HFpEF & acute HF

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Conflict of interest

Travel Grant by St. Jude Medical
What is HFpEF
General Considerations
Definitions
HFpEF Trials
Mechansims of HFpEF
Acute HFpEF
Heart failure with preserved ejection fraction: a clinical dilemma

HFpEF as a transitory stage to HFrEF

Unimodal distribution of LVEF in HF trials

Eccentric LV remodelling in some hypertensive heart disease

Subtle LV systolic dysfunction in HFpEF and severe diastolic dysfunction in HFrEF

HFpEF as a distinct entity from HFrEF

Bimodal distribution of LVEF in HF epidemiologic studies and registries

Distinct pattern of LV remodelling

Distinct cellular, subcellular and interstitial characteristics (Table 1)

Distinct response to HF therapies in trials

Komajda et Lam, Eur Heart J; 2014: 1022-32
General considerations

Asymptomatic diastolic dysfunction in the general population:

USA (Olmsted County, avg. 67 years) : 28%

Europe (Belgium, avg. 58 years) : 27%

Prevalence of symptomatic Heart Failure: 2-3%,
(44% with HFpEF, EF> 50%)

Redfield et al, JAMA 2003; 194-202
Koutznretsova T et al. Circ 2012
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
- Psychiatric Disorders Depression
- Elevated Blood
  - Inadequate BP response to exercise
  - Pulmonary hypertension
- Vascular Dysfunction
  - Vascular stiffening
  - Ventrículo-arterial coupling
- Valvular
  - Dynamic mitral regurgitation
- Autonomic Dysfunction
  - Chronotropic incompetence
- Hypertension
  - Diabetes
  - ROS Production
### ESC Definitions of HFrEF vs. HFpEF

<table>
<thead>
<tr>
<th></th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs</td>
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</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></td>
<td>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).</td>
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</table>
Echocardiographic diastolic function parameters

### Structural alterations:

- LAVI $> 34\text{ml/m}^2$
- LVMI $\geq 115\text{g/m}^2$ for males
- LVMI $\geq 95\text{g/m}^2$ for females

### Functional alterations:

- $E/e' \geq 13$
- Mean septal and lateral $e' < 9\text{cm/s}$

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NEW Guidelines

$T =$ deceleration time of MV-E; $e' =$ early diastolic tissue velocity; $E/e'$ = a ratio between early mitral inflow velocity and mitral annular early diastolic velocity; IVRT = isovolumic relaxation time; MV = mitral valve; MV-A = mitral valve late diastolic inflow; MV-E = mitral valve early diastolic inflow.

ESC Guidelines, Eur Heart J, 2016
Inclusion Criteria of HFpEF Trials

CHARM-Preserved

- Age > 18
- NYHA II – IV
- Hx of cardiac hospitalization
- LVEF > 40%

I-Preserve

- Age ≥ 60
- NYHA II – IV
- EF ≥ 45%
- HF hospitalization within 6 months OR class III-IV with corroborative evidence (pulm congestion, LVH, LAA, LBBB)

TOPCAT

- Age ≥ 50
- HF sings and symptoms
- LVEF ≥ 45%
- HF hospitalization within 1 yr OR elevated BNP > 100 or NTpBNP > 360
Outcome trials in HFpEF

**PEP-CHF**

Proportion having an event (%)

- Placebo
- Perindopril

Number at risk

- Placebo: 426
- Perindopril: 434

**CHARM-Preserved**

Proportion with cardiovascular death or hospital admission for HF (%)

- Placebo
- Candesartan

Number at risk

- Placebo: 1509
- Candesartan: 1514

**I-PRESERVE**

Cumulative incidence of primary outcome (%)

- Placebo
- Irbesartan

Number at risk

- Irbesartan: 2067, 1999, 1812, 1730, 1640, 1560, 1493, 1391, 1291, 1108, 816, 497
- Placebo: 2061, 1991, 1808, 1718, 1618, 1519, 1466, 1426, 1351, 776, 446

