Current management of Heart Failure with Preserved Ejection Fraction

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Disclosures

Speaker: Gregory Giamouzis, MD, PhD

None associated with this presentation
HFpEF treatment: The Challenge!!!

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
HFpEF - Challenge #1: Epidemiology
Global prevalence of HFpEF

HF Registries 2003-2012

% HFpEF

- EF cut-off ≥ 50%
- EF cut-off ≥ 40%

UK-Heart: 31.2
GTWG: 36
ADHERE: 50.4
OPTIMIZE-HF: 51.2
ADHERE-I: 45.7
J-CARE-CARD: 52.3

Dhingra Curr Heart Fail Rep 2014
HFpEF is increasing in Prevalence in US

Rosemond. ARIC 2013 Unpublished
HFpEF: Epidemiology

High prevalence ↔ 1-5.5% of general population
High incidence ↔ 52.3% (2008-2010)
Adverse prognosis ↔ Mortality

In-hospital 3-6.5%
Short-term 5-9.5%
Long-term (5 yrs) 55-74%
Annual 3.5-15%
Non-CV 30-49%

Re-admissions
1-yr rate 13.5%
Long-term 33-39%

Health-care cost

Upadhya B & Kitzman DW, Am J CV Drugs 2017
HFpEF - Challenge #2: Diagnosis
Diagnosis of HfP EF

- Symptoms ± Signs
- LVEF ≥50%

1. Elevated levels of natriuretic peptides
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).

BNP > 35 pg/ml or NT-proBNP > 125 pg/ml

LV mass ≥ 95/115 g/m² w/m or LAVI > 34 ml/m²

Average septal-lateral e’ < 9 cm/s and Average E/e’ ≥ 13
EACVI/ASE Recommendations for the Evaluation of LV Diastolic Function by Echocardiography

High Prevalence of Diastolic Dysfunction Regardless of Clinical Status

- Healthy, n = 371: E' = 7.5 ± 1.9, E/E' = 9.1 ± 3.0, NT-proBNP = 90 (83, 97)
- Co-Morbid, n = 4,555: E' = 6.9 ± 1.9, E/E' = 10.2 ± 3.8, NT-proBNP = 120 (116, 123)
- HFpEF, n = 474: E' = 6.7 ± 1.9, E/E' = 11.2 ± 4.7, NT-proBNP = 209 (188, 232)

- Healthy: 30% Normal, 26% Mild DD, 1.6% Moderate DD, 15% Severe DD, 5.5% Unclassifiable
- Co-Morbid: 42% Normal, 41% Mild DD, 2.3% Moderate DD, 42% Severe DD, 5% Unclassifiable
- HFpEF: 43% Normal, 42% Mild DD, 10% Moderate DD, 42% Severe DD, 15% Unclassifiable

Amil Shah et al. Circulation 2017
This degree of diastolic dysfunction progresses with age.

Myocardial Strain in Normals, HTN, HFP EF and HFREF

1. Kraigher-Krainer E, JACC 2013
2. Knappe D, Circ HF 2011
3. TOPCAT, 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

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>P &lt; 0.001</td>
<td>P = 0.005</td>
</tr>
<tr>
<td>E/E'</td>
<td>P &lt; 0.001</td>
<td>P = 0.017</td>
</tr>
<tr>
<td>LV Mass</td>
<td>P &lt; 0.001</td>
<td>P = 0.025</td>
</tr>
<tr>
<td>Global Longitudinal Strain</td>
<td>P &lt; 0.001</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Left Atrial Volume</td>
<td>P = 0.009</td>
<td>P = 0.083</td>
</tr>
<tr>
<td>LVEF</td>
<td>P = 0.081</td>
<td>P = 0.70</td>
</tr>
</tbody>
</table>
Diagnostic Algorithms for HFpEF have not been validated in RCTs....

