>0.91</td>
<td>0.87–0.94</td>
</tr>
<tr>
<td>Lean mass, legs (per 500 g increase)</td>
<td>0.81</td>
<td>0.75–0.87</td>
</tr>
<tr>
<td>Appendicular lean mass (per 500 g increase)</td>
<td>0.85</td>
<td>0.80–0.90</td>
</tr>
<tr>
<td>Muscle wasting (present)</td>
<td>5.07</td>
<td>1.90–13.50</td>
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</tr>
<tr>
<td>Number of co-morbidities (per 1 increase)$^2$</td>
<td>1.41</td>
<td>1.02–1.95</td>
</tr>
</tbody>
</table>

11.3 Cachexia and sarcopenia (for frailty, please refer to Section 14)

Cachexia is a generalized wasting process affecting all body compartments [i.e., lean tissue (skeletal muscle), fat tissue (energy reserves) and bone tissue (osteoporosis)]. It may occur in 5–15% of patients with HF, especially those with HFrEF, and more advanced disease status.\(^4^{14}\,\text{–}\,4^{16}\) This serious complication is associated with more severe symptoms and reduced functional capacity, more frequent hospitalization and decreased survival. Cachexia in HF can be diagnosed and defined as involuntary non-oedematous weight loss ≥6% of total body weight within the previous 6–12 months.\(^4^{14}\,\text{–}\,4^{17}\)

The causes are multifactorial, and in individual patients they are difficult to determine. These may include pro-inflammatory immune activation, neurohormonal derangements, poor nutrition and malabsorption, impaired calorie and protein balance, anabolic hormone resistance, reduced anabolic drive, prolonged immobilization and physical deconditioning, together characterized by catabolic/anabolic imbalance.\(^4^{18}\) Skeletal muscle wasting, when associated with impaired mobility and symptoms (termed sarcopenia or myopenia), occurs in 30–50% of patients with HFrEF.\(^4^{19}\) In its most severe form it is associated with frailty and poor morbidity and mortality.\(^4^{20}\)

Potential treatments may include appetite stimulants, exercise training\(^4^{20}\), and anabolic agents, including testosterone, in combination with the application of nutritional supplements and anti-catabolic interventions, although none is of proven benefit and their safety is unknown.\(^4^{21}\)

11.4 Cancer

Certain chemotherapeutic agents can cause (or aggravate) LV systolic dysfunction and HF. The best recognized of these are the
11.6 Diabetes

“Recently, empagliflozin, an inhibitor of sodium-glucose cotransporter 2, reduced hospitalization for HF and mortality, but not myocardial infarction or stroke, in patients with diabetes at high cardiovascular risk, some of whom had HF. In the absence of other studies with drugs from this group, the results obtained with empagliflozin cannot be considered as a proof of a class effect.”
Diabetes mellitus: Empagliflozin

Hospitalization for heart failure

Empagliflozin 10 mg
HR 0.62
(95% CI 0.45, 0.86)
p = 0.004

Empagliflozin 25 mg
HR 0.68
(95% CI 0.50, 0.93)
p = 0.02

Placebo

## Not Recommended Treatments for Co-morbidities

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep apnoea</strong></td>
<td>III</td>
<td>B</td>
<td>473</td>
</tr>
<tr>
<td>Adaptive servo-ventilation is not recommended in patients with HFrEF and a predominant central sleep apnoea because of an increased all-cause and cardiovascular mortality.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>III</td>
<td>A</td>
<td>209, 210</td>
</tr>
<tr>
<td>Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.</td>
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</tr>
<tr>
<td><strong>Arthritis</strong></td>
<td>III</td>
<td>B</td>
<td>211–213</td>
</tr>
<tr>
<td>NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.</td>
<td></td>
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</tr>
</tbody>
</table>
10. Enrol the patients with HF in a multidisciplinary care management program in order to reduce the risk of HF hospitalization and mortality.
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)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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)