Busting the Myths of Heart Failure with Preserved Ejection Fraction

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Disclosures

- Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Celladon, Gilead, GlaxoSmithKlein, Ionis Pharmaceuticals, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, Theracos, and has consulted for Alnylam, Amgen, AstraZeneca, Bayer, BMS, Corvia, Gilead, GSK, Ironwood, Merck, Novartis, Pfizer, Takeda, Theracos
The Two Faces of Heart Failure

HFrEF

HFpEF
Heart Failure Definition

- The inability to provide adequate cardiac output to the body at rest or with exertion, or to do so only in the setting of elevated cardiac filling pressures.
  
  - E. Braunwald modified by B. Borlaug and M. Redfield

- Clinically: A clinical syndrome characterized by breathlessness, fatigue and edema caused by an abnormality of the heart
HFpEF Accounts for Nearly 50% of HF Admissions, Signs and Symptoms are Nearly Identical to HFrEF, Morbidity and Mortality are high, and the Incidence is Rising

OPTIMIZE-HF Registry, N=41,267
Documented LVEF Measured
Prior to or During Hospitalization

Left Ventricular Ejection Fraction (%)

Annual Event Rate (per 1000 pts)
White Men
Black Men
White Women
Black Women

Owan TE, et al. NEJM 2006; 355:251-9

Rosemond. ARIC 2013 Unpublished
You have all been fed “Alternative Facts”
MYTH

We Understand the Etiology of HFpEF
...Some potential mechanisms of diastolic dysfunction in HFpEF

Dysfunctional Calcium handling

Abnormalities in spring-like Titin protein

Increased extracellular fibrosis, reduced ventricular compliance & shift in the PV relationship

Myocardial cGMP in HFpEF

![Graph showing cGMP levels in HFpEF and AS](image)

*Van Heerebeek L, ... Paulus WJ. AHA 2011 AOS 503.02*
Myth: HFpEF is a Collection of Comorbidities and NOT a Disease!

### Table 1. Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reduced Ejection Fraction (&lt;40%) (N = 1570)</th>
<th>Preserved Ejection Fraction (&gt;50%) (N = 880)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LVEF — %</td>
<td>23.9</td>
<td>62.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age — yr</td>
<td>71.8 ± 12</td>
<td>75.4 ± 11.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>983 (62.6)</td>
<td>302 (34.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>HFrEF</th>
<th>HFpEF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.8 ± 12</td>
<td>75.4 ± 11.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49.2%</td>
<td>55.1%</td>
<td>0.005</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>23.6%</td>
<td>31.8%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>13.2%</td>
<td>17.7%</td>
<td>0.002</td>
</tr>
<tr>
<td>Anemia</td>
<td>9.9%</td>
<td>21.1%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- **Hemoglobin <10 g/dl — no. (%)**
  - HFrEF: 76 (4.5)
  - HFpEF: 49 (5.6)
  - P-value: 0.43

- **Serum sodium <136 mmol/liter — no. (%)**
  - HFrEF: 362 (23.1)
  - HFpEF: 209 (23.8)
  - P-value: 0.70

- **Serum creatinine >150 mmol/liter — no. (%)**
  - HFrEF: 296 (18.9)
  - HFpEF: 195 (22.2)
  - P-value: 0.95

- **Dialysis — no. (%)**
  - HFrEF: 18 (1.1)
  - HFpEF: 9 (1.0)
  - P-value: 0.78
HF Hospitalization and Mortality Higher in HFpEF than in Studies of Similar Comorbidity
Myth: We know what we mean by “Preserved”

There is no therapy for Heart Failure with LVEF > 40%!
The middle child in heart failure: heart failure with mid-range ejection fraction (40–50%)

Carolyn S.P. Lam¹* and Scott D. Solomon²

¹National University Health System, Singapore; and ²Brigham and Women’s Hospital, Boston, MA, USA

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signsᵃ</td>
<td>Symptoms ± Signsᵃ</td>
<td>Symptoms ± Signsᵃ</td>
</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 peptidesᵇ; 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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<td></td>
</tr>
</tbody>
</table>

ON MY MIND

Fussing Over the Middle Child
Heart Failure With Mid-Range Ejection Fraction

Lam C & Solomon SD. Circulation 2017
HFmrEF: Most Baseline Characteristics Intermediate, Outcomes more similar to HFpEF