What are their diagnostic properties?
Method: Simultaneous echocardiographic-catheterization studies were prospectively conducted at rest and during exercise in subjects with invasively-proven HFpEF (n=50) and participants with dyspnea but no identifiable cardiac pathology (n=24).
## Diagnosis of HFpEF According to Contemporary Guidelines

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Indeter (%)</th>
<th>Positive LR</th>
<th>Negative LR</th>
<th>C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASE/EACVI algorithm</td>
<td>34 (22-48)</td>
<td>83 (64-93)</td>
<td>94 (74-99)</td>
<td>53 (37-68)</td>
<td>24</td>
<td>2.0</td>
<td>0.8</td>
<td>0.65 (0.57-0.72)</td>
</tr>
<tr>
<td>ESC criteria</td>
<td>60 (46-72)</td>
<td>75 (55-88)</td>
<td>83 (68-92)</td>
<td>47 (32-63)</td>
<td>0</td>
<td>2.4</td>
<td>0.5</td>
<td>0.68 (0.55-0.78)</td>
</tr>
<tr>
<td>ESC + Leg raise E/e'</td>
<td>56 (42-69)</td>
<td>79 (60-91)</td>
<td>85 (69-93)</td>
<td>46 (32-61)</td>
<td>0</td>
<td>2.7</td>
<td>0.6</td>
<td>0.68 (0.56-0.77)</td>
</tr>
<tr>
<td>ESC + Ex Echo</td>
<td>70 (56-81)</td>
<td>75 (55-88)</td>
<td>85 (72-93)</td>
<td>55 (38-70)</td>
<td>0</td>
<td>2.8</td>
<td>0.4</td>
<td>0.73 (0.60-0.82)</td>
</tr>
<tr>
<td>ESC + Ex E/e' alone</td>
<td>90 (79-96)</td>
<td>71 (51-85)</td>
<td>87 (75-93)</td>
<td>77 (57-90)</td>
<td>0</td>
<td>3.1</td>
<td>0.1</td>
<td>0.80 (0.68-0.89)*</td>
</tr>
<tr>
<td>ESC + 20W E/e' alone</td>
<td>80 (67-89)</td>
<td>88 (69-96)</td>
<td>93 (81-98)</td>
<td>68 (50-81)</td>
<td>0</td>
<td>6.7</td>
<td>0.2</td>
<td>0.84 (0.73-0.91)*</td>
</tr>
<tr>
<td>Rest Cath</td>
<td>56 (42-69)</td>
<td>100 (86-100)</td>
<td>100 (88-100)</td>
<td>52 (38-66)</td>
<td>0</td>
<td>$+\infty$</td>
<td>0.4</td>
<td>0.78 (0.70-0.84)</td>
</tr>
<tr>
<td>Rest Cath + 20W Cath</td>
<td>94 (84-98)</td>
<td>100 (86-100)</td>
<td>100 (92-100)</td>
<td>89 (72-96)</td>
<td>0</td>
<td>$+\infty$</td>
<td>0.1</td>
<td>0.97 (0.91-0.99)†</td>
</tr>
<tr>
<td>Rest Cath + Ex Cath</td>
<td>100 (93-100)</td>
<td>100 (86-100)</td>
<td>100 (93-100)</td>
<td>100 (86-100)</td>
<td>0</td>
<td>$+\infty$</td>
<td>0</td>
<td>1.00 (1.00-1.00)†</td>
</tr>
</tbody>
</table>
Proportion of subjects with HFpEF and non-Cardiac Dyspnea identified according to the different guideline recommended algorithms

40% for HFpEF
10% for Non-Cardiac Dyspnea

Post-Test Diagnosis of HFpEF:
- Positive
- Negative
- Indeterminate

HFpEF - Challenge #3: Pathophysiology
HFpEF: challenge 3 - pathophysiology

HFpEF: a lot more beyond LV diastolic dysfunction

other CV abnormalities beyond diastole

Multiple co-morbidities

Ventricular Dysfunction
- Impaired relaxation
- Impaired filling
- Systolic Dysfunction

Lung Disease
COPD

Iron deficiency
and anemia

Renal dysfunction
Volume overload

Aging &
Deconditioning

Obesity &
Sarcopenia

Psychic Disorders
Depression

Valvular disease
Dynamic mitral regurgitation

Elevated blood pressure
Inadequate BP response to exercise
Pulmonary hypertension

Vascular dysfunction
Vascular stiffening
Ventriculo-arterial coupling

Atrial dysfunction

Autonomic dysfunction
Chronotropic incompetence

Heart failure with preserved EF
Myth: HFpEF is a Collection of Comorbidities and NOT a Disease!

