Why Clinical Trials of HFpEF have Failed: Is it due to Comorbidities?

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Grant Support and/or Consulting from:
NIH/NHLBI, Cardiorentis, Amgen, Roche Diagnostics, Medtronic, Otsuka, Singulex
Normal

Systolic Heart Failure

Diastolic Heart Failure

Aurigemma, Zile, Gaasch
Circulation 2005
Prevalence of Heart Failure

<table>
<thead>
<tr>
<th>Country</th>
<th>Age Range</th>
<th>Mean Age</th>
<th>Proportion with decreased LV systolic function</th>
<th>Proportion with preserved LV systolic function</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (CHS)</td>
<td>66-103</td>
<td>78</td>
<td>8.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Finland (Helsinki)</td>
<td>75-86</td>
<td>76</td>
<td>8.2</td>
<td>4.2</td>
</tr>
<tr>
<td>England (Poole)</td>
<td>70-84</td>
<td>75</td>
<td>7.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Sweden (Vasteras)</td>
<td></td>
<td></td>
<td>6.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Denmark (Copen.)</td>
<td></td>
<td></td>
<td>6.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Spain (Asturias)</td>
<td></td>
<td></td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Portugal (EPICA)</td>
<td></td>
<td></td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Netherlands (Rotter.)</td>
<td></td>
<td></td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>England (Poole)</td>
<td></td>
<td></td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Mean age: Netherlands (Rotter.) 65

Proportion with decreased LV systolic function: USA 8.8%, Finland 8.2%, England 7.5%, Sweden 6.7%, Denmark 6.4%, Spain 4.9%, Portugal 4.2%, Netherlands 2.1%

Proportion with preserved LV systolic function: USA 4.8%, Finland 4.2%, England 5.1%, Sweden 3.1%, Denmark 4.5%, Spain 2.9%, Portugal 1.7%, Netherlands 1.5%
Why Target Co-Morbidities

- Heterogeneity of population problematic
- No therapeutic advances in broad approach
- Comorbidities associated with high risk
- May be differential association in HFpEF and HFrEF
European Heart Failure Pilot Survey

- 3226 outpatients with chronic HF
- 74% had at least one co-morbidity
  - CKD (41%), anemia (29%), and diabetes (29%)
- Co-morbidities were independently associated with higher age, higher NYHA class, ischemic etiology of HF, higher heart rate, HTN and AF
- Only diabetes, CKD, and anemia were independently associated with a higher risk of mortality and/or HF hospitalization.
- There were marked regional differences in prevalence and prognostic implications of co-morbidities.

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Noncardiac Comorbidities in Heart Failure With Reduced Versus Preserved Ejection Fraction

Robert J. Mentz, MD,* Jacob P. Kelly, MD,* Thomas G. von Lueder, MD, PhD,† Adriaan A. Voors, MD,‡ Carolyn S.P. Lam, MBBS,§ Martin R. Cowie, MD, MSc,∥ Keld Kjeldsen, MD, DSc,¶ Ewa A. Jankowska, MD, PhD,# Dan Atar, MD, PhD,† Javed Butler, MD, MPH,** Mona Fiuzat, PharmD,* Faiez Zannad, MD,†† Bertram Pitt, MD,‡‡ Christopher M. O’Connor, MD*
**HFpEF vs. HFrEF**

<table>
<thead>
<tr>
<th></th>
<th>ADHERE Registry(2)</th>
<th>GWTG Registry(8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced</td>
<td>Preserved</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>70 ± 14</td>
<td>74 ± 13</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>40%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD or asthma</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>CRI</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Anemia</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Mentz RJ, O’ Connor CM et al. JACC 2014
## Bidirectional Impact

