Heart Failure with Preserved Ejection Fraction

Advances in Heart Failure CME Course

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Disclosures

- I have no financial disclosures
Overview

1. Definitions
2. Demographics and Epidemiology
3. Mortality
4. Pathophysiology
5. Diagnosis
6. Clinical Trials
7. Guidelines

Definitions
Ejection Fraction Terminology

- Heart Failure with Reduced Ejection Fraction (<40%)
- Heart Failure with Mid-Range Ejection Fraction (EF 40-49%)
- Heart Failure with Preserved Ejection Fraction (≥50%)

Issues with “Systolic” and “Diastolic”

- Often have an increase in LV wall thickness and/or increased LA size as a sign of increased filling pressures.
- Most have ‘evidence’ of impaired LV filling or suction capacity, also classified as diastolic dysfunction.
- Most patients with HFrEF also have diastolic dysfunction.
- HFP EF patients have subtle abnormalities of systolic function.
Definition of HFpEF (EF ≥ 50%)
Direct Quote from the 2013 ACC/AHA HF Guidelines

“Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. 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.”


Definition of HFpEF (EF ≥ 50%)
From the 2016 ESC HF Guidelines

- Signs/symptoms of heart failure
- Elevated levels of natriuretic peptides (BNP>35 pg/ml and/or NT-proBNP>125 pg/mL)
- At least 1 of the following:
  - Relevant structural heart disease (LVH and/or LAE)
  - Diastolic dysfunction

Ponikowski et al. EHJ. Volume 37, Issue 27, 14 July 2016
The 1 Common HFpEF Denominator

Elevated filling pressures
In the LV
In diastole

Demographics and Epidemiology
How Common is HFpEF?

- Framingham: 12,857 person-observations, 1985-2014
- The frequency of:
  - HF with reduced EF (EF <40%) decreased over time
  - HF with mid-range EF (40% to <50%) remained stable
  - HF with preserved EF (EF ≥50%) increased over time

Vasan et al. JACC Cardiovasc Imaging. 2018; 11:1–11

Increasing Hospitalizations for HFpEF
**HFpEF Demographics**

Pooled Data from CHARM-preserved, I-PRESERVE, and TOPCAT

- **CHARM-Preserved:** candesartan, Lancet 2003, LVEF >40%
- **I-PRESERVE:** irbesartan, NEJM 2013, LVEF ≥45%
- **TOPCAT:** spironolactone, NEJM 2014, LVEF ≥45%
- Excluded patients with an LVEF <45% from CHARM-preserved and patients from Russia and Georgia in TOPCAT due to doubts about the reliability of diagnosis of HFpEF

Tromp, J. et al. JACC. 2019;74(5):601-12

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**Younger patients:**
More often obese black or Asian men with a lower comorbidity burden, yet had worse quality of life.

**Older patients:**
More often white women with a higher comorbidity burden.

CHANGING EPIDEMIOLOGY OF OVERT HF. Using the same standardized criteria for HF consistently over a 30-year period, we confirm and extend prior observations made in Olmsted County from 2000 to 2010 (10) (using validated International Classification of Diseases, Ninth Revision codes) documenting the increasing predominance of HFpEF over HFrEF.

Temporal trends in risk factors for HFrEF versus HFpEF (a lower prevalence of CHD and rising hypertension rates among those with HF) (1) explained about 75% of the observed shift toward a greater prevalence of HFpEF. An increased awareness of HFpEF in recent decades may have also contributed to this trend.

Among HF patients in our investigation, the prognosis of those with HFrEF improved over the last 2 decades, as evidenced by a 30% to 40% decline in cardiovascular mortality. All-cause and cardiovascular mortality for the HFmrEF and HFpEF groups remained unchanged. The absolute mortality distribution suggests that the decline in prevalence of LVSD was not limited to the lower extreme (LVEF < 40%) of the distribution. Temporal trends in risk factors accounted for about 45% of the shift in LVEF distribution. This observation likely reflects the net balance between positive (rising burden of hypertension and obesity, and declining rates of smoking and total to high-density lipoprotein cholesterol) and negative correlates of LVEF (increase in prevalence of diabetes [1] and MI).

