Heart Failure with Preserved Ejection Fraction

Ioana Dumitru, MD, FACC
Medical Director AHF and Cardiac Transplantation
MRH
No Disclosures
Objectives

• Review pathophysiology, diagnosis and treatment of HFpEF
• How do we risk stratify patients
• Review + trials/negative trials
• Monitoring/cardiomems
• What's in the pipe
## Treatment of HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>
### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and noncardiovascular co-morbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>
Pathophysiology

J of CV Transl Research 2017
A Traditional Model

- **Systemic hypertension**
  - Vascular dysfunction

Left Ventricle

- Concentric hypertrophy
- Fibrosis
- Diastolic dysfunction

  - Left atrial hypertension

Left Atrium

- Remodeling
  - Diastolic dysfunction
  - Systolic dysfunction

  - Pulmonary hypertension
  - Atrial fibrillation

Right Ventricle

- Remodeling
  - Diastolic dysfunction
  - Systolic dysfunction

  - Right atrial hypertension

Right Atrium

- Remodeling
  - Diastolic dysfunction
  - Systolic dysfunction

B Emerging Model

- **Proinflammatory coexisting conditions**

  - Systemic microvascular endothelial inflammation

  - Increases in oxidative stress
  - Decreases in NO–cyclic GMP signaling

  - Muscle inflammation

  - Microvascular dysfunction and rarefaction

  - Myofiber stiffness
  - Cardiomyocyte hypertrophy

  - Fibrosis

  - Global cardiac remodeling and dysfunction
  - Impaired coronary flow reserve
  - Impaired oxygen delivery, uptake, and utilization in skeletal muscle
Pheno-group #1
BNP deficiency syndrome
HFpEF phenotype

Pheno-group #2
Obesity-cardiometabolic
HFpEF phenotype

Pheno-group #3
RV failure + cardiorenal
HFpEF phenotype

Least cardiac remodeling/dysfunction
Lowest BNP

Most severely impaired myocardial relaxation
Highest prevalence of diabetes

Most severe electrocardiographic remodeling, RV dysfunction, renal dysfunction
<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Values</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong>2 <strong>H</strong>eavy</td>
<td>Body mass index &gt; 30 kg/m²</td>
<td>2</td>
</tr>
<tr>
<td><strong>H</strong>ypertensive</td>
<td>2 or more antihypertensive medicines</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong>trial <strong>F</strong>ibrillation</td>
<td>Paroxysmal or Persistent</td>
<td>3</td>
</tr>
<tr>
<td><strong>P</strong>ulmonary <strong>H</strong>ypertension</td>
<td>Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure &gt; 35 mmHg</td>
<td>1</td>
</tr>
<tr>
<td><strong>E</strong>lder</td>
<td>Age &gt; 60 years</td>
<td>1</td>
</tr>
<tr>
<td><strong>F</strong>illing <strong>P</strong>ressure</td>
<td>Doppler Echocardiographic E/e’ &gt; 9</td>
<td>1</td>
</tr>
</tbody>
</table>

**H₂FPEF score**

<table>
<thead>
<tr>
<th>Total Points</th>
<th>Probability of HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>0.2-0.95</td>
</tr>
</tbody>
</table>
# ESC HFA-PEFF Score