### Table 1. Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HFrEF</th>
<th>HFpEF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LVEF — %</td>
<td>25.9</td>
<td>62.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age — yr</td>
<td>71.8 ± 12</td>
<td>75.4 ± 11.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>983 (62.6%)</td>
<td>302 (43.4%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- **Age**
  - HFrEF: 71.8 ± 12
  - HFpEF: 75.4 ± 11.5
  - P-value: < 0.001

- **Hypertension**
  - HFrEF: 49.2%
  - HFpEF: 55.1%
  - P-value: 0.005

- **Atrial Fibrillation**
  - HFrEF: 23.6%
  - HFpEF: 31.8%
  - P-value: < 0.001

- **COPD**
  - HFrEF: 13.2%
  - HFpEF: 17.7%
  - P-value: 0.002

- **Anemia**
  - HFrEF: 9.9%
  - HFpEF: 21.1%
  - P-value: < 0.001

- **Dementia**
  - HFrEF: 76 (4.8%)
  - HFpEF: 49 (5.6%)
  - P-value: 0.43

- **Hemoglobin < 10 g/dl**
  - HFrEF: 155 (9.9%)
  - HFpEF: 216 (21.1%)
  - P-value: < 0.001

- **Mean systolic blood pressure — mm Hg**
  - HFrEF: 146
  - HFpEF: 156
  - P-value: < 0.001

- **Mean respiratory rate — breaths/min**
  - HFrEF: 26
  - HFpEF: 26
  - P-value: 0.17

- **Serum sodium < 136 mmol/liter**
  - HFrEF: 362 (23.1%)
  - HFpEF: 209 (23.8%)
  - P-value: 0.70

- **Serum creatinine > 150 mmol/liter**
  - HFrEF: 296 (18.9%)
  - HFpEF: 195 (22.2%)
  - P-value: 0.95

- **Dialysis**
  - HFrEF: 18 (1.1%)
  - HFpEF: 9 (1.0%)
  - P-value: 0.78

---

Bhatia et al. NEJM 2006
HF Hospitalization and Mortality Higher in HFpEF than in Studies of Similar Comorbidity
HFpEF - Challenge #4: Treatment
### Treatment of HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic <strong>blood pressure</strong> should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>Diuretics</strong> should be used for relief of symptoms due to volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td><strong>Coronary revascularization</strong> 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><strong>Management of AF</strong> 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</td>
<td>No Benefit</td>
</tr>
</tbody>
</table>

2013 ACCF/AHA Guideline for the Management of Heart Failure
A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines
Outcome-studies 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

HR (95% CI) = 0.95 (0.86–1.05)
Log-rank p = 0.35

N = 4,128

Mean follow-up 49.5 months

TOPCAT

Placebo: 20.4%
Spironolactone: 18.6%

HR = 0.89 (0.77 – 1.04)
p = 0.138
## Important RCTs of HF meds in HFpEF

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Intervention</th>
<th>Duration/Inclusion Criteria</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM-preserved</td>
<td>Candesartan</td>
<td>18 years/NYHA class II–IV HF</td>
<td>CV death or HF admission, Fewer HF admissions</td>
</tr>
<tr>
<td>The PEP-CHF</td>
<td>Perindopril</td>
<td>70 years/diagnosis of HF and treated with diuretics and an echo-DD</td>
<td>All-cause mortality and HF admission, Fewer HF admissions</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>Irbesartan</td>
<td>≥60 years/hospitalized for HF during the previous 6 months and have current NYHA class II–IV symptoms</td>
<td>Death from any cause or hospitalization for a CV cause, Neutral</td>
</tr>
<tr>
<td>Kitzman et al.</td>
<td>Enalapril</td>
<td>Elderly (70 ± 1 years), predominant female (80%) with compensated HF</td>
<td>Peak VO₂ and 6 MWD, Neutral</td>
</tr>
<tr>
<td>TOPCAT</td>
<td>Spironolactone</td>
<td>≥50 years, symptomatic HF. Patients had a history of HF hospitalization within previous 12 months and elevated BNP within 60 days before randomization</td>
<td>CV death or aborted cardiac arrest, HF hospitalization, Neutral</td>
</tr>
<tr>
<td>Aldo-DHF</td>
<td>Spironolactone</td>
<td>≥50 years ambulatory patients/NYHA class II–III symptoms, grade I DD and normal or near-normal BNP levels</td>
<td>Peak VO₂, change in $E'/e'$, Neutral</td>
</tr>
<tr>
<td>RAAM-PEF</td>
<td>Eplerenone</td>
<td>Elderly, symptomatic NYHA class II/III, increased BNP within 60 days</td>
<td>6 MWD, Neutral</td>
</tr>
<tr>
<td>J-DHF</td>
<td>Carvedilol (low-dose)</td>
<td>≥20 years/ambulatory patients with NYHA class II–III symptoms, grade I DD, and normal or near-normal BNP levels</td>
<td>Death or HF hospitalization, Neutral</td>
</tr>
<tr>
<td>ELANDD</td>
<td>Nebivolol</td>
<td>≥40 years/ambulatory patients with NYHA class II–III symptoms, grade I DD, and normal or near-normal BNP levels</td>
<td>6 MWD, Neutral</td>
</tr>
<tr>
<td>NEAT-HFPEF trial</td>
<td>Isosorbide mononitrate</td>
<td>≥50 years/ambulatory HF patients, prior hospitalization for HF within 12 months or increased invasively measured LV filling pressure or elevated BNP or echo-DD</td>
<td>Daily activity level, 6 MWD, Neutral</td>
</tr>
</tbody>
</table>

