Heart Failure with Preserved Ejection Fraction: Pathophysiology and treatment

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Disclosures

Speaker: Gregory Giamouzis, MD, PhD

I have the following potential conflicts of interest to report:

Lecture fees: Astra-Zeneca, Bayer, Boehringer-Ingelheim,
               Menarini, MSD, Novartis, Pfizer, Servier.

Advisory Boards: Menarini, MSD, Novartis, Servier.
Epidemiology
Between 30-50% of all Heart Failure Admissions are with Preserved Ejection Fraction

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

HFrEF

HFpEF

Left Ventricular Ejection Fraction (%)

Global prevalence of HFpEF

HF Registries 2003-2012

% HFpEF

- EF cut-off ≥50%
- EF cut-off ≥40%

<table>
<thead>
<tr>
<th>Registry</th>
<th>EF ≥50%</th>
<th>EF ≥40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK-Heart</td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td>GTWG</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>ADHERE</td>
<td>50.4</td>
<td></td>
</tr>
<tr>
<td>OPTIMIZE-HF</td>
<td>51.2</td>
<td></td>
</tr>
<tr>
<td>ADHERE-I</td>
<td></td>
<td>45.7</td>
</tr>
<tr>
<td>JCARE-CARD</td>
<td></td>
<td>52.3</td>
</tr>
</tbody>
</table>

Dhingra Curr Heart Fail Rep 2014
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
Pathophysiology
Hypothesis: HFpEF and HFrEF Are Overlapping Phenotypes Within the Heart Failure Spectrum

Spectrum Paradigm of Heart Failure
**Pathophysiological Models of HFpEF**

**A. Traditional**

- **Left ventricle**
  - Systemic hypertension
  - Vascular dysfunction
  - 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**

- **Proinflammatory coexisting conditions**
  - Systemic microvascular endothelial inflammation
  - Increases in oxidative stress
  - Decreases in NO-cGMP signaling

- **Muscle inflammation**
  - Myofiber stiffness
  - Cardiomyocyte hypertrophy
  - Fibrosis
  - Global cardiac remodeling and dysfunction
  - Impaired coronary flow reserve
  - Impaired oxygen delivery, uptake, and utilization in skeletal muscle

The Laplace Law and Development of LV Hypertrophy

Nadruz W. Journal of Human Hypertension 2015; 29:1–6
Emerging Pathophysiologica l Model of HFpEF

- Hypertension
- Overweight/Obesity
- Diabetes Mellitus
- Kidney disease
- Iron deficiency
- COPD

- IL-6
- TNF-α
- sST2
- Pentraxin 3

Endothelium

Cardiomyocytes

Paulus WJ, Tschoepe C. JACC 2013; 62:263-71
Growing Evidence Linking Microvascular Dysfunction With Heart Failure With Preserved Ejection Fraction

Gregory Giamouzis, MD, PhD; Erik B. Schelbert, MD; Javed Butler, MD, MPH, MBA

Hypertension
Diabetes
Obesity

Comorbidities
Coronary Artery Disease
Lung Disease
Kidney Disease

Oxidative Stress,
Reduced NO bioavailability

Inflammatory state
Fibroblast differentiation,
Vascular Rarefaction

Endothelial Dysfunction
Abnormal CFR and IMR with Acetylcholine

Inflammation

Microvascular Dysfunction
Abnormal CFR and IMR with Adenosine

Hypophosphorylation of Titin

Myocardial Stiffness
Vascular Stiffness

Extracellular Membrane
Collagen, Fibrosis

HF symptoms
HFpEF

Giamouzis G.
J Am Heart Assoc. 2016
Feb 23;5(2). pii: e003259
HFpEF: pathophysiology

HFpEF: a lot more beyond LV diastolic dysfunction

Other CV abnormalities beyond diastole

Multiple co-morbidities

"Heart failure" with preserved EF

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
HFpEF: Patients’ Characteristics and Comorbidities
Co-Morbidities in HF Patients: the European Heart Failure Pilot Survey

