Biomarkers for HFpEF

16th Annual Biomarkers and Personalized Medicine in Cardiology, San Diego (virtual)
Session II: Biomarkers in Heart Failure

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I wish I could have traveled to SD
Content

• Biomarkers for diagnosis
• Biomarkers for prognosis
• Biomarkers to understand the disease
• Biomarkers to guide treatment
ESC 2016 Key Diagnostic HFpEF Criteria

“Preserved” EF: \( \geq 50\% \)

**Structural alterations:**
- LAVI \( >34 \text{ ml/m}^2 \) or LVMI \( \geq 115 \text{ (males)}/\geq 95 \text{ (females) mg/m}^2 \)

**Functional alterations:**
- E/é \( \geq 13 \)
- é (mean septal and lateral) \( <9 \text{ cm/s} \)

**NT-proBNP:**
- \( >125 \text{ pg/ml or (SR; increase with AF!)} \)

**BNP:**
- \( >35 \text{ pg/ml} \)
Prediction of New Onset Heart Failure

Predicting Heart Failure With Preserved and Reduced Ejection Fraction
The International Collaboration on Heart Failure Subtypes

Jennifer E. Ho, MD*; Danielle Enserro, MA*; Frank P. Brouwers, MD, PhD*;
Jorge R. Kizer, MD*; Sanjiv J. Shah, MD; Bruce M. Psaty, MD, PhD, MPH;
Traci M. Bartz, MS; Rajalakshmi Santhanakrishnan, MBBS; Douglas S. Lee, MD, PhD;
Cheeling Chan, MS; Kiang Liu, PhD; Michael J. Blaha, MD, MPH; Hans L. Hilleges, MD, PhD;
Pim van der Harst, MD, PhD; Wiek H. van Gilst, MD, PhD; Willem J. Kop, PhD;
Ron T. Gansevoort, MD, PhD; Ramachandran S. Vasan, MD; Julius M. Gardin, MD, MBA;
Daniel Levy, MD, John S. Gottlieber, MD*; Rudolf A. de Boer, MD, PhD*;
Martin G. Larson, ScD*

- 28,820 healthy subjects, > 10 years FU
- 982 new onset HFpEF
- 909 new onset HFrEF

Ho, JE et al. Circ Heart Fail. 2016; 9:e003116
# Predicting Heart Failure With Preserved and Reduced Ejection Fraction

## The International Collaboration on Heart Failure Subtypes

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<table>
<thead>
<tr>
<th>HFpEF</th>
<th>sHR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 y</td>
<td>1.90 (1.74–2.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.93 (0.78–1.11)</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic BP, per 20 mm Hg</td>
<td>1.14 (1.05–1.24)</td>
<td>0.003</td>
</tr>
<tr>
<td>Body mass index, per 4 kg/m²</td>
<td>1.28 (1.21–1.37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>1.42 (1.18–1.71)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1.48 (1.12–1.96)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Ho, JE et al. Circ Heart Fail. 2016; 9:e003116
Association of Cardiovascular Heart Failure With Preserved Ejection Fraction (HFpEF) and Heart Failure With Reduced Ejection Fraction (HFrEF) in Multivariable-Adjusted Analyses

de Boer, RA et al. *JAMA Cardiol.* 2018: 3:215-224
CENTRAL ILLUSTRATION  Associations of Cardiovascular Biomarkers With Incident Heart Failure: Men Versus Women

Subdistribution Hazard Ratio (sHR) per Standard Deviation Change in Natural Log-Transformed Biomarker

Interim conclusion

- Predicting HFpEF is not as easy as HFrEF
- **Natriuretic peptides** are the best biomarkers
- hs-Tn are reasonable
- Interesting signals for UACR and PAI-1
How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)


*EACVI Representatives

The HFA-PEFF Algorithm for the Diagnosis of HFpEF

**P**
Initial Workup (Step 1 (P) : Pretest Assessment)
- Symptoms and/or Signs of HF
- Comorbidities / Risk factors
- ECG
- Standard Echocardiography
- Natriuretic Peptides
- Ergometry / 6 min walking test or Cardiopulmonary Exercise Testing

**E**
Diagnostic Workup (Step 2 (E) : Echocardiographic and Natriuretic Peptide Score)
- Comprehensive Echocardiography
- Natriuretic Peptides, if not measured in Step 1

**F1**
Advanced Workup (Step 3 (F1) : Functional testing in Case of Uncertainty)
- Diastolic Stress Test: Exercise Stress Echocardiography
- Invasive Haemodynamic Measurements

**F2**
Aetiological Workup (Step 4 (F2) : Final Aetiology)
- Cardiovascular Magnetic Resonance
- Cardiac or Non-Cardiac Biopsies
- Scintigraphy / CT / PET
- Genetic testing
- Specific Laboratory Tests

# The HF-PEFF SCORE

## Step E: Sophisticated echo, Cardiologist

<table>
<thead>
<tr>
<th>Major Criteria: 2 points</th>
<th>Minor Criteria: 1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5 points; HFpEF</td>
<td>2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional</th>
<th>Morphological</th>
<th>Biomarker (SR)</th>
<th>Biomarker (AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>septal e' &lt; 7 cm/s or lateral e' &lt; 10 cm/s or Average E/e' &gt; 15 or TR velocity &gt; 2.8 m/s (PASP &gt; 35 mmHg)</td>
<td>LAVI &gt; 34 ml/m² or LVMI ≥ 149/122 g/m² (m/w) and RWT &gt; 0.42 #</td>
<td>NT-proBNP &gt; 220 pg/ml or BNP &gt; 80 pg/ml</td>
<td>NT-proBNP &gt; 660 pg/ml or BNP &gt; 240 pg/ml</td>
</tr>
<tr>
<td>Average E/e' 9 -14 or GLS &lt; 16 %</td>
<td>LAVI 29-34 ml/m² or LVMI &gt; 115/95 g/m² (m/w) or RWT &gt; 0.42 or LV wall thickness &gt; 12 mm</td>
<td>NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml</td>
<td>NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml</td>
</tr>
</tbody>
</table>