*Upadhya B & Kitzman DW, Am J CV Drugs 2017*
RCTs: huge challenge in HFpEF

- **HFpEF diagnosis and pathophysiological approach**
  - Lack of consistent diagnostic criteria for HFpEF
  - No single cut-off for EF until recently: latest 50% (guidelines 2016)
  - Is ‘one size fits all’ the appropriate approach for a disease with various phenotypes and probably distinct pathophysiological mechanisms?

- **RCTs – design and implementation**
  - Inappropriate patient inclusion (TOPCAT)
  - Mixed populations – few patients with EF>50% included
  - High drop-out rate, open label tx instead of double-blind
  - Expensive and of short duration
  - Few hard end-points: correct approach?
MRAs; an opportunity missed in TOPCAT with spironolactone.
SPIRIT-HFpEF
Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction

Prospective, randomized, multicenter, safety/efficacy, parallel assignment, open-label treatment, blinded endpoint (PROBE), phase 3, interventional trial

- In HFPEF (EF ≥ 40%, NT-proBNP ≥ 300 SR / 750 AF / 500 acute SR / 1250 acute AF)
- of spironolactone + 4 K/creat checks vs. 4 K/creat checks alone
- Outcome CV death, event driven
- Event rate 8.5% / year, RRR 20% → 632 events over 5 years 2017-2022
- Sample size 3200 included over 3 years 2017-2020

Courtesy Lars Lund
HFpEF; multifaceted approach
Several therapeutic targets under investigation

Zakeri R & Cowie MR, Heart 2018
**PHENOTYPE-SPECIFIC TREATMENT OF HFpEF: A MULTIORGAN ROADMAP**

<table>
<thead>
<tr>
<th>HFpEF Clinical Presentation Phenotypes</th>
<th>Lung Congestion</th>
<th>+Chronotropic Incompetence</th>
<th>+Pulmonary Hypertension (CpcPH)</th>
<th>+Skeletal muscle weakness</th>
<th>+Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight/obesity/metabolic syndrome/ type 2 DM</td>
<td>• Diuretics (loop diuretic in DM) • Caloric restriction • Statins • Inorganic nitrite/nitrate • Sacubitril • Spironolactone</td>
<td>+Rate adaptive atrial pacing</td>
<td>+Pulmonary vasodilators (e.g. PDE5i)</td>
<td>+Exercise training program</td>
<td>+Cardioversion + Rate Control + Anticoagulation</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>+ACEI/ARB +Rate adaptive atrial pacing</td>
<td>+ACEI/ARB +Pulmonary vasodilators (e.g. PDE5i)</td>
<td>+ACEI/ARB +Exercise training program</td>
<td>+ACEI/ARB +Cardioversion + Rate Control + Anticoagulation</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>+Ultrafiltration if needed +Rate adaptive atrial pacing</td>
<td>+Ultrafiltration if needed +Pulmonary vasodilators (e.g. PDE5i)</td>
<td>+Ultrafiltration if needed +Exercise training program</td>
<td>+Ultrafiltration if needed +Cardioversion + Rate Control + Anticoagulation</td>
<td></td>
</tr>
<tr>
<td>+CAD</td>
<td>+ACEI +Revascularization +Rate adaptive atrial pacing</td>
<td>+ACEI +Revascularization +Pulmonary vasodilators (e.g. PDE5i)</td>
<td>+ACEI +Revascularization +Exercise training program</td>
<td>+ACEI +Revascularization +Cardioversion + Rate Control + Anticoagulation</td>
<td></td>
</tr>
</tbody>
</table>