## HFpEF workup

<table>
<thead>
<tr>
<th>Functional</th>
<th>Morphological</th>
<th>Biomarker (SR)</th>
<th>Biomarker (AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| septal $e' < 7 \text{cm/s}$ or lateral $e' < 10 \text{cm/s}$ or
  Average $E/e' \geq 15$ | LAVI $> 34 \text{ml/m}^2$ + or $LVMi \geq 149/122 \text{g/m}^2 \text{(m/w)}$ and $RWT > 0.42$ | NT-proBNP $> 220 \text{pg/ml}$ or $BNP > 80 \text{pg/ml}$ | NT-proBNP $> 660 \text{pg/ml}$ or $BNP > 240 \text{pg/ml}$ |
| **Minor**  |               | NT-proBNP 125-220 pg/ml or $BNP 35-80 \text{pg/ml}$ | NT-proBNP 365-660 pg/ml or $BNP 105-240 \text{pg/ml}$ |
| Average $E/e' 9 - 14$ or $TR \text{velocity} > 2.8 \text{m/s}$ or $GLS < 16\%$ | LAVI 29-34 ml/m² or $LVMi > 115/95 \text{g/m}^2 \text{(m/w)}$ or $RWT > 0.42$ or $LV \text{wall thickness} \geq 12 \text{mm}$ | NT-proBNP 125-220 pg/ml or $BNP 35-80 \text{pg/ml}$ | |
|           |               |                |                |
| Major Criteria: 2 points | Minimum Criteria: 1 point | ≥ 5 points: HFpEF | 2–4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements |
Diagnosis

- ECG: LVH, LAE, A fib
- CxR: cardiomegaly, edema, effusion
- BNP>100, NT proBNP>400
- Echo: LVH, LAV>34, E/A >2, E/e’>15, DT <140, septal e’<8
- PASP>35
- RVE, RV systolic dysfunction
Other Testing

• Stress test
• RHC, LHC
• Exercise hemodynamic testing in lieu of normal resting hemodynamics
• Cardio pulmonary exercise testing
• PYP r/o attr amyloidosis
Treatment

• Diuretics
TOPCAT: Results by Region

Potential benefit in patients who actually HAD heart failure!

**US, Canada, Argentina, Brazil**

HR=0.82 (0.69-0.98)

**Russia, Rep Georgia**

HR=1.10 (0.79-1.51)

Interaction p=0.122

Placebo:
- US, Canada, Argentina, Brazil: 280/881 (31.8%)
- Russia, Rep Georgia: 71/842 (8.4%)

Treatment of comorbidities

Evaluate and manage underlying cardiovascular diseases and coexisting conditions

- Hypertension
  - Diuretics
    - ACE or ARB (if patient has chronic kidney disease)
    - Other agents according to side effects and effectiveness
- Elevated cardiovascular risk
- Coronary disease
- Atrial fibrillation
- Obesity
- Kidney disease
- Lung disease/Sleep apnea

Consider rhythm control for persistent symptoms

Education regarding heart failure and self-care
Aerobic exercise training

NEJM 11/2016
Outcomes Trials in HFpEF

**CHARM-Preserved**
- Placebo: 366 (24.3%)
- Candesartan: 333 (22.0%)

HR 0.89 (95% CI 0.77-1.03), P=0.118
Adjusted HR 0.86, P=0.051

**PEP-CHF**
- Perindopril
- Placebo
HR 0.92; 95% CI 0.70 to 1.21; P=0.545

**I-PRESERVE**
- Placebo
- Irbesartan
N=4,128
(Mean follow-up 49.5 months)

**TOPCAT**
- Placebo
- Spironolactone
HR = 0.89 (0.77 – 1.04)
p=0.138
No Support for a Sildenafil in HFPeF

**Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction**
A Randomized Clinical Trial

### Table I. Primary, Secondary, and Safety End Points

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sildenafil</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 24 wk, median (IQR), ml/kg/min</td>
<td>94</td>
<td>0.26 (-0.16 to 1.93)</td>
<td>94</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 24 wk, median (IQR), m</td>
<td>94</td>
<td>15.6 (-26.6 to 60.5)</td>
<td>94</td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 12 wk, median (IQR), ml/kg/min</td>
<td>94</td>
<td>0.29 (-1.16 to 0.67)</td>
<td>94</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 12 wk, median (IQR), m</td>
<td>94</td>
<td>18.6 (-41.5 to 41.6)</td>
<td>94</td>
</tr>
<tr>
<td><strong>Compelments of clinical trial score at 24 wk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, No. (%)</td>
<td>103</td>
<td>0</td>
<td>113</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular related cause, No. (%)</td>
<td>103</td>
<td>12 (12)</td>
<td>113</td>
</tr>
<tr>
<td>Change in MHS (HS), median (25-75)</td>
<td>94</td>
<td>-1 (-2.1 to 0.7)</td>
<td>94</td>
</tr>
<tr>
<td>Safety end points, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>103</td>
<td>78 (75)</td>
<td>113</td>
</tr>
<tr>
<td>Severe adverse events</td>
<td>103</td>
<td>16 (15)</td>
<td>113</td>
</tr>
</tbody>
</table>