**TOPCAT**

- Placebo
- Spironolactone (HR = 0.89 (0.77 – 1.04), p=0.138)

Number at risk

- Placebo: 1732, 1502, 1102, 870, 514, 300, 03
- Spironolactone: 1732, 1492, 1145, 824, 581, 321, 03

J. Clealand, Heart Fail Clinics 2014;10:511-523
Echo Substudy of I-Perserve

LVH & Concentric Remodeling

A

- Normal: 46%
- LV Hypertrophy: 29%
- Concentric Remodeling: 25%

B

- Normal: 41%
- LV Hypertrophy: 29%
- Concentric Remodeling: 30%

M. Ziele; Circulation 2011;124:2491-2501
Echo Substudy of TOPCAT

A. Shah, Circ Heart Fail. 2014;7:104-115
Mechanisms of HFpEF

Diabetes, Obesity, Hypertension

Endothelial Dysfunction

Diastolic Dysfunction
Endothelial Dysfunction of HFpEF

Prevalence of endothelial dysfunction:
- controls: 0%
- Hypertension: 28% p=0.056
- HFpEF: 48% p=0.05
Mechanisms of HFpEF

- Diabetes, Obesity, Hypertension
- Endothelial Dysfunction
- Diastolic Dysfunction
Cardiac endocardial damage leads to mechanical alterations of the cardiomyocyte performance.
Cardiac endothelial cells (in endocardium and myocardial capillaries)

RELEASE OF MANY CARDIO-ACTIVE FACTORS

- ET-1
- PGI-2
- NRG-1
- DKK3
- NO
- periostin
- TSP-1
- APELIN
- FST
- CTGF

SYNERGISM and INTERDEPENDENCE

rhythm, contraction, relaxation, stiffness, growth, viability, ....

Cardiomyocyte

S. Lim, Eur Heart J 2015, 36:2050-2060
CAPILLARY endothelial cross-talk with local tissue cells → DIRECT control of organ function

VASCULAR endothelial cross-talk with smooth muscle cells → regulation of blood pressure, vessel capacity and flow

Pulmonary endothelium
- Vascular E - smooth muscle cells
- Capillary E - alveolar epithelial cells

Cardiac endothelium
- Capillary E - cardiomyocytes
- Endocardial E - cardiomyocytes

Systemic
- Vascular E - smooth muscle cells (including coronary vasculature)

& peripheral endothelium
- Capillary E - renal glomerular cells, tubular cells
- Capillary E - skeletal muscle cells
- Capillary E - hepatocytes

risk factors
- Pulmonary hypertension
- LV remodeling & diastolic dysfunction

Arterial impedance
- Renal dysfunction
- Exercise intolerance

S. Lim, Eur Heart J 2015, 36:2050-2060
A positive correlation between cardiac collagen, as well as the amount of inflammatory cells, and diastolic dysfunction was evident and suggests a direct influence of inflammation on fibrosis triggering diastolic dysfunction.

D. Westerman, Circ Heart Fail 2011, 4:44-52
Autopsy of HFpEF hearts

Microvascular rarefication

Myocardial fibrosis

124 HFpEF patients compared to 104 controls (non-cardiac death, no HF) from Olmsted County

S. Mohammed, Circ 2015, 10:550-559
Cardiomyocyte stiffness – TITIN in diabetic HFpEF

Adapted from C. Tschöpe; Herz 2012
Mechanisms of HFpEF

- Diabetes, Obesity, Hypertension
  - Oxidative Stress, NO-cGMP-PKG
  - Titin changes
- Endothelial Dysfunction
  - Inflammation, EndMT, Fibroblast Activation
- Fibrosis
- Diastolic Dysfunction

Adapted from C. Tschöpe; Herz 2012
HFpEF and acute HF

Definition of AHF: rapid onset or worsening of symptoms and or signs of HF. It is a life threatening medical condition.
Outcomes after acute HF in HFpEF vs. HFrEF

Adjusted Survival Curves for Patients with Heart Failure with Reduced or Preserved Ejection Fraction during the Year after the First Hospital Admission.