Shah SJ et al, Circulation 2016
RELAX: PDE-5 inhibition in HFpEF

Redfield et al. JAMA 2013;309(12):1268-77
## RELAX Endpoints

### Table 3. 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 -0.20 (-0.70 to 1.00)</td>
<td>91 -0.2 (-1.70 to 1.11)</td>
<td>.90</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical rank score, mean&lt;sup&gt;a&lt;/sup&gt;</td>
<td>94 95.8</td>
<td>95 94.2</td>
<td>.85</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 24 wk, median (IQR), m</td>
<td>95 15.0 (-26.0 to 45.0)</td>
<td>90 5.0 (-37.0 to 55.0)</td>
<td>.92</td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min</td>
<td>95 0.03 (-1.10 to 0.77)</td>
<td>97 0.01 (-1.35 to 1.25)</td>
<td>.99</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 12 wk, median (IQR), m</td>
<td>96 18.0 (-14.5 to 48.0)</td>
<td>99 10.0 (-25.0 to 36.0)</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Components of clinical rank score at 24 wk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>103 0</td>
<td>113 3 (3)</td>
<td>.25</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular or renal cause, No. (%)</td>
<td>103 13 (13)</td>
<td>113 15 (13)</td>
<td>.99</td>
</tr>
<tr>
<td>Change in MLHFO, median (IQR)</td>
<td>91 -6 (-21 to 5)</td>
<td>91 -8 (-19 to 0)</td>
<td>.44</td>
</tr>
<tr>
<td><strong>Safety endpoints, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>103 78 (76)</td>
<td>113 90 (80)</td>
<td>.49</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>103 16 (16)</td>
<td>113 25 (22)</td>
<td>.22</td>
</tr>
<tr>
<td>Change in left ventricular structure by CMRI at 24 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular mass by CMRI, g</td>
<td>47 0.6 (-5.7 to 7.8)</td>
<td>49 -1.5 (-5.9 to 7.1)</td>
<td>.93</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume by CMRI, mL</td>
<td>47 -4.3 (-15.5 to 8.1)</td>
<td>49 3.7 (-4.9 to 14.5)</td>
<td>.13</td>
</tr>
<tr>
<td>Change in diastolic function parameters at 24 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial e', m/s</td>
<td>83 0.00 (-0.01 to 0.01)</td>
<td>77 0.00 (-0.01 to 0.01)</td>
<td>.86</td>
</tr>
<tr>
<td>E/e&lt;sup&gt;c&lt;/sup&gt;</td>
<td>80 -1.6 (-4.7 to 2.2)</td>
<td>75 0.2 (-2.4 to 3.1)</td>
<td>.16</td>
</tr>
<tr>
<td>PA systolic pressure, mm Hg</td>
<td>58 -2 (-8 to 8)</td>
<td>45 2 (-5 to 7)</td>
<td>.94</td>
</tr>
<tr>
<td>Change in core laboratory biomarkers at 24 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>94 0.01 (-0.10 to 0.09)</td>
<td>94 0.05 (-0.04 to 0.15)</td>
<td>.047</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
<td>96 0.01 (-0.08 to 0.11)</td>
<td>96 0.05 (-0.04 to 0.16)</td>
<td>.01</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>94 -23 (-198 to 126)</td>
<td>95 15 (-90 to 372)</td>
<td>.03</td>
</tr>
<tr>
<td>Endothelin-1, pg/mL</td>
<td>95 -0.01 (-0.48 to 0.47)</td>
<td>95 0.38 (-0.10 to 0.97)</td>
<td>.046</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
<td>95 0 (-7.0 to 4.8)</td>
<td>95 1 (-10.7 to 3.0)</td>
<td>.85</td>
</tr>
<tr>
<td>NT-procollagen III, pg/L</td>
<td>93 -0.03 (-1.49 to 1.54)</td>
<td>95 0.07 (-1.17 to 1.42)</td>
<td>.77</td>
</tr>
</tbody>
</table>
Soluble guanylate cyclase – a novel target for the treatment of heart failure
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 ± SD

Pieske et al. ESC-HF 2016
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

NEJM 2015
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.
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 prEraveD left ventricular ejection fraction chronic heart Failure with ivabradine studY (EDIFY) Investigators†

