Current Treatment of Chronic Heart Failure

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In patients with clinical HF, studies estimate that the prevalence of HF with Preserved EF (HFpEF) is approximately 50% (range 40% to 71%).
HFpEF: a clinical dilemma

HFpEF as a transitory stage to HFrEF
- Unimodal distribution of LVEF in HF trials
- Eccentric LV remodelling in some hypertensive heart disease
- Subtle LV systolic dysfunction in HFpEF and severe diastolic dysfunction in HFrEF

HFpEF as a distinct entity from HFrEF
- Bimodal distribution of LVEF in HF epidemiologic studies and registries
- Distinct pattern of LV remodelling
- Distinct cellular, subcellular and interstitial characteristics (Table 1)
- Distinct response to HF therapies in trials
Heart Failure

**HF With Reduced EF (HFrEF)**
- The definition of HFrEF has varied, with guidelines of left ventricular ejection fraction (LVEF) ≤35%, <40%, and ≤40%.

**HF With Preserved EF (HFpEF)**
- HFpEF has been variably classified as EF >40%, >45%, >50%, and ≥55%.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Heart Failure with Reduced Ejection Fraction (HFrEF)</td>
<td>≤40%</td>
<td>Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>II. Heart Failure with Preserved Ejection Fraction (HFpEF)</td>
<td>≥50%</td>
<td>Also referred to as diastolic HF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFpEF, Borderline</td>
<td>41% to 49%</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HFpEF.</td>
</tr>
<tr>
<td>b. HFpEF, Improved</td>
<td>&gt;40%</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFpEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>
Diagnosis

The diagnosis of HF-REF requires three conditions to be satisfied:

1. Symptoms typical of HF
2. Signs typical of HF
3. Reduced LVEF

The diagnosis of HF-PEF requires four conditions to be satisfied:

1. Symptoms typical of HF
2. Signs typical of HF
3. Normal or only mildly reduced LVEF and LV not dilated
4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction (see Section 4.1.2)
# Classification of HF

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF.</td>
<td>Systemic hypertension coronary artery disease diabetes mellitus</td>
</tr>
<tr>
<td>B</td>
<td>Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.</td>
<td>Left ventricular hypertrophy or fibrosis; left ventricular dilatation or hypocontractility; asymptomatic valvular heart disease; previous myocardial infarction.</td>
</tr>
<tr>
<td>C</td>
<td>Patients who have current or prior symptoms of HF associated with underlying structural heart disease.</td>
<td>Dyspnea or fatigue due to left ventricular systolic dysfunction; asymptomatic patients who are undergoing treatment for prior symptoms of HF.</td>
</tr>
<tr>
<td>D</td>
<td>Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.</td>
<td>Patients who are frequently hospitalized for HF or cannot be safely discharged from the hospital; patients in the hospital awaiting heart transplantation;</td>
</tr>
</tbody>
</table>
Transition **from stage B to stage C** is associated with a 5-fold increase in mortality risk in both men and women.
Targets of Therapy in Heart Failure

**Basic targets**
- Controlling symptoms and signs
- Reducing mortality
- Reducing re-hospitalization
- Increasing functional capacity
- Improving quality of life

**Clinical targets**
- Slowing, stopping or reversing disease progression
- Controlling congestion
- Decreasing natriuretic peptide levels
- Increasing peak oxygen consumption
- Providing an increase in a 6-min walk distance
- Providing a decrease in systolic/diastolic ventricle volumes
Therapeutic Options in Treatment of HFrEF

• **Lifestyle/non-pharmacological**

Aerobic training intensities as low as **40% peak VO2** have proven to be effective in CHF patients.

<table>
<thead>
<tr>
<th>Intensity</th>
<th>%HRR/VO2R</th>
<th>%peak VO2</th>
<th>%peak HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very light</td>
<td>&lt;20</td>
<td>&lt;25</td>
<td>&lt;35</td>
</tr>
<tr>
<td>Light</td>
<td>20–39</td>
<td>25–44</td>
<td>35–54</td>
</tr>
<tr>
<td>Moderate</td>
<td>40–59</td>
<td>45–59</td>
<td>55–69</td>
</tr>
<tr>
<td>Heavy</td>
<td>60–84</td>
<td>60–84</td>
<td>70–89</td>
</tr>
<tr>
<td>Very heavy</td>
<td>≥85</td>
<td>≥85</td>
<td>≥90</td>
</tr>
<tr>
<td>Maximal</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Therapeutic Options in Treatment of HFrEF

- **Lifestyle/non-pharmacological**

  **Salt restriction**
  
  - **2013 ACCF/AHA**: <3 gr/day
  - **HFSA 2010**: 2 gr/day
  
  **Canadian Society HF 2012**
  
  - No recommendation
  
  **ESC-HFA 2012**
  
  - May be beneficial in NYHA Class III and IV patients
• Lifestyle/non-pharmacological