HFpEF and acute HF

• Most RCT's of AHF therapies have restricted enrollment to patients with HFrEF.

  ✓ ASCEND      – nesiritide
  ✓ CARRESS-HF  – Ultrafiltration
  ✓ UNLOAD      – Ultrafiltration
  ✓ DOSE        – diuretic dosing strategies
  ✓ RELAX-AHF   – serlaxine
Decongestion relief in HFpEF patients with AHF

- As in patients with HFrEF, the use of diuretics in the setting of volume overload in individuals with HFpEF is an important key to symptom relief.

- Avoidance of over-diuresis is important as HFpEF patients are particularly sensitive to excessive reductions in preload (steeper end-systolic pressure-volume relation)

  ✓ in the ADHERE AHF registry, as compared to HFrEF, patients with HFpEF were slightly more likely to receive intravenous diuretic therapy, but had similar weight loss and similar symptom relief at discharge

  ✓ The two larger RCT’s of ultrafiltration in AHF (UNLOAD and CARESS-HF) did not report in potential differences in response to ultrafiltration in HFpEF vs. HFrEF,
Decongestion relief in HFpEF patients with AHF

F. Peacock, Congest Hear Fail. 2009; 15: 256-264
Vasodilator therapy in HFP EF patients with AHF

PATIENT WITH ACUTE HEART FAILURE

Bedside assessment to identify **hemodynamic profiles**

**PRESENCE OF CONGESTION?**

- **YES** (95% of all AHF patients)
- **NO** (5% of all AHF patients)

- **‘Wet’ patient**
- **‘Dry’ patient**

**ADEQUATE PERIPHERAL PERFUSION?**

- **YES**
  - **‘Wet and Warm’ patient** (typically elevated or normal systolic blood pressure)
    - Vascular type – fluid redistribution
      - Hypertension predominates
      - Vasodilator
      - Diuretic
    - Cardiac type – fluid accumulation
      - Congestion predominates
      - Diuretic
      - Vasodilator
      - Ultrafiltration (consider if diuretic resistance)
  - ‘Dry and warm’ Adequately perfused
    - Compensated
    - Adjust oral therapy

- **NO**
  - **‘Dry and cold’ patient** Hypoperfused, Hypovolemic
    - Consider fluid challenge
    - Consider inotropic agent if still hypoperfused
  - ‘Wet and Cold’ patient
    - Systolic blood pressure <90 mm Hg
    - Inotropic agent
      - Consider vasoressor in refractory cases
    - Diuretic (when perfusion corrected)
    - Consider mechanical circulatory support if no response to drugs
    - Vasodilators
    - Diuretics
    - Consider inotropic agent in refractory cases
## CCS HF Algorithm

### Recommended Follow-up Frequency

<table>
<thead>
<tr>
<th>Follow-up Frequency*</th>
<th>High Risk Individual</th>
<th>Intermediate Risk Individual</th>
<th>Low Risk Individual</th>
</tr>
</thead>
</table>
| Follow-up every 1-4 weeks or as clinically indicated (remote monitoring possible for some titrations) | • NYHA IIIb or IV symptoms  
• Recent HF hospitalization  
• During titration of HF medications  
• New onset heart failure  
• Complications of HF therapy (rising creatinine, hypotension)  
• Need to down-titrate or discontinue beta-blockers or ACEi/ARB  
• Severe concomitant and active illness (e.g. COPD, frailty)  
• Frequent ICD firings (1 month) | • No clear features of high or low risk. |
| Follow-up every 1-6 months | • NYHA I or II  
• No hospitalization in past year  
• No recent changes in medications  
• Receiving optimal medical/device HF therapies | |
| Follow-up every 6-12 months | • Stable NYHA I or II for 6-12 months  
• On optimal therapies  
• Reversible causes of HF fully controlled  
• Having access to General Practitioner with expertise in management of HF | • Stable adherence to optimal HF therapy  
• No hospitalization for >1 year  
• LVEF >35% (consistently shown if more than one recent EF measurement)  
• Primary care provider has access to urgent specialists reassessment |