<table>
<thead>
<tr>
<th>COMORBIDITY</th>
<th>BIDIRECTIONAL IMPACT ON DISEASE PROGRESSION</th>
<th>HEART FAILURE SPECIFICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary</td>
<td>Inflammation; hypoxia; parenchymal changes; airflow limitation, leading to pulmonary congestion; abnormal left ventricular (LV) diastolic filling; inhaled beta-agonist cardiovascular effects</td>
<td>More prevalent in preserved ejection fraction (HFP EF), compared to reduced (HFr EF). Higher mortality risk in HFP EF</td>
</tr>
<tr>
<td>disease</td>
<td>Elevated LV end-diastolic pressure and beta-blocker use may compromise lung function</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Adverse LV remodeling; adverse cardiorenal effects; increased neurohormonal and inflammatory cytokines</td>
<td>More prevalent in HFP EF. Similar increased risk for mortality in both groups</td>
</tr>
<tr>
<td></td>
<td>Inflammation; hemodilution; renal dysfunction; metabolic abnormalities exacerbate</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diabetic cardiomyopathy; mitochondrial dysfunction; abnormal calcium homeostasis; oxidative stress; renin-angiotensin-aldosterone system (RAAS) activation; atherosclerosis; coronary artery disease</td>
<td>More prevalent in HFP EF. Similar increased risk for mortality in both groups</td>
</tr>
<tr>
<td></td>
<td>Incident and worsening diabetes mellitus via sympathetic and RAAS activation</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Sodium and fluid retention; anemia; inflammation; RAAS and sympathetic activation</td>
<td>Similar prevalence in both groups</td>
</tr>
<tr>
<td></td>
<td>Cardiorenal syndrome through low cardiac output; accelerated atherosclerosis; inflammation; increased venous pressure</td>
<td>Similar increased risk for mortality in both groups</td>
</tr>
<tr>
<td>Sleep-disordered breathing</td>
<td>Hypoxia; systemic inflammation; sympathetic activation; arrhythmias; hypertension (pulmonary and systemic); RV dysfunction; worsening congestion</td>
<td>Similar prevalence in both groups</td>
</tr>
<tr>
<td></td>
<td>Rostral fluid movement may worsen pharyngeal obstruction; instability of ventilatory control system</td>
<td>Unknown mortality differential associated with HFP EF vs. HFr EF</td>
</tr>
<tr>
<td>Obesity</td>
<td>Inflammation; reduced physical activity and deconditioning; hypertension; metabolic syndrome; diabetes mellitus</td>
<td>More prevalent in HFP EF. Obesity paradox; potential for a U-shaped association with mortality</td>
</tr>
<tr>
<td></td>
<td>Fatigue and dyspnea may limit activity; spectrum of metabolic disorders including nutritional deficiencies</td>
<td></td>
</tr>
</tbody>
</table>
HFpEF and Comorbidities

Myocardial Remodeling in HFPEF
Importance of Comorbidities

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

Endothelium

- ONOO
- NO
- VCAM
- E-selectin
- Leukocytes
- TGF-β
- Fibroblasts
- Myofibroblasts
- Collagen

Cardiomyocytes

- sGC
- cGMP
- Fpassive
- PKG
- Hypertrophy
PATHOPHYSIOLOGIC TARGETS

- Diastolic dysfunction
- Ventriculo-arterial disociation
- Pulmonary Hypertension
- Chronotropic Incompetance
- Systemic Hypertension
HFpEF – Clinical Trials to Date

“I have not failed. I've just found 10,000 ways that won't work.”
– Thomas A. Edison
**HFpEF – Landmark Trials**

- **No proven therapy**
  - All treatment recommendations – Class C evidence

- **Completed**
  - **Dig** (Mortality↔, HF Hospitalizations↓)
  - **CHARM-Preserved** (trend towards ↓ HF hosp / CV mortality)
  - **PEP-CHF** (trend towards ↓ mortality / hf hospitalization, ¼ of pts withdrew to go on open label ACEI at 1 year)
  - **SENIORS** - nebivolol (↓ time to death/hf hospitalization, but few LVEF>50%)
  - **I-PRESERVE** (ARB): did not improve outcomes

- **Recent Trials**
  - **TOPCAT** (Spironolactone)
  - **RELAX** (sildenafil)
  - Paramount
Have HFpEF Trials Failed?

Cleland JG, Pellicori P, Dierckx R.
Heart Fail Clin. 2014 Jul;1
Reasons for Failure:
Should the Trialists be on Trial?

- Was it Heart Failure?
- Different Demographics?
- Too many Co-Morbidities?
- Trial Design?
HFpEF?