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>Endpoint</th>
<th>Baseline Median</th>
<th>Q1–Q3</th>
<th>Change (last post-baseline value from baseline)</th>
<th>Between-group estimate (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ivabradine (n = 84)</td>
<td>12.6</td>
<td>9.7–16.2</td>
<td>0.970</td>
<td>−0.8 to 2.9</td>
<td>1.4 (0.3–2.5)</td>
</tr>
<tr>
<td>Placebo (n = 83)</td>
<td>12.9</td>
<td>10.1–16.0</td>
<td>−0.590</td>
<td>−2.2 to 1.4</td>
<td>−3.8 (−19.1 to 11.6)</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>323.0</td>
<td>243.5–375.0</td>
<td>0.0</td>
<td>−28.5 to 35.0</td>
<td>6.5 (1.1–11.8)</td>
</tr>
<tr>
<td>ivabradine (n = 84)</td>
<td>321.0</td>
<td>256.5–368.0</td>
<td>11.0</td>
<td>−15.5 to 40.0</td>
<td>10.0 (2.6–17.4)</td>
</tr>
<tr>
<td>Placebo (n = 82)</td>
<td>343.0</td>
<td>238.0–631.0</td>
<td>16.5</td>
<td>−134.0 to 126.0</td>
<td>10.0 (2.6–17.4)</td>
</tr>
</tbody>
</table>
Effect of Exercise Training on Measures of Diastolic Function

Edelmann F., Pieske B. JACC 2011
Lessons learned from the prevention of HFpEF
SPRINT: Intensive BP lowering reduces adverse outcomes

HF hospitalization reduced by 38%
LCZ696 – A first-in-class Angiotensin Receptor Neprilysin Inhibitor – Simultaneously Inhibits NEP and the RAS

Vasoactive Peptide System
- pro-BNP
- NT-pro BNP
- Sacubitril (AHU377)
- LBQ657

Heart Failure

Renin Angiotensin System
- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II
- AT₁ receptor

Neprilysin

LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio

Vasodilation
- blood pressure
- sympathetic tone
- aldosterone levels
- fibrosis
- hypertrophy
- Natriuresis/Diuresis

Vasoconstriction
- blood pressure
- sympathetic tone
- aldosterone
- fibrosis
- hypertrophy

Inactive fragments
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

- **Improvement in NT-proBNP**
  - Valsartan: 862 (733, 1012)
  - LCZ696: 835 (710, 981)
  - LCZ696/Valsartan: 0.77 (0.64, 0.92)
  - P = 0.005

- **Improvement in Left Atrial Size**
  - LCZ696: P = 0.003
  - Valsartan: P = 0.18

- **Improvement in NYHA Class**
  - P = 0.11
  - P = 0.05

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

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

Solomon et al. JACC-HF 2017
Pts with T2DM at high CV risk (n=7020) randomized to receive 10 mg or 25 mg of empagliflozin or placebo once daily (median observation time, 3.1 years). The primary composite outcome was death from CV causes, nonfatal MI, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group.

Empagliflozin reduced arterial stiffness

EMPEROR-Reduced and EMPEROR-Preserved Heart Failure Outcome Trials

AIM: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with reduced\(^1\) and preserved\(^2\) ejection fraction.

**Synopsis\(^{1,2}\)**
- T2D and non-T2D
- Event-driven trial

**Patients:**
- Aged $\geq 18$ y
- Chronic HF
- NYHA II–IV
- EF: >40% or $\leq 40%$

**Plan to enroll**
- **EMPEROR-Reduced\(^1\)**
  - 2850 patients
- **EMPEROR-Preserved\(^2\)**
  - 4126 patients

**Study timings\(^{1,2}\)**
- Start: March 2017
- Estimated finish: June 2020

chronic HF NYHA class II-IV

HFpEF (LVEF > 40%)
Elevated NT-proBNP
- $> 300$ pg/ml for patients without AF
- $> 900$ pg/ml for patients with AF

1. NCT03057977 2. NCT03057951
www.clinicaltrials.gov
Take home message
We need to improve the specificity of a HFpEF dx
   - Exercise echo - new imaging techniques (strain-CMR)
   - New cut-off values for NPs in several clinical situations

It is reasonable to use:
   - spironolactone for reducing hospitalizations
   - strategies of monitoring using devices and exercise
   - the distinct phenotype approach

New therapies are currently being investigated in many trials (Phase III: sacubitril/valsartan, empagliflozin)

Until then, management of HFpEF includes:
   - treating congestion, reducing BP, rate control for AF, and optimizing treatment for comorbid conditions

Take home message
39th Panhellenic Congress of Cardiology

Thank You

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October 20th 2018, Athens, Greece
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