Improved management of MI and decline in the occurrence of ST-segment elevation MI (28) may have also contributed. It is important to note that more than one-half of the changes remained unexplained, suggesting the need for additional study. We did not observe any change in prognosis of LSVD over time, with a 2- to 4-fold increased risk of the composite outcome, despite availability of evidence-based treatment recommendations for those with LVEF < 40% (29).


HFrEF
HFmrEF
HFpEF

The horizontal line indicates median survival, and the vertical lines show median survival time for participants with new-onset heart failure (HF) for each subtype of HF.
### Mortality

Data from CHARM-preserved, I-PRESERVE, and TOPCAT

- **Age ≤55 years:** 30 (6%) died after 5 years
  - Event rate: 1.9 (95% CI: 1.3 to 2.7) per 100 patient-years
- **Age ≥85 years:** 190 (47%) died after 5 years
  - Event rate: 16.7 (95% CI: 14.5 to 19.3) per 100 patient-years

Tromp, J. et al. JACC. 2019;74(5):601-12
Tromp, J. et al. JACC. 2019;74(5):601-12

Pathophysiology
**Neurohormonal Activation in HFrEF**

Myocardial injury to the heart (CAD, HTN, CMP, valvular disease)

- Initial ↓ in LV performance, ↑ wall stress
- Activation of RAAS and SNS
- Remodeling and progressive worsening of LV function
- Fibrosis, apoptosis, hypertrophy, cellular/molecular alterations, myotoxicity
- Peripheral vasoconstriction, hemodynamic alterations
- Morbidity and mortality
  - Arrhythmias
  - Pump failure

RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system

Adapted from Goodman & Gilman’s The Pharmacological Basis of Therapeutics. 2011. McGraw-Hill Education/Medical

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**PATHOPHYSIOLOGIC PHENOTYPES IN HFrEF**

- **Arterial Stiffening**
  - Aortic compliance
  - Vasorelaxation with exercise
  - Blood pressure lability
- **Skeletal Myopathy**
  - Diffusive O2 conductance
  - Capillary density
  - Muscle quality
  - Exercise capacity
- **Myocardial Ischemia**
  - Myocyte injury
  - Exercise capacity
  - LV reserve
  - Mortality
- **Obesity**
  - Plasma volume
  - Filling pressure
  - Ventricular remodeling
  - Myocardial FA uptake
  - Exercise capacity
  - Ventricular interaction
  - PV disease
  - RV-PA coupling
  - RV function
- **Coronary microvascular dysfunction**
  - PA pressure
  - PV remodeling
  - RV reserve
  - Exercise capacity
  - Mortality
- **Pulmonary Vascular & RV Dysfunction**
  - PA pressure
  - PV remodeling
  - RV reserve
  - Exercise capacity
  - Mortality
- **Inflammation**
  - NO-cGMP
  - Endothelial fxn
  - LV fibrosis
  - LV stiffness
  - Epicardial adipose tissue
- **Cardiometabolic Comorbidities**
  - Ventricular stiffening
  - Myocardial efficiency
  - LV/RV reserve
  - Exercise capacity
- **Atrial dysfunction & Atrial fibrillation**
  - Exercise capacity
  - Mortality
  - Pulmonary capillary pressure

Obokata, et al. JACC: CV Imaging 2019
LV Diastolic Dysfunction

- **Definition:** Impairment in relaxation and/or an increase in chamber stiffness
- **Symptoms:** caused by elevated filling pressures at rest or with exertion
- **Declines:** in LV relaxation and compliance seen with normal aging or with cardiometabolic comorbidities (e.g., obesity, insulin resistance, and HTN)
- **Not all patients:** with diastolic dysfunction have or will develop clinical HFpEF
LV Systolic Dysfunction

- LV systolic performance is not normal in HFpEF
  - Abnormal endocardial and midwall shortening, twisting, or circumferential and longitudinal shortening using tissue Doppler or strain imaging
- Subtle impairments in systolic function at rest become dramatic during exercise in patients with HFpEF
  - Decreased exercise capacity, impaired early diastolic recoil and LV suction, impaired cardiac output, and elevation in LV filling pressures

Pulmonary Hypertension

- Seen in ~ 80% of HFpEF patients
- Predominantly related to LA hypertension
- Substantial number develop pulmonary vascular disease (elevation in PVR and reduction in PA compliance)
  - Adverse outcomes, worse exercise capacity
  - During exercise can see impaired recruitment of LV preload due to excessive R-heart congestion and blunted RV systolic reserve
- May only see during exercise
Invasive cardiopulmonary exercise testing has emerged as the gold standard to definitively identify or exclude HFpEF as the cause of dyspnea.