- Neither clinical history nor echo is a reliable diagnostic method in patients with HFpEF

- Prior Hospitalization

- Natriuretic Peptide Level
Natriuretic Peptide Enhances Risk

Fig. 2. Outcome according to quartiles of the plasma concentration of NT-proBNP in patients with HFrEF enrolled in the PEP-CHF study. (From Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27(19):2338-45; with permission.)
Increase Mortality after Hospitalization
Both HF and non-HF

Mortality After Discharge from Hospital

(Time since discharge for hospitalized group, or time since randomization for no hospitalization group)
Risk of Events in HFP EF: The I-Preserve Model

- Previous hospitalization
- Natriuretic Peptide
- Age
- Diabetes
- Renal Disease
- COPD
- CAD

Komajda, Circ HF 2011
A high degree of disease heterogeneity exists within heart failure patients and there is a need for improved phenotyping of the syndrome. A new taxonomy of heart failure based on both clinical and molecular measures may provide a more accurate classification of disease and ultimately enhance diagnosis and treatment.
Cluster analysis is an unsupervised learning task of grouping a set of objects in such a way that objects in the same group are more similar to each other than to those in other groups.
Cluster Analysis of Heart Failure to Uncover Distinct Phenotypes?

Phenomapping for Novel Classification of Heart Failure with Preserved Ejection Fraction

Running title: Shah et al.; Phenomapping of HFrEF

Sanjiv J. Shah, MD; Daniel H. Katz, MD; Senthil Selvaraj, MD, MA; Michael A. Burke, MD; Clyde W. Yancy, MD, MSc; Mihai Gheorghiade, MD; Robert O. Bonow, MD; Chiang-Ching Huang, PhD; Rahul C. Deo, MD, PhD

Log-rank P<0.0001

Survival free of CV hospitalization or death

Pheno-group #1
Pheno-group #2
Pheno-group #3

Circulation. 2014; Nov 14
# Objective Measures of Heart Failure

## Cluster Analysis

**Cluster 1:**
- 773 Patients
- Eldest
- Caucasian
- Ischemic CMP
- High Comorbidity Rate
- Advanced Disease
- Highest Mortality Rates

**Cluster 2:**
- 287 Patients
- Youngest
- Obese
- African American
- Non-ischemic CMP
- High rates of rehospitalization
- Lower SES and QOL
- Milder disease on CPET and biomarker assessments

**Cluster 3:**
- 313 Patients
- Caucasian
- Ischemic CMP
- Severe angina symptoms
- High rates of rehospitalization
- Lower SES and QOL
- Advanced HF based on CPET and biomarkers

**Cluster 4:**
- 246 Patients
- Caucasian
- Highest percentage of females
- Non-ischemic CMP
- Low rates of comorbidities
- Low rates of clinical outcomes
- Higher SES and QOL

## Biomarker Analysis

<table>
<thead>
<tr>
<th>Patient Biomarkers</th>
<th>Cluster 1 (n = 773)</th>
<th>Cluster 2 (n = 287)</th>
<th>Cluster 3 (n = 313)</th>
<th>Cluster 4 (n = 246)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>25 (20-30)</td>
<td>25 (20-30)</td>
<td>25 (20-30)</td>
<td>24 (19-30)</td>
<td>0.606</td>
</tr>
<tr>
<td>Peak VO₂, ml/kg/min</td>
<td>13.5 (11.0-16.5)</td>
<td>15.0 (12.1-18.0)</td>
<td>14.7 (12.0-17.9)</td>
<td>17.5 (14.2-20.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>VEVCO₂ slope</td>
<td>34 (30-40)</td>
<td>30 (26-34)</td>
<td>33 (29-39)</td>
<td>31 (27-35)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>351 (290-416)</td>
<td>394 (320-439)</td>
<td>376 (305-441)</td>
<td>427 (363-476)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NT-proBNP, pg/ml (n = 1,011)</td>
<td>1,079 (461-2,517)</td>
<td>418 (194-978)</td>
<td>775 (359-1,663)</td>
<td>558 (206-1,606)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Galectin-3, ng/ml (n = 664)</td>
<td>15.4 (11.9-21.0)</td>
<td>11.9 (9.8-14.9)</td>
<td>14.5 (10.8-20.1)</td>
<td>12.3 (10.2-16.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ST2, ng/ml (n = 677)</td>
<td>26.2 (20.5-35.1)</td>
<td>21.2 (15.7-28.3)</td>
<td>23.5 (19.0-30.5)</td>
<td>21.1 (16.3-26.7)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Clinical Implications on Outcomes