Distribution of Deaths in Studies of HFpEF

Chan MMY, Lam CSP. European Journal of Heart Failure 2013; 5:604–613
HF Hospitalization and Mortality Higher in HFpEF than in Studies of Similar Comorbidity
### Characteristics of Hospitalized HF Patients

<table>
<thead>
<tr>
<th></th>
<th>LVEF ≥ 50% (n=40,354)</th>
<th>40%≤LVEF&lt;50% (n=15,184)</th>
<th>LVEF&lt;40% (n=55083)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>78 (67-85)</td>
<td>76 (65-84)</td>
<td>70 (58-80)</td>
</tr>
<tr>
<td><strong>Female sex (%)</strong></td>
<td>63</td>
<td>47</td>
<td>36</td>
</tr>
<tr>
<td><strong>Body mass index&gt;30 kg/m^2 (%)</strong></td>
<td>33</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>22</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>80</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td><strong>Diabetes (oral therapy)</strong></td>
<td>24</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td><strong>Diabetes (insulin)</strong></td>
<td>22</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td><strong>Chronic/recurrent atrial fibrillation</strong></td>
<td>34</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>44</td>
<td>54</td>
<td>52</td>
</tr>
<tr>
<td><strong>Pulmonary disease</strong></td>
<td>33</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong></td>
<td>52</td>
<td>52</td>
<td>48</td>
</tr>
</tbody>
</table>

Non Cardiac Comorbidities: the European Heart Failure Pilot Survey

3,226 European outpatients with chronic HF

<table>
<thead>
<tr>
<th></th>
<th>N=1580</th>
<th>N=1249</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HFpEF (LVEF &lt;40%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>541 (41)</td>
<td>383 (39)</td>
<td>0.381</td>
</tr>
<tr>
<td>Anaemia</td>
<td>349 (28)</td>
<td>306 (30)</td>
<td>0.130</td>
</tr>
<tr>
<td>Diabetes</td>
<td>470 (30)</td>
<td>343 (28)</td>
<td>0.191</td>
</tr>
<tr>
<td>COPD</td>
<td>255 (16)</td>
<td>173 (14)</td>
<td>0.101</td>
</tr>
<tr>
<td>Stroke</td>
<td>166 (11)</td>
<td>129 (10)</td>
<td>0.892</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>69 (4)</td>
<td>49 (4)</td>
<td>0.578</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>152 (10)</td>
<td>96 (8)</td>
<td>0.062</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>54 (4)</td>
<td>32 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Frequency of Comorbidities in the Total HF Population (n=1064)

Heart Failure Clinic, Larissa University Hospital

- Hypertension: 76.3%
- Myocardial infarction: 44.0%
- Dyslipidaemia: 42.1%
- Obesity: 37.8%
- Atrial fibrillation: 31.1%
- Anaemia: 30.8%
- Chronic kidney disease: 28.0%
- Diabetes mellitus: 24.1%
- COPO: 14.6%

Heart Failure Clinic, Larissa University Hospital, Unpublished data
Frequency of Comorbidities by HF Phenotype

Heart Failure Clinic, Larissa University Hospital

Heart Failure Clinic, Larissa University Hospital, Unpublished data
Frequency of Mono-comorbidity by HF Phenotype (n=94/1064)

Heart Failure Clinic, Larissa University Hospital, Unpublished data
Hypertension, Obesity, Diabetes, and MI are the Major Determinants of HF Phenotype

1019 consecutive HF patients (age 71.7±12.3 years, male 56.9%, mean LVEF 42.8±14.4%, HFrEF 46.6%) referred to the outpatient HF Clinic of a tertiary University Hospital were screened for major HF comorbidities, from January 2014 to December 2015.