### Make inactive or consider for discharge from HF clinic if a minimum of 2 of the following characteristics are present:

- Stable NYHA I or II for 6-12 months
- On optimal therapies
- Reversible causes of HF fully controlled
- Having access to General Practitioner with expertise in management of HF

*Visit frequency may increase during medication titration

Cardiac Reha – EX-DHF-P

**Spiroergometry**

- **Panel A**
  - Change in peak VO2 [mL/min/kg]
  - Green bars: Training
  - Red bars: Control
  - P < 0.001

- **Panel B**
  - Change in maximum workload [Watt]
  - Green bars: Training
  - Red bars: Control
  - P < 0.001

**Echocardiography**

- **Panel C**
  - Change in E/e' ratio
  - Green bars: Training
  - Red bars: Control
  - P < 0.001

- **Panel D**
  - Change in left atrial volume index [mL/m^2]
  - Green bars: Training
  - Red bars: Control
  - P < 0.001

F. Edelmann JACC 2011; 58:1780-91
THIS GUY IS OUT THERE GETTING IT DONE WHY AREN'T YOU??
Thank you

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Vasodilator therapy in HFpEF patients with AHF
Endothelial dysfunction causes fibrosis

- Endothelial-to-mesenchymal transition contributes to cardiac fibrosis (E. Zeisberg, Nat Med 2007)