Figure 1: Risk of Clinical Events Compared With Cluster 1 (Highest Risk)*

- All-cause mortality or all-cause hospitalization (primary endpoint): P ≤ 0.001
- Cardiovascular mortality or cardiovascular hospitalization: P ≤ 0.001
- Cardiovascular mortality or heart failure hospitalization: P ≤ 0.001
- All-cause mortality: P ≤ 0.001

*Note: Cluster 1 refers to the highest risk group.
Clinical Implications: Some Clusters Respond to Exercise

- Caucasian
- Female
- NICM
- Few Co-Morbidities
Implications of Co-Morbidities

- Increase heterogeneity
- Complicates management (Beta agonists; NSAID)
- Associated with worse outcomes
- Increase in non-cardiac outcomes

Mentz RJ and Felker GM. Heart Fail Clin 2013
Risk of Co-Morbidity and Death in HFpEF

- COPD
- Rheumatologic Disorders
- More dangerous in HFpEF than HFrEF
Total Hospitalizations I-Preserve: Many Co-Morbid Hospitalizations

FIGURE 2 Total Hospitalizations—EVENTS (%)

- Myocardial Infarction, 154 (2.6%)
- Other Cardiovascular, 176 (3.0%)
- Stroke, 187 (3.2%)
- Unstable Angina, 204 (3.5%)
- Atrial Dysrhythmia, 218 (3.7%)
- Chest Pain, 250 (4.3%)
- Cardiovascular Procedure, 328 (5.6%)
- Other, 4.6%
- Worsening Heart Failure, 1236 (21.1%)
- No Category Specified, 156 (2.7%)
- Peripheral Vascular Disease, 116 (2.0%)
- Syncope/ Presyncope, 103 (1.8%)
- Hypertension, 73 (1.2%)
- Hypotension, 37 (0.6%)
- TIA, 42 (0.7%)
- Ventricular Dysrhythmia, 17 (0.3%)
**Mode of Death I-Preserve**

- 60% cardiovascular death
- 40% non-cardiovascular death or unknown
- May require a doubling of sample size for mortality component
- Similar Issue with HFH

**Table 4. Mortality Rate for Each Mode of Death**

<table>
<thead>
<tr>
<th>Mode of Death</th>
<th>Total</th>
<th>Placebo</th>
<th>Irbesartan</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause</td>
<td>52.4</td>
<td>52.3</td>
<td>52.6</td>
<td>0.98</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>31.7</td>
<td>31.8</td>
<td>31.5</td>
<td>0.91</td>
</tr>
<tr>
<td>Sudden death</td>
<td>13.8</td>
<td>14.2</td>
<td>13.3</td>
<td>0.64</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7.4</td>
<td>6.6</td>
<td>8.3</td>
<td>0.21</td>
</tr>
<tr>
<td>MI</td>
<td>2.7</td>
<td>2.8</td>
<td>2.6</td>
<td>0.83</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.5</td>
<td>4.8</td>
<td>4.3</td>
<td>0.59</td>
</tr>
<tr>
<td>Cardiovascular procedure</td>
<td>0.8</td>
<td>0.2</td>
<td>1.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Other cardiac death</td>
<td>0.6</td>
<td>0.7</td>
<td>0.5</td>
<td>0.51</td>
</tr>
<tr>
<td>Other vascular death</td>
<td>1.9</td>
<td>2.5</td>
<td>1.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>16</td>
<td>16.1</td>
<td>15.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Unknown</td>
<td>4.8</td>
<td>4.4</td>
<td>5.2</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Mortality rate is expressed as rate per 1000 patient-years.
<table>
<thead>
<tr>
<th>Cause</th>
<th>TM</th>
<th>Non-CV 1</th>
<th>Non-CV 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncardiovascular</td>
<td>268 (30)</td>
<td>134 (31)</td>
<td>134 (30)</td>
</tr>
<tr>
<td>Renal</td>
<td>9 (3)</td>
<td>3 (2)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>19 (7)</td>
<td>11 (8)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Cancer</td>
<td>104 (39)</td>
<td>52 (39)</td>
<td>52 (39)</td>
</tr>
<tr>
<td>Trauma</td>
<td>6 (2)</td>
<td>2 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Infection/sepsis</td>
<td>72 (27)</td>
<td>39 (30)</td>
<td>33 (25)</td>
</tr>
<tr>
<td>Suicide</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>51 (19)</td>
<td>24 (18)</td>
<td>27 (20)</td>
</tr>
<tr>
<td>Unknown</td>
<td>81 (9)</td>
<td>37 (8)</td>
<td>44 (10)</td>
</tr>
</tbody>
</table>
Regional Differences in Therapy

