Managing Heart Failure with Preserved Ejection Fraction (HFpEF)

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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
HFpEF is common (>50% of all HF), growing in prevalence

Comorbidities are common and drive outcomes

Associated with high morbidity and mortality

5-year survival is only 35% after HF hospitalization

The diagnosis is often not straightforward
Treatment of patients with HFpEF

- No therapy has been approved specifically for HFpEF
- Preliminary results from many phase II trials followed by unsuccessful phase III studies
- Unability to identify homogeneous subsets of patients
- Consider therapies that facilitate reverse remodeling by directly targeting the heart itself

Gheorghiade M. Developing new treatments for heart failure. Circulation Heart Failure 2016;9:e002727
Patients at Risk of Developing HFpEF

- Older age
- Hypertension
- Atherosclerotic heart disease
- Diabetes mellitus
- Obesity
- Metabolic syndrome
- Prior use of cardiotoxic drugs
- Previous myocardial infarction
- Unstable angina
- Left ventricular hypertrophy
- Valvular heart disease
- Patients with known structural heart disease
- Chronic obstructive pulmonary disease
- Anemia
- Renal dysfunction
- Sleep disordered breathing
Heterogeneity of Heart Failure with Preserved Ejection Fraction (HFpEF)

Heart Failure with Preserved EF

- Ventricular dysfunction
  - Diastolic dysfunction
  - Systolic dysfunction
- Atrial dysfunction
  - Atrial fibrillation
- Autonomic dysfunction
  - Chronotropic incompetence
- Vascular dysfunction
  - Vascular stiffening
  - Ventriculo-arterial uncoupling
- Pulmonary hypertension
  - Inadequate BP response to exercise
- Valvular
  - Dynamic mitral regurgitation
- Lung Disease
  - COPD
- Iron deficiency and Anemia
- Renal Dysfunction
  - Volume overload
- Aging & Deconditioning
- Obesity & Sarcopenia
- HTN
  - Diabetes
  - ROS production

Diastolic dysfunction
Systolic dysfunction
Atrial dysfunction
Atrial fibrillation
Autonomic dysfunction
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ROS production
Role of biomarkers as a clinical bridge-tool between HFpEF cardiac structural phenotypes and potential treatment strategies

Cardiac Structural Phenotypes in HFpEF

- Myocardial Hypertrophy
  - Renin Aldosterone Angiotensin II
  - ACE-I ARBs ARNi

- Interstitial Fibrosis
  - Galectin-3 sSt-2
  - MRA

- Myocardial Inflammation and Oxidative Stress
  - Interleukins CRP TNFα Matrix turnover biomarkers
  - Weight loss Metformin AGE crosslink breakers Statins

- Coronary Disease
  - Troponin
  - Ranolazine ARNi Ivabradine Calcium antagonists Beta-blockers