Filling pressures are often normal at rest but become elevated only during the stress of exercise.
### Definition of HFpEF (EF ≥ 50%)

From the 2016 ESC HF Guidelines

- Signs/symptoms of heart failure
- Elevated levels of natriuretic peptides (BNP>35 pg/ml and/or NT-proBNP>125 pg/mL)
- At least 1 of the following:
  - Relevant structural heart disease (LVH and/or LAE)
  - Diastolic dysfunction

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### Making the Diagnosis at Mayo Clinic

- Consecutive patients with unexplained dyspnea referred for invasive hemodynamic exercise testing
  - Derivation cohort: 414 consecutive patients (267 HFpEF and 147 controls)
  - Test cohort: 100 consecutive patients (61 HFpEF)
- HFpEF Definition: Elevated pulmonary capillary wedge pressure at rest (≥15 mmHg) or during exercise (≥25 mmHg)
Making the Diagnosis, cont.

- **Exclusion criteria:**
  - LVEF <50% (current or prior)
  - Valvular heart disease (>mild stenosis, >moderate regurgitation)
  - Pulmonary arterial hypertension
  - Constrictive pericarditis
  - Primary cardiomyopathies
  - Heart transplant

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<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Values</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong>&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Heavy</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Body mass index &gt; 30 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertensive</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2 or more antihypertensive medicines</td>
<td></td>
</tr>
<tr>
<td><strong>F</strong></td>
<td>Atrial Fibrillation</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal or persistent</td>
<td></td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>Pulmonary Hypertension</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Doppler echocardiographic estimated right ventricular systolic pressure &gt; 35 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>E</strong></td>
<td>Elder</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 60 years</td>
<td></td>
</tr>
<tr>
<td><strong>F</strong></td>
<td>Filling Pressure</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Doppler echocardiographic E/e' &gt; 9</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>H&lt;sub&gt;2&lt;/sub&gt;FPEF score</th>
<th>Sum (0-9)</th>
</tr>
</thead>
</table>

Total Points | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
Probability of HFP EF | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | 0.95 |
Clinical Trials for Medical Therapy

Negative Trials

- ACE/ARB (ESC Heart Failure SRMA 2017)
- Sildenafil (RELAX 2013)
- Nitrates (NEAT-HFpEF 2015)
- Spironolactone*
- Sacubitril/valsartan*
Spironolactone? - TOPCAT, NEJM 2014

- 3445 patients with symptomatic HF and LVEF ≥ 45%
- No significant reduction in the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.

BUT, what about Russia and Georgia (49% of study)?

Primary Outcome

- Hazard ratio for treatment with spironolactone
  - Americas: 0.82 (95% CI, 0.69–0.98)
  - Russia/Georgia: 1.10 (95% CI, 0.79–1.51)
- Interaction between treatment and region was NOT significant (P=0.12)
Sacubitril/Valsartan in PARAGON-HF

- 4822 patients age ≥50, NYHA class II to IV, EF ≥45% and:
  - HF hospitalization within 9 months prior to screening visit and NT-proBNP >200 pg/ml for patients not in AF or >600 pg/ml for patients in AF on screening ECG
  OR
  - NT-proBNP >300 pg/ml for patients not in AF or >900 pg/ml for patients in AF on the screening visit ECG

- **Primary outcome**: composite of total hospitalizations for HF and death from CV causes

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PARAGON-HF Results

- **Primary outcome**: 13% relative risk reduction (RR, 0.87; 95% CI, 0.75 - 1.01; P = .06)

