Het oude en stijve hart bij HFpEF: diagnostiek en behandeling

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Disclosures

• Unrestricted educational grant by Novartis

• P.I. Novartis/PERSPECTIVE: sacubitril/valsartan (Entresto™) for HFmrEF/HFpEF

• P.I. Boehringer-Ingelheim/EMPEROR: empagliflozin (Jardiance™) for HFrEF/HFmrEF/HFpEF
Overview

Diastolisch hartfalen ≈ Heart Failure with preserved Ejection Fraction (HFpEF)

• Diagnosis: complex due to co-morbidity and the limitation of resting measurements

• Treatment: why "classic" heart failure treatment does not work in HFpEF, and upcoming trials
HFpEF: clinical presentation

- Main physical complaint: *exertional* dyspnea
- HFpEF-patients have many *co-morbidities*

**Web Table 4.2** Typical demographics and co-morbidities associated with heart failure with preserved ejection fraction

- Advanced age
- Arterial hypertension
- Atrial fibrillation
- Female gender
- Kidney dysfunction
- Metabolic syndrome
- Obesity
- Physical deconditioning
- Pulmonary disease (e.g. COPD)
- Pulmonary hypertension
- Sleep apnoea

Ponikowski, EHJ 2016
HFpEF: definition

1. Signs and/or symptoms of heart failure
2. A) Preserved ejection fraction (left ventricular ejection fraction or LVEF ≥ 50%)
   B) No other explanation of symptoms (e.g. significant valvular disease, ischaemic heart disease, pulmonary disorder, etc.)
3. Evidence of LV diastolic dysfunction (elevated LV-filling pressures)

Ponikowski, EHJ 2016
Pathophysiology: PV-analysis

Westerhof, Snapshots of Hemodynamics
HFpEF: pathophysiology = stiff LV

n.b.: EF “preserved”

Westerhof, Snapshots of Hemodynamics
Diastolic dysfunction by ESC guideline

• Elevated levels of natriuretic peptides:
  BNP >35 pg/L or NTpro-BNP > 125 pg/L

and:

• Elevated LV-filling pressures:
  PCWP ≥ 15 mmHg, LVEDP ≥ 16 mmHg

• Relevant structural heart disease:
  LAVi > 34 ml/m$^2$ or LVMi ≥ ♂: 115, ♀: 95 g/m$^2$

New ASA/EACVI diagnostic algorithm
for LV diastolic function (2016)

Ponikowski, Eur Heart J 2016
New ASE/EACVI algorithm for LV diastolic dysfunction

- E/A (0.8-2.0) ->
  - E/e’ > 14
  - LAVi > 34 ml/m²
  - tricuspid regurgitation peak velocity (TRV) > 2.8 m/s

- sensitivity: 87% specificity: 88%
- PPV 91%, NPV 83%, overall diagnostic accuracy 87%

Nagueh, J Am Soc Echocardiogr 2016
Andersen, JACC 2017
HFpEF: growing health problem

Prevalence HFpEF

HF-hospitalisations

metabolic syndrome

HFpEF

HFrEF

ischaemic heart disease

Owan, NEJM 2006
HFpEF ≈ HFrEF: grim prognosis

Figure 2. Kaplan–Meier Survival Curves for Patients with Heart Failure and Preserved or Reduced Ejection Fraction.

Owan, NEJM 2006
HFpEF: no effective therapy

Owan, NEJM 2006
## Treatment HFpEF

- ESC HF-guideline: 1 page (of 85)!

### Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref&lt;sup&gt;c&lt;/sup&gt;</th>
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<tr>
<td>it is recommended to screen patients with HFpEF or HFrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.</td>
<td>I</td>
<td>C</td>
<td></td>
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<tr>
<td>Diuretics are recommended in congested patients with HFpEF or HFrEF in order to alleviate symptoms and signs.</td>
<td>I</td>
<td>B</td>
<td>178, 179</td>
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</tbody>
</table>

HFmREF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Reference(s) supporting recommendations.

Ponikowski, EHJ 2016
Treatment HFrEF

Patient with symptomatic HFrEF

Therapy with ACE-I and beta-blocker (Up-titer to maximum tolerated evidence-based doses)

Still symptomatic and LVEF ≤35%

Add MR antagonist (up-titer to maximum tolerated evidence-based dose)

Still symptomatic and LVEF ≤35%

Able to tolerate ACEI (or ARB)

Sinus rhythm, QRS duration ≥130 msec

Sinus rhythm, HR ≥70 bpm

ARNI to replace ACE-I

Evaluate need for CRT

Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

Yes

Consider digoxin or H-ISDN or LVAD, or heart transplantation

No

No further action required

Consider reducing diuretic dose

Diuretics to relieve symptoms and signs of congestion

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

Class I

Class Ia

Ponikowski, EHJ 2016
HFrEF-medication in HFpEF

- (Lis)diuretics
- ACE inhibitors (ACEi)
- Angiotensin receptor blocker (ARB)
- Mineralocorticoid receptor antagonist (MRA)
- Beta-blockers
- $L_f$ channel inhibitors (ivabradine)
- ARB/neprilysin inhibitor (ARNI: sacubitril/valsartan)
- Digoxin
- Nitrates
(Lis)diuretics

- Symptomatic relief
- Euvolemic state?
ACE inhibitor / ARB

PEP-CHF (perindopril)

- Time to first occurrence of death and unplanned heart failure related hospitalization
- Proportion having an event (%)
- HR 0.92 (95% CI 0.70 - 1.21; P = 0.545)
- n=850 (LVEF > 40%)
- HR 0.92 (0.70-1.21)

I-PRESERVE (irbesartan)