- Endothelial NADPH Oxidase-2 Promotes Interstitial Cardiac Fibrosis and Diastolic Dysfunction Through Proinflammatory Effects and Endothelial-Mesenchymal Transition (C. Murdoch JACC 2014;63:2734-41)
**Web Table 9.1**  Phase II and III clinical trials performed in patients with heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Major inclusion criteria</th>
<th>Mean follow-up</th>
<th>Primary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP-CHF\textsuperscript{320}</td>
<td>Perindopril vs placebo.</td>
<td>LV wall motion index $\geq 1.4$ (corresponding to LVEF $\geq 40%$), symptomatic HF treated with diuretic, diastolic dysfunction in echocardiography, age $\geq 70$ y.</td>
<td>2.1 y</td>
<td>No difference in combined all-cause mortality or cardiovascular hospitalization (36% vs 37%, $P=0.35$).</td>
</tr>
<tr>
<td>I-PRESERVE \textsuperscript{3,8}</td>
<td>Irbesartan vs placebo.</td>
<td>LVEF $\geq 45%$, NYHA III–IV with corroborative evidence, or NYHA II with HF hospitalization in recent 6 months, age $\geq 60$ y.</td>
<td>4.1 y</td>
<td>No difference in combined all-cause mortality or HF hospitalization (24% vs 25%, $P=0.54$).</td>
</tr>
<tr>
<td>CHARM-Preserved\textsuperscript{19}</td>
<td>Candesartan vs placebo.</td>
<td>LVEF $&gt;40%$, NYHA II–IV, history of cardiac hospitalization.</td>
<td>3.0 y</td>
<td>Trend towards a reduction in combined cardiovascular mortality or HF hospitalization by 11% (22% vs 24%, unadjusted $P=0.12$, adjusted $P=0.051$).</td>
</tr>
<tr>
<td>Aldo-DHF\textsuperscript{30}</td>
<td>Spironolactone vs placebo.</td>
<td>LVEF $\geq 50%$, NYHA II–III, peak VO\textsubscript{2} $\leq 25$ mL/min/kg, diastolic dysfunction on echocardiography or atrial fibrillation, age $\geq 50$ y.</td>
<td>1.0 y</td>
<td>Reduction in $E'/e'$ by $–1.5$ ($P&lt;0.001$).</td>
</tr>
<tr>
<td>TOPCAT\textsuperscript{30}</td>
<td>Spironolactone vs placebo.</td>
<td>LVEF $\geq 45%$, $\geq 1$ HF sign, $\geq 1$ HF symptom, HF hospitalization within recent 12 months, or BNP $\geq 100$ pg/mL or NT-proBNP $\geq 360$ pg/mL, age $\geq 50$ y.</td>
<td>3.3 y</td>
<td>No difference in combined cardiovascular death, aborted cardiac arrest, or HF hospitalization (19% vs 20%, $P=0.14$).</td>
</tr>
<tr>
<td>SENIORS\textsuperscript{73}</td>
<td>Nebivolol vs placebo.</td>
<td>HF confirmed as HF hospitalization in recent 12 months and/or LVEF $\leq 35%$ in recent 6 months, age $\geq 70$ y, 36% with LVEF $&gt;35%$.</td>
<td>1.8 y</td>
<td>Reduction in combined all-cause mortality or cardiovascular hospitalization by 14% (31% vs 35%, $P=0.04$).</td>
</tr>
<tr>
<td>DIG-PEF\textsuperscript{321}</td>
<td>Digoxin vs placebo.</td>
<td>HF with LVEF $&gt;45%$, sinus rhythm.</td>
<td>3.1 y</td>
<td>No difference in combined HF mortality or HF hospitalization (21% vs 24%, $P=0.14$)</td>
</tr>
<tr>
<td>PARAMOUNT\textsuperscript{200}</td>
<td>Sacubitril/valsartan vs valsartan.</td>
<td>HF with LVEF $\geq 45%$, NYHA II–III, NT-proBNP $&gt;400$ pg/mL.</td>
<td>12 w</td>
<td>Reduction in NT-proBNP: ratio of change sacubitril/valsartan 0.77–95% CI 0.64–0.92 ($P=0.005$).</td>
</tr>
<tr>
<td>RELAX\textsuperscript{311}</td>
<td>Sildenafil vs placebo.</td>
<td>HF with LVEF $\geq 45%$, NYHA II–IV, peak VO\textsubscript{2} $&lt;60%$ of reference values, NT-proBNP $&gt;400$ pg/mL or high LV filling pressures.</td>
<td>24 w</td>
<td>No change in peak VO\textsubscript{2} ($P=0.90$).</td>
</tr>
</tbody>
</table>
CCS HF Algorithm
Recommended Initial Referral And Wait Time

- **Routine, Elective Referral**
  - Chronic HF disease management NYHA II
  - NYHA I – minimal or no symptoms
  - See within 12 weeks, ideally within 6

- **Semi-Urgent, Intermediate Risk**
  - New diagnosis of HF, stable, compensated
  - NYHA II/III
  - Worsening HF on therapy
  - Mild symptoms with valvular or renal disease or hypotension
  - See within 4 weeks, ideally within 2

- **Urgent**
  - New diagnosis of HF, not improving on therapy (unstable, decompensated)
  - Progression to NYHA IV HF
  - Post-hospitalization or ER visit for HF
  - Severe HF with valvular or renal disease or hypotension
  - Post myocardial infarction HF
  - See within 4 weeks, ideally within 2

- **Emergent**
  - Acute severe myocarditis
  - Rapidly progressive heart failure cardiogenic shock
  - Heart failure with ACS or MI
  - Transplant and device evaluation of unstable patients
  - New-onset acute pulmonary edema
  - See within 24 hours

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Vasodilator therapy in HFP EF patients (with AHF)

Sodium Nitrite in acute HFP EF
N= 28

Inotropes in HFP EF patients (no AHF)

The only inotropic therapy tested in HFP EF was DIGOXIN, where among ambulatory HFP EF patients, digoxin therapy was associated with a trend toward reduction in HF hospitalizations but an increase in acute coronary syndrome hospitalizations.

A. Ahmed, Circ. 2006; 114:397-403