- For sacubitril/valsartan as compared to valsartan:
  - No difference in death from cardiovascular causes (HR 0.95; 95% CI, 0.79 to 1.16)
  - Suggestion of reduction in total HF hospitalizations (rate ratio, 0.85; 95% CI, 0.72 to 1.00)
  - Improvement in NYHA class (odds ratio, 1.45; 95% CI, 1.13 to 1.86);
12 Pre-Specified PARAGON Subgroups

- In multivariable model, suggestion of heterogeneity of treatment effect with possible benefit in:
  - Women (RR 0.73, 95% CI 0.59-0.90)
  - Patients with EF in lower range of 45% to 57% (RR 0.78, 95% CI 0.64-0.95)
- Similar benefit as for EF < 40%

Pooling Sacubitril/Valsartan Data

- Pre-specified pooled analysis of 13,195 patients from PARADIGM-HF and PARAGON-HF
- Overall, sacubitril/valsartan was superior for:
  - 1st CV death or HF hospitalization (HR 0.84, 95% CI 0.78, 0.90)
  - Cardiovascular death (HR 0.84, 95% CI 0.76, 0.92)
  - Heart failure hospitalization (HR 0.84, 95% CI 0.77, 0.91)
  - All-cause mortality (HR 0.88, 95% CI 0.81, 0.96)
Continuous Treatment Effects of ARNI vs. Active Comparator by Sex

Coming Soon...

- Dapagliflozin (10 mg)
  - DELIVER – dapagliflozin versus placebo
    - Goal: 4700 patients
    - Estimated completion: 2021

- Empagliflozin (10 mg)
  - EMPEROR-Preserved – empagliflozin versus placebo
    - Goal: 5720 patients
    - Estimated completion: 2020
Guideline-Directed Medical Therapy

Medications with a Class I Recommendation for HFpEF
### Recommendations for Stage C HfPEF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
<th>COMMENT/RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B</td>
<td>Systolic and diastolic blood pressure should be controlled in patients with HfPEF in accordance with published clinical practice guidelines to prevent morbidity (164,165).</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>I</td>
<td>C</td>
<td>Diuretics should be used for relief of symptoms due to volume overload in patients with HfPEF.</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td>Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HfPEF despite GDIMT.</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td>Management of AF according to published clinical practice guidelines in patients with HfPEF is reasonable to improve symptomatic HF.</td>
<td>2013 recommendation remains current (Section 9.1 in the 2013 HF guideline).</td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td>The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HfPEF.</td>
<td>2013 recommendation remains current.</td>
</tr>
</tbody>
</table>

### 2017 ACC/AHA/HFSA Update, cont.

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIB</td>
<td>B-R</td>
<td></td>
<td>In appropriately selected patients with HfPEF (EF ≥45%, elevated BNP levels or HF admission w/ 1 year, eGFR &gt;30 mL/min, Cr &lt;2.5 mg/dL, K+ &lt;5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations</td>
<td>Current recommendation reflects new RCT data.</td>
</tr>
<tr>
<td>IIB</td>
<td>B</td>
<td></td>
<td>The use of ARBs might be considered to decrease hospitalizations for patients with HfPEF</td>
<td>2013 recommendations remain current.</td>
</tr>
<tr>
<td>III – No Benefit</td>
<td>B-R</td>
<td></td>
<td>Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HfPEF is ineffective</td>
<td>Current recommendation reflects new data from RCTs.</td>
</tr>
<tr>
<td>III – No Benefit</td>
<td>C</td>
<td></td>
<td>Routine use of nutritional supplements is not recommended for patients with HfPEF.</td>
<td>2013 recommendations remain current.</td>
</tr>
</tbody>
</table>
Treat the Comorbidities

- Diuresis
- Manage HTN
- Treat atrial fibrillation
- Wear CPAP
- Lose weight
- Control blood sugar

Conclusions
HFpEF is Tough

- No therapies with mortality benefit
- Outcomes just as bad as HFrEF
- Increasing prevalence

Conclusions

- Elevated filling pressures in the LV in diastole
- Think about HFpEF when you see syndrome of HF
- Rule out other potential etiologies
- Exercise hemodynamics
- Treat the comorbidities
Thank you!

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