D’Elia E. European Journal of Heart Failure 2015;17:1231
### Web Table 9.1  Phase II and III clinical trials performed in patients with heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Major inclusion criteria</th>
<th>Mean follow-up</th>
<th>Primary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP-CHF220</td>
<td>Perindopril vs placebo.</td>
<td>LV wall motion index ≥1.4 (corresponding to LVEF ≥40%), symptomatic HF treated with diuretic, diastolic dysfunction in echocardiography, age ≥70 y.</td>
<td>2.1 y</td>
<td>No difference in combined all-cause mortality or cardiovascular hospitalization (36% vs 37%, P = 0.35).</td>
</tr>
<tr>
<td>I-PRESERVE 318</td>
<td>Irbesartan vs placebo.</td>
<td>LVEF ≥45%, NYHA III–IV with corroborative evidence, or NYHA II with HF hospitalization in recent 6 months, age ≥60 y.</td>
<td>4.1 y</td>
<td>No difference in combined all-cause mortality or HF hospitalization (24% vs 25%, P = 0.54).</td>
</tr>
<tr>
<td>CHARM-Preserved219</td>
<td>Candesartan vs placebo.</td>
<td>LVEF &gt;40%, NYHA II–IV, history of cardiac hospitalization.</td>
<td>3.0 y</td>
<td>Trend towards a reduction in combined cardiovascular mortality or HF hospitalization by 11% (22% vs 24%, unadjusted P = 0.12, adjusted P = 0.051).</td>
</tr>
<tr>
<td>Aldo-DHF230</td>
<td>Spironolactone vs placebo.</td>
<td>LVEF ≥50%, NYHA II–III, peak VO₂ ≤25 mL/min/kg, diastolic dysfunction on echocardiography or atrial fibrillation, age ≥50 y.</td>
<td>1.0 y</td>
<td>Reduction in E/e’ by − 1.5 (P &lt; 0.001) No change in peak VO₂ (P = 0.81).</td>
</tr>
<tr>
<td>TOPCAT310</td>
<td>Spironolactone vs placebo.</td>
<td>LVEF ≥45%, ≥1 HF sign, ≥1 HF symptom, HF hospitalization within recent 12 months, or BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL, age ≥50 y.</td>
<td>3.3 y</td>
<td>No difference in combined cardiovascular death, aborted cardiac arrest, or HF hospitalization (19% vs 20%, P = 0.14).</td>
</tr>
<tr>
<td>SENIORS173</td>
<td>Nebivolol vs placebo.</td>
<td>HF confirmed as HF hospitalization in recent 12 months and/or LVEF ≤35% in recent 6 months, age ≥70 y. 36% with LVEF &gt;35%.</td>
<td>1.8 y</td>
<td>Reduction in combined all-cause mortality or cardiovascular hospitalization by 14% (31% vs 35%, P = 0.04).</td>
</tr>
<tr>
<td>DIG-PEF123</td>
<td>Digoxin vs placebo.</td>
<td>HF with LVEF &gt;45%, sinus rhythm.</td>
<td>3.1 y</td>
<td>No difference in combined HF mortality or HF hospitalization (21% vs 24%, P = 0.14).</td>
</tr>
<tr>
<td>PARAMOUNT309</td>
<td>Sacubitril/valsartan vs valsartan.</td>
<td>HF with LVEF ≥45%, NYHA II–III, NT-proBNP &gt;400 pg/mL.</td>
<td>12 w</td>
<td>Reduction in NT-proBNP: ratio of change sacubitril/valsartan 0.77, 95% CI 0.64–0.92 (P = 0.005).</td>
</tr>
<tr>
<td>RELAX311</td>
<td>Sildenafil vs placebo.</td>
<td>HF with LVEF ≥45%, NYHA II–IV, peak VO₂ &lt;60% of reference values, NT-proBNP &gt;400 pg/mL or high LV filling pressures.</td>
<td>24 w</td>
<td>No change in peak VO₂ (P = 0.90).</td>
</tr>
</tbody>
</table>
Borlaug B. Redfield MM. Are systolic and diastolic heart failure overlapping or distinct phenotypes within the heart failure spectrum? Circulation 2011;123:2006-2014
Table 3.1  Definition of heart failure with preserved (HFrEF), mid-range (HFmrEF) and reduced ejection fraction (HFpEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs(^a)</td>
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</tr>
<tr>
<td>2</td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>3</td>
<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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</tr>
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\(^a\)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.
Potential approach for matching key HFpEF phenotypes to select therapeutic interventions (I)

HF symptoms, EF ≥ 50%+ primary Comorbidity(es)

- HTN
  - ARB/ACEI
  - MRA
  - MRA
  - Autonomic modulation

- Fluid retention
  - Elevated filling pressure
  - ARNi

- Diabetes
  - Obesity
  - Metabolic syndrome
  - Glycemic control
    - Metformin
    - Weight loss
    - Bariatric surgery
    - Diet
    - PKG stimulation
    - AGE crosslink breakers?

Potential approach for matching key HFpEF phenotypes to select therapeutic interventions (II)

HF symptoms, EF ≥ 50%+ primary Comorbidity(es)

- Pulmonary hypertension or right heart involvement
  - PD5 Inhibitor
  - Orally active soluble guanylate cyclase stimulator

- Ischemia coronary heart disease
  - Na channel blockers
  - Nitrates
  - Beta blockers
  - Calcium antagonists
  - Ivabradine

- Renal disease
  - Sodium restriction
  - ACEI or ARB

Role of the nitric oxide-cyclic guanosine monophosphate protein kinase pathway in the cardiomyocyte.

Cardiomyocyte signalling pathways involved in regulating cardiac titin stiffness


<table>
<thead>
<tr>
<th>Trial acronym</th>
<th>Target intervention</th>
</tr>
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<tbody>
<tr>
<td>FAIR-HPEF (not yet recruiting)</td>
<td>Iron deficiency: ferric carboxymaltose (iv. iron)</td>
</tr>
<tr>
<td>Mito-HPEF (not yet recruiting)</td>
<td>Energy deficit: bendavia (mitochondrial enhancer)</td>
</tr>
<tr>
<td>EDIFY</td>
<td>Heart rate: ivabradine (sinus node inhibition)</td>
</tr>
<tr>
<td>Ex-DHF</td>
<td>Deconditioning: endurance/resistance training</td>
</tr>
<tr>
<td>OPTIM-EX</td>
<td>Deconditioning: high intensity interval training</td>
</tr>
<tr>
<td>SOCRATES-Preserved</td>
<td>cGMP deficiency: vericiguat (soluble guanilate cyclase stimulation)</td>
</tr>
<tr>
<td>PARAGON-HF</td>
<td>cGMP deficiency: LCZ 696 (neprilysin inhibition)</td>
</tr>
</tbody>
</table>
Lack of therapies for HFpEF continues to be a huge unmet need

The macroscopic and microscopic structural abnormalities of the heart should be the focus of HF research and drug development

Testing novel therapeutic hypothesis to extend healthy life among HF patients must continue