Treating HFpEF – One Size Doesn’t Fit All

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Types of Heart Failure

Heart Failure Reduced Ejection Fraction
- Enlarged left ventricle
- Reduced pumping ability
- Thinned walls
- Weakened muscle

Normal Heart

Heart Failure Preserved Ejection Fraction
- Normal or small left ventricle size
- Thickened walls
- Stiff muscle
- Normal pumping capacity

High pressure needed to fill the ventricle
HFpEF

Heart Failure with Preserved Ejection Fraction (HFpEF)

- Signs and symptoms of HF occurring in patients with normal or near-normal EF (>0.50 or 0.45).
- Doesn’t exclude abnormalities in systolic function, but mildly reduced EF is not usually associated with HF in the absence of other factors.
- The constellation of clinical signs and symptoms leading to the consideration of HFpEF can be caused by diverse cardiac (e.g. MS, constriction) and non-cardiac etiologies (e.g. obesity, COPD).
Distribution of EF in HF Patients

N = 482
Mean LVEF = 38±14%
Median LVEF = 35%

Delepaol et al. ESC HF. 2017 May; 4(2): 99–104
Diagnosing HFpEF

- Confirm that signs and symptoms are due to HF – exclude other cardiac (e.g. mitral stenosis, HOCM) or non-cardiac diseases (e.g. anemia, COPD, deconditioning, obesity).

- Echo to measure EF, detect essence presence of ‘fellow travelers’ (LVH, LAE and PHT), assess diastolic function.

- Natriuretic peptide levels are often elevated…but not always.

- Right heart catheterization when there is uncertainty.

- Stress test or angiography to assess CAD in selected cases.
Prevalence of HFP EF
13 Community Based Studies 1997 - 2006

Median = 52%  Mean = 55%

Reviewed by Hogg K et al, 2004 and Owan T et al, 2005, Owan T, NEJM, 2006; Bursi F, JAMA, 2006
Outcomes in HFpEF, HFrEF and HFmrEF

GWTG in the U.S.¹

Shah KS et al, Journal of the American College of Cardiology, Volume 70, Pages 2476-2486

European Registry²


¹Shah KS et al, Journal of the American College of Cardiology, Volume 70, Pages 2476-2486
²Delepaule et al. ESC HF. 2017 May; 4(2): 99–104
ACC/AHA Guidelines – Class I Recommendations

ACC/AHA Guidelines – Class I Recommendations

- Control BP (<130/80 mmHg) *LOE B*
- Diuretics should be used for relief of symptoms due to volume overload *LOE C*

How to Accomplish Treatment Goals

- Agent not specified
ACC/AHA Guidelines

Class IIa

- Coronary revascularization in patients with angina or if ischemia is thought to be affecting HFpEF symptoms despite GDMT
  
  LOE C

- Management of atrial fibrillation according to practice guidelines
  
  LOE C

- The use of beta blockers, ACEIs and ARBs to control BP
  
  LOE C
ACC/AHA Guidelines

Class IIb

• In appropriately selected patients with HFrEF (with EF $\geq$45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate $>30$ mL/min, creatinine $<2.5$ mg/dL, potassium $<5.0$ mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations \textit{LOR B-R}

• The use of ARBs might be considered to decrease hospitalizations for patients with HFrEF \textit{LOE B}
Characteristics of HFpEF vs HFrEF Patients

**Differences**
- More women
- Older
- Less CAD and MI
- More hypertension (past and current)
- Smaller, thicker LV
- Less LBBB and IVCD

**Similarities**
- Race
- Diabetes
- Tobacco
- Atrial fibrillation
- Lipids
- Weight
Biological Phenotypes in HFpEF

Phenotype Heat Map (Phenomap) of HFpEF

Outcomes by HFpEF Phenogroup.

Group 1 – least remodeling and hemodynamic derangement

Group 2 – higher likelihood of obesity and diabetes

Group 3 – more remodeling (LVH, LAE), higher L and R sided filling pressures and PA pressures. More severe diastolic abnormalities on echo
Survival Free of CV Hospitalization or Death

Comorbidities Influence Myocardial and Endothelial Function

Myocardial Remodeling in HFPEF
Importance of Comorbidities

- Overweight/Obesity
- Hypertension
- Diabetes Mellitus
- COPD
- Iron Deficiency

• IL-6
• TNF-α
• sST2
• Pentraxin 3

Endothelium

OnoO-

ROS

VCAM, E-selectin

Leukocytes

TGF-β

ONOO-

NO

Cardiomyocytes

sGC

cGMP

PKG

Hypertrophy

Paulus W and Tschope C. JACC, 2013:62;263–271
Systemic and myocardial signaling in HFPEF. Comorbidities induce systemic inflammation, evident from elevated plasma levels of inflammatory biomarkers such as soluble interleukin 1 receptor-like 1 (IL1RL1), C-reactive protein (CRP), and growth differentiation factor 15 (GDF15).

% Deaths Due to Non-CV Causes

Olmsted County MN 1979-2002
1,063 Pts

Deaths due to Non-CV Causes More Common in HFpEF

5-Year Mortality 55%; HFpEF=HFrEF
Management of HFpEF Patients with Signs/Symptoms of Congestion

- Make sure signs/symptoms are due to volume overload
- Control BP
- Rate control of atrial fibrillation
- Diuresis using loop diuretic
- Experimental approaches
Tissue Doppler and PCWP

Ratio of $E$ to $E'$

- $E/E' > 15-20$: High PCWP
- $E: 160$ cm/s
- $E': 7$ cm/s
- $E/E': 23$
When the Diagnosis is in Doubt…Go to the Table of Truth!