<table>
<thead>
<tr>
<th>Variable name</th>
<th>EF &lt;40%, HFrEF n=4323 (57%)</th>
<th>HFmrEF, EF 40-49% n=1322 (17%)</th>
<th>EF ≥50%, HFpEF n=1953 (26%)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>2155 (49.8%)</td>
<td>667 (50.5%)</td>
<td>980 (50.2%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 11</td>
<td>65 ± 11</td>
<td>67 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>26%</td>
<td>30%</td>
<td>46%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF</td>
<td>30%</td>
<td>44%</td>
<td>58%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1</td>
<td>27.8</td>
<td>28.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>126</td>
<td>130</td>
<td>140</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HF cause, Ischemic</td>
<td>65%</td>
<td>67%</td>
<td>50%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>29%</td>
<td>29%</td>
<td>28%</td>
<td>0.71</td>
</tr>
<tr>
<td>AF</td>
<td>26%</td>
<td>26%</td>
<td>31%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Lund et al. ESC-HFA 2017
MYTH

HFpEF is caused by Diastolic Dysfunction
“Diastolic” Heart Failure

Diastolic Pressure

Diastolic Volume

Normal pressure and volume

Diastolic dysfunction

Normal curve

Zile et al., NEJM, 350 (19): 1953
Age Dependence of Myocardial Relaxation Velocity in Normals

High Prevalence of Diastolic Dysfunction Regardless of Clinical Status

- **Healthy**
  - Healthy
  - No DM, HTN, CHD, HF
  - $E' = 7.5 \pm 1.9$, $E/E' = 9.1 \pm 3.0$
  - NT-proBNP = 90 (83, 97)
  - 30% Normal, 26% Mild DD, 15% Moderate DD, 1.6% Severe DD

- **Co-Morbid**
  - Co-Morbid
  - $E' = 6.9 \pm 1.9$, $E/E' = 10.2 \pm 3.8$
  - NT-proBNP = 120 (116, 123)
  - 41% Normal, 42% Mild DD, 2.3% Moderate DD, 10% Severe DD

- **HFpEF**
  - HFpEF
  - $E' = 6.7 \pm 1.9$, $E/E' = 11.2 \pm 4.7$
  - NT-proBNP = 209 (188, 232)
  - 43% Normal, 42% Mild DD, 5.5% Moderate DD, 10% Severe DD

Amil Shah et al. Circulation 2017
Myth: Systolic Function is Normal in HFP EF

Longitudinal Strain most likely represents Function of subendocardial myofiber bands

Myocardial Strain in Normals, HTN, HFP EF and HFr EF

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal (n=50)</th>
<th>Hypertension and Diastolic dysfunction (n=300)</th>
<th>PARAMOUNT¹ (n~200)</th>
<th>TOPCAT³ (n~438)</th>
<th>MADIT-CRT² (n=1077)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal Strain (%)</td>
<td>-34</td>
<td>-28</td>
<td>-24</td>
<td>-20</td>
<td>-18</td>
</tr>
<tr>
<td>Circumferential Strain</td>
<td>-34</td>
<td>-28</td>
<td>-24</td>
<td>-20</td>
<td>-18</td>
</tr>
</tbody>
</table>

¹Kraigher-Krainer E, JACC 2013
²Knappe D, Circ HF 2011
³TOPCAT, A. Shah Circulation 2015
Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone

Amil M. Shah, MD, MPH; Brian Claggett, PhD; Nancy K. Sweitzer, MD; Sanjiv J. Shah, MD; Inder S. Anand, MD, PhD; Li Liu, MD, PhD; Bertram Pitt, MD; Marc A. Pfeffer, MD, PhD; Scott D. Solomon, MD

Univariate | Multivariate
---|---
P < 0.001 | P = 0.005
P < 0.001 | P = 0.017
P < 0.001 | P = 0.025
P < 0.001 | P = 0.001
P = 0.009 | P = 0.083
P = 0.081 | P = 0.70
Progressive abnormalities in LV diastolic and systolic function underlying heart failure across the LVEF spectrum

Early Compensatory Increase in Circumferential Function

Reduction in Circumferential Function Associated with HF

Hypertension

Diastolic relaxation

Circumferential deformation

Longitudinal deformation

Progressive LV dysfunction

Shah and Solomon. Eur Heart J 2012;33:1716-7
MYTH
There is no evidenced-based therapy for HFpEF
THIS ONE IS TRUE!