**Fluid restriction?**

It is generally accepted that there is no need for fluid restriction, except for Stage D heart failure patients, particularly, with hyponatremia, refractory congestion or diuretic resistance.
Therapeutic Options in Treatment of HFrEF

• Lifestyle/non-pharmacological
• Pharmacological therapy
• Non-surgical devices
• Surgery/Surgical devices
## Drug group Efficacy in Mortality / Morbidity

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Major studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs</td>
<td>CONSENSUS, SOLVD, SAVE, AIRE, TRACE</td>
</tr>
<tr>
<td>ARBs</td>
<td>CHARM Alternative, Val-HEFT</td>
</tr>
<tr>
<td>BBs</td>
<td>US Carvedilol, CIBIS II, MERIT HF, COPERNICUS, CAPRICORN</td>
</tr>
<tr>
<td>MRAs</td>
<td>RALES, EMPHASIS HF</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>SHIFT</td>
</tr>
<tr>
<td>Hydralazin + ISDN</td>
<td>V-HeFT I, V-HeFT II, A-HeFT</td>
</tr>
<tr>
<td>Digoxin</td>
<td>DIG</td>
</tr>
<tr>
<td>Diuretics</td>
<td>?</td>
</tr>
</tbody>
</table>
Ivabradine 5 mg bid  Ivabradine 7.5/5/2.5 mg bid according to HR and tolerability

Screening
7 to 30 days

Matching placebo, bid

D0  D14  D28  M4

Every 4 months

Median follow-up: 22.9 months
Primary and Secondary End Points

- 18%
- 26%
- 26%

Cardiovascular death or hospitalization for worsening heart failure
Hospitalization for worsening heart failure
Death for heart failure

Ischemic HF

**Primary End Points**

- **Severe, placebo (n=369)**
- **Severe, Procoralan (n=343)**
- **Less severe, placebo (n=2895)**
- **Less severe, Procoralan (n=2898)**

*Patients with cardiovascular death and hospitalization for worsening heart failure (primary composite end point in %)*

- **Severe**
  - Time (months): 18 %
  - Time (months): 16 %

- **Less severe**
  - Time (months): 16 %
  - Time (months): 18 %

*P interaction=0.85*

**Sever: NYHA class IV vs NYHA class II-III vs LVEF ≤ 20%**

**Less severe: NYHA class II, III vs LVEF >20%**
Acute Effects of Ivabradine
Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure

Gaetano M. De Ferrari, Antonio Mazzuero, Laura Agnesina, Alessandra Bertoletti, Maddalena Lettino, Carlo Campana, Peter J. Schwartz, Luigi Tavazzi
Fig. 1  Treadmill test (A) and 6-minute walking test (B) showing change in exercise capacity after 2 months of treatment.
Adding ivabradine to carvedilol in patients with chronic heart failure improves the uptitration of β-blocker.
Influence of background treatment with mineralocorticoid receptor antagonists on ivabradine's effects in patients with chronic heart failure

Michel Komajda1,*, Michael Böhm2, Jeffrey Borer3, Ian Ford4, Henry Krum5, Adrian Tase6, Luigi Tavazzi7 and Karl Swedberg8

Abstract Free
» Full Text (HTML)
Influence of background treatment with mineralocorticoid receptor antagonists on ivabradine's effects in patients with chronic heart failure

Table 3
Safety of ivabradine in patients with and without mineralocorticoid receptor antagonists

<table>
<thead>
<tr>
<th></th>
<th>Patients with MRAs at baseline</th>
<th>Patients without MRAs at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ivabradine (n = 1977)</td>
<td>Placebo (n = 1938)</td>
</tr>
<tr>
<td>Serious emergent adverse events</td>
<td>856 (44%)</td>
<td>930 (48%)</td>
</tr>
<tr>
<td>Emergent adverse events leading to withdrawal</td>
<td>305 (15%)</td>
<td>274 (14%)</td>
</tr>
<tr>
<td>Emergent adverse events</td>
<td>1476 (75%)</td>
<td>1446 (75%)</td>
</tr>
<tr>
<td>Selected emergent adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>472 (24%)</td>
<td>542 (28%)</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>86 (4%)</td>
<td>12 (&lt;1%)</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>106 (5%)</td>
<td>26 (1%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>171 (9%)</td>
<td>140 (7%)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>40 (2%)</td>
<td>29 (2%)</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>22 (1%)</td>
<td>35 (2%)</td>
</tr>
<tr>
<td>Hypercreatininaemia</td>
<td>3 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Renal failure</td>
<td>45 (2%)</td>
<td>47 (2%)</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>53 (3%)</td>
<td>9 (&lt;1%)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>9 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
</tr>
</tbody>
</table>

The effect of ivabradine on reducing the primary endpoint was similar in patients with and without MRAs (P = 0.916 for interaction, adjusted for prognostic factors at baseline), as were its effects on cardiovascular death (P = 0.279), hospitalizations for heart failure (P = 0.304), and death from heart failure and from all causes (P = 0.723 and 0.366, respectively).
Ivabradine effectively reduces HR, markedly increases stroke volume (51%).