**Change in left ventricular structure by CMR at 24 wk**
Left ventricular mass by CMR, g
- 47 | 0.6 (-5.7 to 13.6) | 49 | 1.8 (-0.8 to 7.1) | .33 |
- 47 | -4.0 (-11.3 to 3.2) | 49 | 3.7 (-4.6 to 14.0) | .13 |

**Change in diastolic function parameters at 24 wk**
E, cm/s
- 132 | 0.02 (-0.01 to 0.03) | 77 | 0.00 (-0.01 to 0.01) | .18 |
IVCT, ms
- 132 | 0.0 (-4.7 to 3.0) | 75 | 0.0 (-4.0 to 3.1) | .18 |
IVRT, ms
- 132 | -2 (-3.4 to 1.8) | 45 | 0.0 (-1.6 to 7.7) | .34 |

Change in core laboratory biomarkers at 24 wk
Oxidase, nM/L
- 94 | 0.00 (-0.10 to 0.00) | 94 | 0.00 (-0.01 to 0.13) | .67 |
NT-proBNP, pg/mL
- 95 | 0.00 (-0.00 to 0.11) | 95 | 0.00 (-0.01 to 0.15) | .20 |
Elastase 1, nM/L
- 93 | -0.2 (-0.43 to 0.02) | 93 | -0.3 (-0.51 to 0.01) | .08 |
Alkaline, nM/L
- 93 | 0.0 (-7.7 to 4.1) | 93 | -1.1 (-7.7 to 3.6) | .05 |
NT-proBNP, pg/mL
- 93 | -0.5 (-1.18 to 1.29) | 93 | 0.01 (-1.17 to 1.42) | .77 |

**Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial**

Elke S. Hoendermis, Lisette C.Y. Liu, Yoran M. Hummel, Peter van der Meer, Rudolf A. de Boer, Rolf M.F. Berger, Dirk J. van Veldhuisen, and Adriaan A. Voors

[Diagram showing sildenafil and placebo effects on NYHA classes and hemodynamics parameters over time]
EDIFY: No improvement in any of the co-primary endpoints with ivabradine

![Graph showing heart rate changes over time for ivabradine and placebo groups.]

**Figure 3** Mean heart rate during the study by treatment group. M1, month 1; M2, month 2; M4, month 4; M8, month 8.

**Table 2** Co-primary endpoints at baseline and change over the 8-month treatment period

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Baseline (Median, Q1–Q3)</th>
<th>Change (last post-baseline value from baseline) (Median, Q1–Q3)</th>
<th>Between-group estimate&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/e</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine (n = 84)</td>
<td>12.6, 9.7–16.2</td>
<td>0.970, −0.8 to 2.9</td>
<td>1.4 (0.3–2.5), P = 0.135</td>
</tr>
<tr>
<td>Placebo (n = 83)</td>
<td>12.9, 10.1–16.0</td>
<td>−0.590, −2.2 to 1.4</td>
<td></td>
</tr>
<tr>
<td>6MWT, m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine (n = 84)</td>
<td>323.0, 243.5–375.0</td>
<td>−28.5 to 35.0</td>
<td>−3.8 (−19.1 to 11.6), P = 0.882</td>
</tr>
<tr>
<td>Placebo (n = 84)</td>
<td>321.0, 256.5–368.0</td>
<td>−15.5 to 40.0</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine (n = 83)</td>
<td>385.0, 263.0–738.0</td>
<td>19.0, −98.0 to 199.0</td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 82)</td>
<td>343.0, 238.0–631.0</td>
<td>16.5, −134.0 to 126.0</td>
<td></td>
</tr>
</tbody>
</table>
NEAT-HFpEF: No Difference in Primary or Secondary Endpoints
(including 6 min walk, QOL, NT-proBNP)

