Management of chronic heart failure: pharmacology.

Giuseppe M.C. Rosano, MD, PhD, FHFA
## Declaration of potential conflict of interests

<table>
<thead>
<tr>
<th>Type of job or financial support</th>
<th>Research Institution / Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salary</td>
<td>St George’s Hospital NHS Trust London</td>
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<tr>
<td></td>
<td>IRCCS San Raffaele Roma</td>
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<td></td>
<td>European Medicines Agency – CVWP</td>
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<td></td>
<td>Italian Drug Agency (AIFA) – European Assessment Board</td>
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<tr>
<td>Ordinary funds</td>
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<tr>
<td>Position in Public Committees</td>
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The views presented in this talk are personal and should not be understood or quoted as being made on behalf of or reflecting the position of AIFA or EMA.

| Support                          | St George’s Hospital NHS Trusts |
|                                  | Nutramed Consortium             |
|                                  | IRCCS San Raffaele              |

| Conflict for this presentation   | No competing interests for this talk |
|                                  | No consultancies to Companies related to medicinal products |

Giuseppe M.C. Rosano, EMA - DOI 2005-2016
Pharmacological treatment of heart failure with reduced ejection fraction

Objectives in the management of heart failure

• Reduce mortality
• Improve
  • clinical status
  • functional capacity
  • quality of life, prevent hospital admission

• Preventing HF hospitalization and improving functional capacity are important benefits to be considered in chronic heart failure
Pharmacological treatment of HFrEF

- ACEIs, MRAs and beta-blockers have been shown to improve survival and are recommended for the treatment of every patient.

- The use of diuretics should be modulated according to the patient’s clinical status.

- Beta-blockers and ACEIs are complementary, and can be started together as soon as the diagnosis of HFrEF is made.

- There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started.
Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ACE-I&lt;sup&gt;d&lt;/sup&gt; 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>
</tr>
<tr>
<td>A beta-blocker is recommended, in addition an ACE-I&lt;sup&gt;d&lt;/sup&gt;, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I&lt;sup&gt;d&lt;/sup&gt; and a beta-blocker, to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
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</table>
Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction.

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%

No

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

Sinus rhythm, QRS duration ≥130 msec

Sinus rhythm,\(^h\) HR ≥70 bpm

Class I

Class Ila

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Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction. (cont.)

- Able to tolerate ACEI (or ARB)\textsuperscript{1,2,3,4,5}
  - ARNI to replace ACE-I

- Sinus rhythm,\textsuperscript{h} HR ≥70 bpm
  - 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
Patient with symptomatic* HFrEF

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

Still symptomatic and LVEF ≤35%

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

Still symptomatic and LVEF ≤35%

Able to tolerate ACEi (or ARB)*

ARNI to replace ACE-I

Sinus rhythm, QRS duration ≥130 msec

Evaluate need for CRT*

Sinus rhythm, HR ≥70 bpm

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

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Angiotensin receptor neprilysin inhibitor (Sacubitril/Valsartan)

- LCZ 696 is indicated in patients with:
  - ambulatory, symptomatic HFrEF
  - LVEF ≤35%
  - elevated plasma NP levels (BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL)
  - estimated GFR (eGFR) ≥30 mL/min/1.73 m² of body surface area
  - who are able to tolerate treatment with enalapril (at least 10 mg b.i.d.)

- Some relevant safety issues remain when initiating therapy with this drug in clinical practice:
  - symptomatic hypotension
  - risk of angioedema (ACEI should be withheld for at least 36 h before initiating LCZ696)
  - concerns about its effects on the degradation of beta-amyloid peptide in the brain

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If-channel inhibitor

- Ivabradine is indicated in patients with:
  - symptomatic HFrEF and LVEF ≤35%
  - in sinus rhythm and with a heart rate ≥70 bpm
  - who had been hospitalized for HF within the previous 12 months

- The European Medicines Agency (EMA) approved ivabradine for use in Europe in patients with HFrEF with LVEF ≤35% and in sinus rhythm with a resting heart rate ≥75 bpm, because in this group ivabradine conferred a survival benefit
### Recommendations

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<tr>
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<th>Class</th>
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<tr>
<td><strong>Diuretics</strong></td>
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<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>
</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>
</tr>
<tr>
<td><strong>Angiotensin receptor nephrilysin inhibitor</strong></td>
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<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>
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<td><strong>If-channel inhibitor</strong></td>
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<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>
</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>
</tr>
</tbody>
</table>
Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) HFrEF

Angiotensin II type I receptor blockers

- ARBs are recommended only as an alternative in patients intolerant of an ACEI
- The combination of ACEI/ARB should be restricted to symptomatic HFrEF patients receiving a beta-blocker who are unable to tolerate an MRA, and must be used under strict supervision

Combination of hydralazine and isosorbide dinitrate

- There is no clear evidence to suggest the use of this fix-dose combination therapy in all patients with HFrEF
- This combination may be considered in patients who can tolerate neither ACEi nor ARB
Other treatments with less certain benefit in symptomatic patients with HFrEF

Digoxin and other digitalis glycosides

• Digoxin may be considered in patients in sinus rhythm to reduce the risk of hospitalisation in symptomatic patients with HFrEF

• It is only recommended for the treatment of patients with HFrEF and AF with rapid ventricular rate when other therapeutic options cannot be pursued

• A resting ventricular rate in the range of 70–90 bpm is recommended, although a resting ventricular rate of up to 110 bpm might still be acceptable

• Digitalis should always be prescribed under specialist supervision. Caution should be exerted in females, in the elderly and in patients with reduced renal function.
Treatments **not recommended** (unproven benefit) in symptomatic patients with HFrEF

Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (‘statins’)

- Evidence does not support the initiation of statins in most patients with chronic HF

Oral anticoagulants and antiplatelet therapy

- Other than in patients with AF (both HFrEF and HFpEF), there is no evidence that an oral anticoagulant reduces mortality/morbidity compared with placebo or aspirin
- There is no evidence on the benefits of antiplatelet drugs in patients with HF without accompanying CAD, whereas there is a substantial risk of GI bleeding

Renin inhibitors

- It is not presently recommended as an alternative to an ACEI or ARB
### Recommendations

<table>
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<tr>
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<th>Level</th>
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</thead>
<tbody>
<tr>
<td>Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.</td>
<td>III</td>
<td>A</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>III</td>
<td>B</td>
</tr>
<tr>
<td>Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.</td>
<td>III</td>
<td>C</td>
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<tr>
<td>The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.</td>
<td>III</td>
<td>C</td>
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</table>

Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (NYHA Class II–IV) HFrEF

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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

Available online on Eur J Heart Fail*

www.escardio.org/HFA  * and on Eur Heart J