"Your honor... all the lies I told were true."
Landmark Heart Failure RCTs

**HFrEF**
- 1990: V-HeFT, CONSENSUS
- 1995: SOLVD, SAVE
- 2000: RALES, CIBIS-2, MERIT-HF, COPERNICUS, Val-HeFT, CHARM, EPHESUS, COMPANION
- 2005: CARE-HF, SCD-HeFT, HeartMate II, MADIT-CRT
- 2010: SHIFT, RAFT, EMPHASIS
- 2014: PARADIGM-HF

**HFpEF**
- 1990
- 1995
- 2000: CHARM-P, I-PRESERVE
- 2005: PEP-CHF
- 2010
- 2014: TOPCAT
2012 ESC-Guidelines

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.

2016 ESC-Guidelines

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.
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**
- Treatment Group
  - Perindopril
  - Placebo
- HR 0.92; 95% CI 0.70 to 1.21; \( P=0.545 \)

**I-PRESERVE**
- Placebo
- Irbesartan
- N=4,128
- HR (95% CI) = 0.95 (0.86-1.05)
- Log-rank \( p=0.35 \)
- (Mean follow-up 49.5 months)

**TOPCAT**
- Placebo
- Spironolactone
- 351/1723 (20.4%)
- 320/1722 (18.6%)
- HR = 0.89 (0.77 – 1.04)
- \( p=0.138 \)
TOPCAT: 1°Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

Probability

0.35

0.30

0.25

0.20

0.15

0.10

0.05

0.00

Number at risk

Spiro 1722 1502 1168 870 614 330 53
Placebo 1723 1462 1145 834 581 331 53

Months

36

48

60

72

351/1723 (20.4%)
320/1722 (18.6%)

Placebo
Spironolactone

HR = 0.89 (0.77 – 1.04)
p = 0.138

Pfeffer et al. NEJM 2014;370(15):1383-92
TOPCAT: Results by Region

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: 280/881 (31.8%)
Placebo: 71/842 (8.4%)
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. Hoendermis¹*, Licette C.Y. Liu¹, Yoran M. Hummel¹, Peter van der Meer¹, Rudolf A. de Boer¹, Rolf M.F. Berger², Dirk J. van Veldhuisen¹, and Adriaan A. Voors¹

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!![](image)

Eur Heart J 2016

**•** No benefits of sildenafil in HFrEF with pulmonary hypertension in contrast to prior publications but in accordance with the NIH RELAX trial.
NEAT-HFpEF: Trend towards lower activity level with Nitrates
(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

- No benefits of isosorbide mononitrate in HFpEF with a suggestion of worsening of activity level
Vericiguat in HFpEF: 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

- No hint of cardiac benefit overall for vericiguat in HFpEF
- Whether a hypothesis generating QOL benefit is due to other potential mechanisms or random

Data are mean ± standard error of the mean.

Pieske et al. ESC-HF 2016
Effect of ivabradine in patients with heart failure with preserved ejection fraction: the EDIFY randomized placebo-controlled trial

Michel Komajda¹*, Richard Isnard¹, Alain Cohen-Solal², Marco Metra³, Burkert Pieske⁴, Piotr Ponikowski⁵, Adriaan A. Voors⁶, Fabienne Dominjon⁷, Cécile Henon-Goburdhun⁷, Matthieu Pannaux⁸, and Michael Böhm⁹, on behalf of the prEserveD left ventricular ejection fraction chronic heart Failure with ivabradine studY (EDIFY) Investigators†

- 179 patients NYHA class II and III, in sinus rhythm, with HR of ≥ 70b.p.m.
- NT-proBNP of ≥ 220pg/mL (BNP ≥80pg/mL) and left ventricular ejection fraction of ≥45%.
- Ivabradine (or placebo) was titrated to 7.5 mg b.i.d.
- Patients were followed for 8 months on the change and assessed for three co-primary endpoints: echo-Doppler E/e·ratio, distance on the 6-min walking test (6MWT), and plasma NT-proBNP concentration.
EDIFY: No improvement in any of the co-primary endpoints with ivabradine