Influence of Global Region on Outcomes in Heart Failure Beta-Blocker Trials

Christopher M. O'Connor, MD,* Mona Fiuza, PharmD,* Karl Swedberg, MD,†
Michael Caron, PharmD,‡ Bruce Koch, PharmD,‡ Peter E. Carson, MD,§
Wendy Gattis-Stough, PharmD,¶ Gordon W. Davis, MS,¶¶ Michael R. Bristow, MD, PhD¶¶

Durham and Butes Creek, North Carolina; Goteborg, Sweden; Foster City, California; Washington, DC;
and Broomfield and Aurora, Colorado

B
Beta-blocker trials
US vs. ROW

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>ROW</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPERNICUS</td>
<td>1013</td>
<td>997</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>1.05</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>CIBIS II</td>
<td>0.91</td>
<td>0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BEST</td>
<td>0.92</td>
<td>0.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall</td>
<td>0.92</td>
<td>0.64</td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk

0.7 0.8 0.9 1.0 1.1 1.2

0.6 0.7 0.8 0.9 1.0 1.1
Lessons from the TOPCAT Trial

John J.V. McMurray, M.D., and Christopher O'Connor, M.D.
1° **Outcome**
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

- **Placebo**
  - HR = 0.89 (0.77 – 1.04)
  - p = 0.138
  - 320/1722 (18.6%)

- **Spironolactone**
  - HR = 0.89 (0.77 – 1.04)
  - p = 0.138
  - 351/1723 (20.4%)

**Number at risk**
- **Spiro**: 1722, 1502, 1168, 870, 614, 330, 53
- **Placebo**: 1723, 1462, 1145, 834, 581, 331, 53
Placebo Rates: Primary Outcome, by Region

US, Canada, Argentina, Brazil
12.6 per 100 pt-yr
Placebo: 280/881 (31.8%)

Russia, Rep Georgia
2.3 per 100 pt-yr
Placebo: 71/842 (8.4%)
Exploratory (post-hoc): Placebo vs. Spiro 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
Of 22 pre-specified, only 1 - Stratum - showed a significant interaction with treatment

<table>
<thead>
<tr>
<th>Enrolled by:</th>
<th>Spiro</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natriuretic peptide</td>
<td>78/490</td>
<td>116/491</td>
<td>0.65 (0.49-0.87)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart Failure Hosp</td>
<td>242/1232</td>
<td>235/1232</td>
<td>1.01 (0.84-1.21)</td>
<td>0.923</td>
</tr>
</tbody>
</table>

\( \*P=0.013 \) for interaction
ACEI/ARB Meta-Analysis Favors Treatment (HR=0.88, p=0.05)

Shah, JCF, 2010
The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John JV McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction (PARAMOUNT) Investigators*
LCZ696: Favorable on the most likely Surrogate

- Reduced NT-proBNP
- Reduced LA size
- Improved NYHA Class
- PARAGON OUTCOME Trial
Developing Therapies for Heart Failure With Preserved Ejection Fraction

Current State and Future Directions

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Have we failed in HFpEF?

- As clinical trialists we have sometimes failed (unknowingly) in the design and conduct of HFpEF studies

- Most traditional therapies (ACEI/ARB/MRA/BB) have not failed (modest reduction in recurrent HFH) but they have not passed regulatory standards – What about guidelines?

- Must address the moderate number of Co-Morbidities differently

- New therapies will have the advantage of our informed journey and will likely yield positive results
HFpEF Trials:
Half Empty Half Full..... Yet No Banners