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>72.3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>26.2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>39.8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21.3</td>
</tr>
<tr>
<td>COPD</td>
<td>13.6</td>
</tr>
<tr>
<td>Obesity</td>
<td>39.4</td>
</tr>
<tr>
<td>CKD</td>
<td>18.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>28.2</td>
</tr>
</tbody>
</table>
### Determinants of the HF Phenotype

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratios* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>9.43 (5.85, 15.17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.06 (0.04, 0.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obesity</td>
<td>3.24 (2.23, 4.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.57 (0.37, 0.90)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Higher odds for: i) HFpEF, if OR>1.0; ii) HFrEF, if OR<1.0

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**ROC Curve**

Area under ROC curve = 0.8978
The Transition From Hypertension to Heart Failure
This degree of diastolic dysfunction progresses with age.
Hypertension in the Elderly

- Aortic stiffness is a cause rather than a consequence of hypertension in middle-aged and older individuals.
- Interventions that reduce arterial stiffness and wave reflections, include drugs prescribed for the treatment of hypertension and HF.

- O'Rourke, and Hashimoto. JACC 2007; 50:1-13
Effect of Increased Arterial Stiffness on Cardiac Function

Increase in LV afterload
Decrease in coronary blood perfusion
Final wave with early reflected wave
Final wave with late reflected wave
Reflected wave

Velocity of the incident wave and early return of the reflected wave

Shifting of the pressure augmentation from diastole to systole

Systolic pressure
Pressure during diastole
LV afterload
Coronary perfusion
LV hypertrophy
Myocardial oxygen demands

Perfusion mismatch - CFR
Pathogenesis and Natural History of HFrEF

- Advanced age
- Female sex
- Obesity
- Hypertension
- Atherosclerosis

Stiff arteries
- Systolic/pulse pressure
- Diastolic flow

Symptomatic concentric LV remodeling/LVH

Death

- Atrial fibrillation
- Anemia
- Diabetes
- Chronic Kidney Disease
- COPD

F. Triposkiadis, Unpublished
HFpEF heterogeneous pathogenesis: time for a new classification?
Heart failure vs. myocardial failure in the setting of preserved LVEF

- Amyloidosis
- Haemochromatosis
- Endomyocardial fibrosis
- Radiation-induced
- Chemotherapy-induced
- Idiopathic

- Constrictive pericarditis
- Constrictive effusive disease
- Post-pericardiotomy syndrome

Pericardial disease

- Restrictive CMP
- Hypertrophic CMP

HF signs and symptoms normal LVEF

- Pulmonary arterial hypertension
- ARVC
- Sarcoidosis
- Tricuspid regurgitation

Storage disease

- Fabry
- LAMP2
- PRKAG2

HF-PEF

Hypertensive

Desai AS, Jhund PS. Eur Heart J 2016;37:3135-40
Proposed classification of HFpEF based on phenotype

HFpEF

- BNP, LAE, LVH, Diastolic/systolic dysfunction
- Abnormal hemodynamics

Phenotypes

- Hypertensive (majority)
- Non-hypertensive (minority)

Risk factors/comorbidities
- Advanced age
- Anemia
- Atrial fibrillation
- Chronic obstructive pulmonary disease
- Coronary artery disease
- Diabetes mellitus
- Female gender
- Sleep apnea

Valvular
- Mitral stenosis
- Aortic stenosis

Cardiomyopathic
- Hypertrophic
- Restrictive

Extramycocardial
- Pericardial disease

Xanthopoulos A., Triposkiadis F, Starling R. 2018
Treatment
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
<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 <strong>controlled</strong> 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: No Benefit</td>
<td>C</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%), 333 (22.0%)

Candesartan

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

Irbesartan

(Mean follow-up 49.5 months)

TOPCAT

HR = 0.89 (0.77 – 1.04)
p=0.138

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

Probability

0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35

Number at risk
- Spiro 1722
- Placebo 1723

0 12 24 36 48 60 72 Months

p=0.138
### Important RCTs of HF meds in HFpEF

<table>
<thead>
<tr>
<th>Study</th>
<th>Medication</th>
<th>Eligibility</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM-preserved [52]</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 [53]</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 [54]</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. [55]</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 [60]</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 [57]</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 [58]</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 [63]</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>ELANDDD [64]</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 [68]</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*
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