In Conclusion:

1. CV death or hospital admission for WHF 18%
2. Death from heart failure 26%
3. Hospital admission for WHF 26%
4. Cardiovascular mortality 17%
5. All cause mortality 17%

Adding ivabradine to β-blocker in patients with chronic heart failure improves the up titration of β-blocker.

Ivabradine reduces significantly LV end-systolic volume index and increases ejection fraction. (2.4%)
An expanded indication for cardiac resynchronization therapy (CRT)

Recommendations for the use CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class II heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB QRS morphology</td>
<td></td>
<td></td>
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<tr>
<td>CRT, preferably CRT-D is recommended in patients in sinus rhythm with a QRS duration of $\geq 130$ ms, LBBB QRS morphology, and an EF $\leq 30%$, who are expected to survive for $&gt;1$ year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

2 trials: MADIT-CRT and RAFT
When to consider CRT and ICD

Still NYHA class II-IV and LVEF ≤35%?

- Yes
- No

QRS duration ≥120 ms?

- Yes
- No

Consider CRT-P/CRT-D

Consider ICD

Still NYHA class II-IV?

- Yes
- No

Consider digoxin and/or H-ISDN
If end-stage consider LVAD and/or transplantation

No further specific treatment
Continue in disease management programme

European Heart Journal (2012) 33, 1787–1847
European Journal of Heart Failure (2012) 14, 803–869
Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF.

2013 ACCF/AHA Guideline for the Management of Heart Failure

May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤45% who are unable to tolerate a beta-blocker (ivabradine is an alternative in patients with a heart rate ≥70 b.p.m.). Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB).

ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012
Compared with subjects not receiving glycosides, digoxin was associated with a 29% increased mortality risk in the subgroup of publications comprising 235047 AF patients.

Among 91,379 heart failure patients, digoxin-associated mortality risk increased by 14% (HR 1.14, 95% CI, 1.06 to 1.22).
Indications for MCS

<table>
<thead>
<tr>
<th>Recommendations</th>
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<th>Level</th>
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</thead>
<tbody>
<tr>
<td>An LVAD or BiVAD is recommended in selected patients with end-stage HF despite</td>
<td></td>
<td></td>
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<tr>
<td>optimal pharmacological and device treatment and who are otherwise suitable</td>
<td></td>
<td></td>
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<tr>
<td>for heart transplantation, to improve symptoms and reduce the risk of HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospitalization for worsening HF and to reduce the risk of premature death</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>while awaiting transplantation.</td>
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</table>

Graph showing survival rates with continuous-flow LVAD (2009), pulsatile-flow LVAD (2009), pulsatile-flow LVAD (2001), and medical therapy (2001) with corresponding P-values: 0.08 (2009) and 0.09 (2001).
World Heart Failure Alliance

Global Heart Failure Awareness Programme

- Eliminate infections
- Educate public and patients about risk
- Use preventive treatments
- Support people most at risk
- Reduced burden
- First episode of heart failure
- Raise public and professional awareness of symptoms
- Provide equity of access to diagnostic tools
- Research new diagnostic tests
- Develop better measures of care quality
- Research new treatments
- Provide equity of access to treatment
- Optimize transition to long-term management
- Research remote monitoring and community clinics
- Treatment
- Diagnosis
- Long-term management
- Prevention
- Reduced burden
- Death
- Subsequent episode(s)
Heart Failure Journey

Immediate (ER, ICU, CCU)  
Cardiology ward  
Pre-discharge and long-term
Heart Failure Journey

Immediate (ER, ICU, CCU)

- Alleviate symptoms
- Improve oxygenation
- Increase peripheral organ perfusion
- Improve central haemodynamics
- Avoid vital organ damage
- Achieve clinical stabilization and optimization of i.v. therapies
- Limit ICU/CCU length of stay
Start and, where appropriate, up-titrate oral life-saving chronic medications
Detect the subpopulations that need CRTs and/or ICDs
Minimize the length of in-hospital stay
Heart Failure Journey

Pre-discharge and long-term

- Optimize pre-discharge fluid status
- Ensure clinically stable
- Refer to outpatient heart failure clinic and cardiac rehabilitation centre
- Educate and give instructions for lifestyle modification
- Prevent new heart failure exacerbations
- Support psychosocial status
- Improve quality of life and prognosis
Current Treatment of Chronic Heart Failure

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