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></th>
<th>Baseline</th>
<th>Change (last post-baseline value from baseline)</th>
<th>Between-group estimatea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Q1–Q3</td>
<td>Median</td>
</tr>
<tr>
<td>E/e'</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVabradine (n = 84)</td>
<td>12.6</td>
<td>9.7–16.2</td>
<td>0.970</td>
</tr>
<tr>
<td>Placebo (n = 83)</td>
<td>12.9</td>
<td>10.1–16.0</td>
<td>-0.590</td>
</tr>
<tr>
<td>6MWT, m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVabradine (n = 84)</td>
<td>323.0</td>
<td>243.5–375.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Placebo (n = 83)</td>
<td>321.0</td>
<td>256.5–368.0</td>
<td>-15.5 to 40.0</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</td>
<td>263.0–738.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Placebo (n = 82)</td>
<td>343.0</td>
<td>238.0–631.0</td>
<td>16.5</td>
</tr>
</tbody>
</table>

b
PARAMOUNT: Study Design

**Primary objective**
NT pro-BNP reduction from baseline at 12 weeks

**Secondary objectives**
- Echocardiographic measures of diastolic function, left atrial size, LV size and function, PASP
- HF symptoms, Clinical composite assessment and Quality of life (KCCQ)
- Safety and tolerability

Baseline randomization visit and visit at end of 12 weeks of core study

Clinicaltrials.gov NCT00887588

Solomon et al. ESC Hotline 2012
Lancet 2012
PARAMOUNT: Significant Improvement in Several Domains with Sacubitril/Valsartan

Improvement in NT-proBNP

NT-proBNP (pg/ml)

- LCZ696: 862 (733, 1012) vs. 783 (670, 914)
- Valsartan: 835 (710, 961) vs. 605 (512, 714)

p = 0.063

Improvement in Left Atrial Size

Change in Left Atrial Volume (ml)

- LCZ696: 12 Weeks: 0.77 (0.64, 0.92) P = 0.005
- Valsartan: 36 Weeks

P = 0.18
P = 0.003

Improvement in NYHA Class

Percent of Patients

- LCZ696: Week 12 P = 0.11, Week 36 P = 0.05
- Valsartan

Solomon et al. Lancet 2012
Target patient population: ~4,800 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%

Randomization 1:1

Active run-in period

Screening → Valsartan 80 mg BID* → LCZ696 100 mg BID

up to 2 weeks → 3–8 weeks

Double-blind treatment period

LCZ696 200 mg BID

Valsartan 160 mg BID

On top of optimal background medications for co-morbidities (excluding ACEIs and ARBs)

~240 weeks

Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)

Steering Cmt: S. Solomon, co-Chair, J. McMurray, Co-Chair, I. Anand, F. Zannad, A. Maggioni, M. Packer, M. Zile, B. Pieske, J. Rouleau, M. Redfield, C. Lam, D. Van Veldhuisen, F. Martinez, J. Ge, H. Krum, M. Pfeffer
SPRINT: BP Lowering Reduces Adverse Outcomes

HF Hospitalization Reduced 38%
Heart Failure Hospitalizations Reduced Substantial with the SGLT-2 Inhibitor Empagliflozin

HR: 0.66
(95% CI: 0.55–0.79)
\(P < 0.001\)

No. of patients
- Empagliflozin: 4687, 4614, 4523, 4427, 3988, 2950, 2487, 1634, 395
- Placebo: 2333, 2271, 2226, 2173, 1932, 1424, 1202, 775, 168

Fitchett et al. Eur Heart J 2016
Inter-Atrial Shunt Device\(^1\) - MOA

**Hypothesis**

Elevated LV filling pressures (Elevated LAP)

Venous congestion (Elevated PCWP\(^1\))

Pulmonary edema, Dyspnea at rest/exercise

\(^1\) PCWP at rest is predictor of mortality (Dorfs, EHJ 2014)
RAAS inhibition may be beneficial in the “Mid-Range” of Heart Failure

Lund. CHARM Invest. To Be Presented ESC-HF 2017

Solomon SD et al. Eur Heart J. 2015
Conclusions

- HFpEF is alive, and not well.
- It is a heterogeneous disorder, associated with comorbidities but accounts for half of heart failure.
- The cardiac phenotype is broader than we previously thought.
- Diastolic dysfunction CANNOT account for the disorder and abnormalities of systole are becoming more recognized.
- There is no “evidenced-based” therapy currently, but there are promising potential therapies being tested.
My goodness, he's out of sync!