A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction

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

H<sub>2</sub>FPEF score

<table>
<thead>
<tr>
<th>Total Points</th>
<th>Probability of HFPoEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>7</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>0.95</td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Dyspneic Patient
LVEF ≥ 50%

HFA-PEEF Algorithm

Algorithm: “Not HFP EF”
- Rule out
- Intermediate
- Rule out

Algorithm: “Confirmed HFP EF”
- Rule in
- Intermediate
- Rule in

Invasive Stress Test

HFP EF inv
n=12/47

HFP EF inv
n=40/63

Algorithm Criteria:
PWP ≥ 15 or ePWP ≥ 25 mmHg

HFP EF inv
n=14/50

HFP EF inv
n=57/95

HFP EF inv
n=10/11

“Rule Out” (0-1)
Intermediate Risk (2-5)
“High Confidence” (6-9)

H2FPEEF Score

% HFP EF

Exercise Hemodynamics

Peak VO₂

Peak Exercise Heart Rate

Exercise PCWP

Peak VO₂

Peak Exercise Heart Rate

Exercise PCWP

Interaction – Sex – Obesity – NT-proBNP

- NT-proBNP levels are higher in women than in men
- NT-proBNP levels are lower in obese subjects
- Men are on an average heavier than women
Sex-specific associations of obesity and N-terminal pro-B-type natriuretic peptide levels in the general population

Navin Suthahar¹, Wouter C. Meijers¹, Jennifer E. Ho², Ron T. Gansevoort³, Adriaan A. Voors¹, Peter van der Meer¹, Stephan J.L. Bakker³, Stephane Heymans⁴, Vanessa van Empel⁴, Blanche Schroen⁵, Pim van der Harst¹, Dirk J. van Veldhuisen¹, and Rudolf A. de Boer¹*
Biomarkers to predict outcomes in HFpEF
Galectin-3 particularly useful in patients with HF with preserved ejection fraction (HFPEF) a substudy of the COACH trial

Galectin-3 has independent prognostic value for death and rehospitalization

Increase Gal-3 level: stronger incremental risk for experiencing primary outcome in patients with HFPEF compared to HFREF, although absolute Gal-3 level did not differ between these patients

Biomarkers to dissect HFpEF
Find the Etiology in HFpEF

<table>
<thead>
<tr>
<th>WCNA Protein Cluster</th>
<th>Number of proteins</th>
<th>Main hub</th>
<th>Exemplar proteins</th>
<th>Primary overrepresented pathway</th>
<th>Number of upregulated inflammation pathways</th>
<th>Conserved in the validation cohort (Cluster color; number of overlapping proteins; P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turquoise</td>
<td>N=53</td>
<td>TNFR1</td>
<td>LTBR, UPAR, PLC, GDF15</td>
<td>Leukocyte degranulation</td>
<td>7</td>
<td>Turquoise (43/53, P&lt;0.001) Orange (17/53, P=0.01)</td>
</tr>
<tr>
<td>Yellow</td>
<td>N=13</td>
<td>IGFBP7</td>
<td>IL1RT1, Notch3, ALCAM, MMP2</td>
<td>Adherens junction organization</td>
<td>5</td>
<td>Turquoise (10/13, P=0.04)</td>
</tr>
<tr>
<td>Red</td>
<td>N=43</td>
<td>TRAILR2</td>
<td>PLGF, SPON2, ADM, IL16</td>
<td>Response to cAMP</td>
<td>4</td>
<td>Turquoise (29/43, P&lt;0.001)</td>
</tr>
<tr>
<td>Blue</td>
<td>N=45</td>
<td>STAMPB</td>
<td>ANG, GP6, PDGFA, VWF</td>
<td>Platelet activation</td>
<td>none</td>
<td>Blue (19/45, P&lt;0.001) Purple (13/45, P&lt;0.001)</td>
</tr>
</tbody>
</table>

Novel heart failure biomarkers: why do we fail to exploit their potential?

Arnold Piek, Weijie Du, Rudolf A. de Boer & Herman H. W. Silljé

Circulating biomarker plasma levels

- Cardiac strain
  - Natriuretic peptides
- Cardiomyocyte injury
  - Replacement fibrosis
  - HsTn/ H-FABP
- Fibrosis
  - Gs13 / sST2 / HE4
- Inflammation
  - IL-6 / GDF-15 / PCT / ADM
- Endothelial dysfunction
  - CD146
- Metabolic dysfunction
  - Metabolic profile / IGFBP-7 / 5-oxoprolinease

Heart

Other organs & tissues

Conclusions

• HFpEF prediction is difficult, and biomarkers help!
• HFpEF prognostication is not so difficult, and biomarkers help (albeit a little)
• HFpEF pathophysiology is complex, and biomarkers help to do split the disease apart (and may guide Tx)
Acknowledgements & Collaborations

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