Transcatheter Interatrial Shunt (REDUCE LAP-HF)

Shah S et al. JAMA Cardiol 2018;3:968-77.
Transcatheter Interatrial Shunt (REDUCE LAP-HF)

Shah S et al. JAMA Cardiol 2018;3:968-77.
Pericardial Release

Borlaug et al. Circ Heart Fail. 2017 Apr; 10(4);
Effects of Releasing Pericardial Restraint

Borlaug et al. Circ Heart Fail. 2017 Apr; 10(4);
Effects of Releasing Pericardial Restraint

Borlaug et al. Circ Heart Fail. 2017 Apr; 10(4);
Management of HFpEF Patients with Low EF


Myocardial Fibrosis Is Associated With Diastolic Dysfunction in HFpEF
Increased Deposition of Collagen in the Myocardium of HFpEF Patients

Zile et al, Circulation 2015 Apr 7;131(14):1247-59
CMR Detected Fibrosis is Associated with Outcomes in HFpEF Patients

HFpEF and Atrial Fibrillation: Vicious Twins

HFpEF in Atrial Fibrillation Studies

Atrial Fibrillation in HFpEF Studies

Atrial Fibrillation in HF Patients According to EF and Gender

Sartipy L et al. JACC:HF: 5; 566-574, 2017
Atrial Fibrillation Is Associated with Increased Risk Regardless of EF

Sartipy L et al. JACC:HF: 5; 566-574, 2017
# Diagnosis and Management of Concomitant HFpEF and A Fib

<table>
<thead>
<tr>
<th>Treatment recommendations for AF and HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognostic</strong></td>
</tr>
<tr>
<td>Anticoagulation with NOACs or VKA (all patients ≥65 years or other risk factors)</td>
</tr>
<tr>
<td><strong>Disease modifying</strong></td>
</tr>
<tr>
<td>• Anti-hypertensive therapy</td>
</tr>
<tr>
<td>• Treatment of myocardial ischemia</td>
</tr>
<tr>
<td>• Management of associated comorbidities</td>
</tr>
<tr>
<td><strong>Symptomatic therapy</strong></td>
</tr>
<tr>
<td>• Diuretics</td>
</tr>
<tr>
<td>• Heart rate control (resting &lt;110 bpm; lower if ongoing symptoms)</td>
</tr>
<tr>
<td>• AF rhythm control</td>
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</tbody>
</table>

Implications of CAD in HFpEF Patients

Impact of Revascularization on Survival in Patients With HFpEF

Relation Between Age and E’

VALIDDD Randomised Patients

LV Pressure Volume Relationship is Altered in HFpEF Patients

Zile M et al: NEJM, 2004
Change in Lateral E’ for Each Quartile of SPB Reduction

Normalized Peak VO2 Increases With Lifelong Exercise

Bhella PS et al JACC, Volume 64, Issue 12, 2014, 1257–1266
Effects of a 20-Week Caloric Restriction Diet on Exercise Capacity and Quality of Life in HFpEF

LV End Diastolic PV Relationships Are Related with Life Long Exercise Patterns
Preventing HFpEF Is the Best Treatment!

I can't believe I ate all that kale for nothing.
**Empa-Reg Outcome**

**Trial design: SGLT2 Inhibitor**

- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m²; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m² (MDRD)
  - 10.2% of patients enrolled with pre-existing heart failure

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EMPA-REG OUTCOME Study

HF Hospitalization or CV Death

HF Hospitalization or HF Death

7020 adults with type 2 diabetes and established CVD
BMI ≤45 kg/m²; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m² (MDRD)

Heart Failure Hospitalization or CV Death in Patients with vs without HF at Baseline

**CANVAS Program**

**Hospitalization for Heart Failure**


<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of participants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>4347</td>
<td>5795</td>
</tr>
<tr>
<td>1 year</td>
<td>4198</td>
<td>5653</td>
</tr>
<tr>
<td>2 years</td>
<td>3011</td>
<td>4437</td>
</tr>
<tr>
<td>3 years</td>
<td>1274</td>
<td>2643</td>
</tr>
<tr>
<td>4 years</td>
<td>1236</td>
<td>2572</td>
</tr>
<tr>
<td>5 years</td>
<td>1180</td>
<td>2498</td>
</tr>
<tr>
<td>6 years</td>
<td>829</td>
<td>1782</td>
</tr>
</tbody>
</table>

HR 0.67
(95% CI 0.52, 0.87)
ARR = 1.6% at 5 y;
NNT3y = 105; NNT5y = 63

**33% RRR**
**NNT = 63**
Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

17,160 patients with type II diabetes, including 10,186 without ASCVD randomized to dapagliflozin 10 mg daily vs placebo, who were followed for a median of 4.2 years.

NEJM 2018
### Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</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>
<td>126, 129, 150, 151</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>
<td>137–140, 152</td>
</tr>
<tr>
<td>Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.</td>
<td>I</td>
<td>C</td>
<td>131–134</td>
</tr>
<tr>
<td>Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.</td>
<td>IIa</td>
<td>C</td>
<td>130, 141, 153–155</td>
</tr>
<tr>
<td>Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.</td>
<td>IIa</td>
<td>B</td>
<td>130</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>
<td>5, 144, 145</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>
<td>5</td>
</tr>
<tr>
<td>ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.</td>
<td>IIa</td>
<td>A</td>
<td>142</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>
<td>146</td>
</tr>
</tbody>
</table>
Management of HFpEF

**Universal**
- Diuresis as needed
- Control BP
- Manage AF according to guideline recommendations

**Personalized**
- Coronary revascularization
- Treat individual co-morbidities
- MRA for low EF
- Caloric restriction and exercise training
- SGLT2 inhibitors for diabetics