TOPCAT: 1st Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)
SPIRIRIT-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
RELAX: PDE-5 inhibition in HFpEF

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

<table>
<thead>
<tr>
<th>Table 3. Primary, Secondary, and Safety End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>No. of Patients</td>
</tr>
<tr>
<td>Primary end point</td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 24 wk, median (IQR), mL/kg/min</td>
</tr>
<tr>
<td>Secondary end points</td>
</tr>
<tr>
<td>Clinical rank score, mean[^8]</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 24 wk, median (IQR), m</td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 12 wk, median (IQR), m</td>
</tr>
<tr>
<td>Components of clinical rank score at 24 wk</td>
</tr>
<tr>
<td>Death, No. (%)[^3]</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular or renal cause, No. (%)</td>
</tr>
<tr>
<td>Change in MLHFQ, median (IQR)</td>
</tr>
<tr>
<td>Safety end points, No. (%)</td>
</tr>
<tr>
<td>Adverse events</td>
</tr>
<tr>
<td>Serious adverse events</td>
</tr>
<tr>
<td>Change in left ventricular structure by CMRI at 24 wk</td>
</tr>
<tr>
<td>Left ventricular mass by CMRI, g</td>
</tr>
<tr>
<td>Change in diastolic function parameters at 24 wk</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume by CMRI, mL</td>
</tr>
<tr>
<td>Medial e', m/s</td>
</tr>
<tr>
<td>E/e'</td>
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<tr>
<td>PA systolic pressure, mm Hg</td>
</tr>
<tr>
<td>Change in core laboratory biomarkers at 24 wk</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
</tr>
<tr>
<td>Endothelin-1, pg/mL</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
</tr>
<tr>
<td>NT-procollagen III, μg/L</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

Pieske et al. ESC-HF 2016
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

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 ≥ 70 b.p.m.
- NT-proBNP of ≥ 220 pg/mL (BNP ≥ 80 pg/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/e⁰ 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
Effect of Exercise Training on Measures of Diastolic Function

![Graphs showing changes in peak VO2, maximum workload, echocardiographic parameters, and quality of life indices before and after exercise training compared to controls.](image)
HFpEF; multifaceted approach
Several therapeutic targets under investigation

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

<table>
<thead>
<tr>
<th>Phenotype</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</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</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>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Ultrafiltration if needed</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>
</tr>
<tr>
<td>+CAD</td>
<td>ACEI + Revascularization</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>
</tr>
</tbody>
</table>

Shah SJ et al, Circulation 2016
Lessons learned from the prevention of HFpEF
SPRINT: Intensive BP lowering reduces adverse outcomes

HF hospitalization reduced by 38%

Empagliflozin, CV Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME trial)

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

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
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)
- Valsartan
- LBQ657

Heart Failure

Renin Angiotensin System

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

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
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: 852 (733, 1012)
- LCZ696: 835 (710, 981)
- LCZ696/Valsartan: 0.77 (0.64, 0.92)
- P = 0.005

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

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

Solomon et al. Lancet 2012
Pts with HTN (n=454, aged ≥60 years) with SBP ≥150 to <180 mmHg and a PP > 60 mm Hg randomised to once daily LCZ696 200 mg or olmesartan 20 mg for 4 weeks, followed by a forced-titration to double the initial doses for the next 8 weeks. Primary outcome was superiority of LCZ696 vs. olmesartan in reducing CASP pressure after 12 weeks of treatment.

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
Comorbidities are frequent in HF, both HFpEF and HFrEF, and together with demographics contribute to the designation of HF phenotype.

Hypertension is the most common single comorbidity associated with the development of HFpEF.

Increased arterial stiffness is implicated in the pathogenesis of HFpEF.

Aggressive management of systolic hypertension in the elderly has been shown to decrease arterial stiffness and therefore the incidence of HFpEF and mortality.
Take home message

- It is reasonable to use:
  - spironolactone for reducing hospitalizations
  - exercise programs
  - 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
Thank You

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February 22\textsuperscript{nd} 2019, Thessaloniki, Greece

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