Isosorbide Mononitrate with dose up-titration (30 to 120 mg/day over 4 weeks)
vs. placebo in crossover design

A Average Daily Accelerometer Units in 120-mg Dose Phase

B Hours of Activity per Day in 120-mg Dose Phase

C Average Daily Accelerometer Units in Three Dose Phases Combined
Vericiguat in HFrEF: SOCRATES-Preserved

Primary endpoint: log-NT-proBNP and LAV
No reduction in log-NT-proBNP or in LAV at week 12 compared with placebo
Secondary QOL endpoints showed significant benefit at highest doses

Pieske et al. EHJ 2017
Fillippatos et al. EJHF 2017
Emerging Therapies

- SGLT2 inhibitors (Emperor trial – Empafligozin)
- ARNI (Paramount)
- ARNI (Paragon)
Persistent Symptoms

- Refer to disease management program for HF
- Referral to trials of agents and devices
Cardiomems

Sensor

Home electronics unit

Database

PA pressure trend data

Daily PA measurement
CHAMPION

**Trial design:** Patients with recent hospitalization for heart failure were implanted with a pulmonary artery pressure monitor and randomized so that providers received daily pulmonary artery pressure information for 6 months (n = 270) vs. control (n = 280).

**Results**
- Hospitalization for heart failure: 0.32 events per patient per 6 months in the treatment group vs. 0.44 events per patient per 6 months in the treatment group (p = 0.0002)
- During the open access period, control patients experienced a 48% reduction in hospitalization for heart failure compared with control patients during the randomization period (p < 0.0001)

**Conclusions**
- Among individuals with recent hospitalization for heart failure, the use of an implantable device to provide daily pulmonary artery hemodynamic information was beneficial
- This device resulted in a reduction in hospitalization for heart failure

Pulmonary Artery Pressure-Guided Therapy for Ambulatory Heart Failure Patients in Clinical Practice: 1-Year Outcomes from the CardioMEMS Post-Approval Study

ACC 2019
Survivor Analysis: Hospitalizations for HF at 1 year, n=1009 (Survival 84%)

Hazard Ratio, 95% Confidence Interval and p-value estimated from the Anderson-Gill model.
All hospitalization events adjudicated by CEC.
Conclusions

- In the commercial setting, PA pressure-guided therapy for HF:
  - Decreased PA pressures
  - Decreased HF Hospitalizations
    - Across sex and race
    - Across all EF ranges
    - Amongst 1-year survivors
  - Decreased All-Cause Hospitalization
- PA pressure-guided therapy was safe with few device/system related complications and a low rate of pressure sensor failure
First REDUCE LAP-HF Trial

- Prospective, non-randomized study
- Symptomatic HF (N=64)
- Preserved EF (>40%)
- Elevated PCWP at rest (>15 mmHg) or during exercise (>25 mmHg)
- Monitored by independent DSMB and CEC
- Assessed by independent Core-Laboratories
  - Echo
  - Hemodynamic
- Three year clinical follow-up
  - One year complete
Cardiac Contractility Modulation Therapy Delivery

- Delivered by an IPG
- Rechargeable Battery
- 1 Atrial Lead (sensing)
- 2 RV Septal Leads (sensing + CCM delivery)
- Signals effect the biology of failing myocardium (genes, proteins, and phosphorylation) that improve function

CCM Signal applied during absolute refractory period to the RV septum via standard pacing leads

Biological effects seen remotely over time

Biological effects seen rapidly in region of signal applications
CONCLUSIONS

• Better understanding about the disease
• Think about amyloid
• Poor therapy still
• Prognosis at least as grim as HFrEF
• Referral to HF disease management program
• EF is not everything and heart transplant still an option