- death or CV hospitalisation
- n=4128 (LVEF $\geq$ 45%)
- HR 0.95 (0.86-1.05)

Cleland, Eur Heart J 2006
Mineralcorticoid receptor antagonist

TOPCAT (spironolacton)

n=3445 (LVEF ≥ 45%)

HR 0.89 (0.77-1.04) CV death, aborted cardiac arrest, HF-hospitalisation

HR 0.83 (0.69-0.99) HF-hospitalisation only

Beta-blockers / $I_f$ channel inhibitor

### SENIORS-PEF (nebivolol)

- **Proportion having an event**
- **Death or CV hospitalisation**
- **n=752 (LVEF>35%)**
- **HR 0.81 (0.63-1.04)**

### EDIFY (ivabradine)

- **Phase II (8 months follow-up):**
  - **E/e: 12.6 vs. 12.9**
  - **6MWT 323 vs. 321 m**
  - **NT-proBNP 385 vs. 341 pg/L (all n.s.)**
  - **n=179 (LVEF≥45%)**

Van Veldhuisen, J Am Coll Cardiol 2009
Komaja, Eur J Heart Fail 2017
HFrEF-medication in HFpEF

- (Lis)diuretics
- ACE inhibitors (ACEi)
- Angiotensin receptor blocker (ARB)
- Mineralocorticoid receptor antagonist (MRA)
- Beta-blockers
- Lf channel inhibitors (ivabradine)
- ARB/neprilysin inhibitor (ARNI: sacubitril/valsartan)
- Digoxin
- Nitrates
ARNI (ARB + neprilysin inhibitor)

PARAMOUNT (sacubitril/valsartan)

Phase II
n=149 (LVEF≥45%)

Figure 2: NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups

Solomon, Lancet 2012
Digoxin

DIG-PEF (digoxin)

n=988 (LVEF≥45%)
HR 0.82 (0.63-1.07)

Ahmed, Circulation 2006
Nitrates

NEAT-HFpEF (ISMN)

Inhaled nitrite (iNO$_2^-$)

Phase II (acute)

n=26 (LVEF$\geq$50%+DD)

PCWP@ex: 25 vs. 31 mmHg, p<0.01

n=110 (LVEF$\geq$50%+DD)

Redfield, N Engl J Med 2015
Borlaug, Circ Res 2016
HFrEF-medications in HFpEF

- (Lis)diuretics
- ACE inhibitors (ACEi)
- Angiotensin receptor blocker (ARB)
- Mineralocorticoid receptor antagonist (MRA)
- Beta-blockers
- $L_f$ channel inhibitors (ivabradine)
- ARB/neprilysin inhibitor (ARNI: sacubitril/valsartan)
- Digoxin
- Nitrates (nitrite)
Medical treatment HFpEF anno 2018

- Judicious use of diuretics
- Possibly a role for MRA, ARNI, nitrite
- Stop ACEi / ARB / beta-blocker / ivabradine / digoxine, *if co-morbidity permits*
Why is HFrEF-treatment not working?

• Co-morbidity and advanced disease
• HFP EF is more than preserved LVEF
• Neurohormonal hypothesis in HFP EF
Co-morbidity and advanced age in HFpEF

**CENTRAL ILLUSTRATION: Mode of Death Distribution in HFrEF and HFpEF**

**HFrEF**
- Cardiovascular (80%-85%)
  - Worsening HF
  - Cardiogenic Shock
  - Low Output State
- Sudden Cardiac Death
  - Ventricular Tachyarrhythmia +++
  - Bradycardia +
- Other Cardiovascular or Noncardiovascular (15%-20%)

**HFpEF**
- Cardiovascular
  - Worsening HF
  - Restrictive Cardiomyopathy
  - Right Heart Failure
- Sudden Death
  - Nonarrhythmic Sudden Death
  - Tachyarrhythmia
  - Bradycardia
- Myocardial Infarction
- Vascular
  - Aortic Aneurysm
  - Pulmonary Embolism
- Cerebrovascular
  - Intracranial Hemorrhage
  - Ischemic Stroke
- Noncardiovascular
  - Renal
    - End-stage Renal Disease
    - Renal Venous Congestion
  - Respiratory
    - Respiratory Failure
    - Pulmonary Hypertension
    - Chronic Obstructive Pulmonary Disease
  - Infection/Sepsis
  - Malignancy
- Multisystem Disease
  - Multisystem Organ Failure

RCT: 20-30%
Registries: 50-60% !

Vaduganathan, JACC 2017
HFpEF is more than preserved LVEF

Definition:
1. Signs and/or symptoms of heart failure
2. A) Preserved ejection fraction (LVEF \( \geq 50\% \))
   B) No other explanation of symptoms (e.g. significant valvular disease, ischaemic heart disease, pulmonary disorder, etc.)
3. Evidence of LV diastolic dysfunction (elevated LV-filling pressures)
Performance ASE/EACVI-algorithm

Diastolic dysfunction (grade)

PCWP (mmHg)

Enait/Handoko, AHA-abstract 2017
Hummel, Eur J Heart Fail 2017
Performance ASE/EACVI-algorithm

For diastolic dysfunction grade II,III:

• sensitivity: 56% (vs. 87%), specificity: 79 % (vs. 88%)
• overall accuracy: 73% (vs. 87%)
Physiological approach: LV EDPVR

Exertional dyspnea in HFpEF is related to elevated LV-filling pressures at exercise (PCWP $\geq 25$mmHg)

Borlaug, Circ Heart Fail 2010
Huis in t Veld/Handoko, Neth Heart J 2016
Physiological approach: X-RHC

![Graph showing PCWP (mmHg) over time with comparison between Control and HFpEF conditions. The graph indicates a statistically significant difference between the two conditions with a p-value of <0.0001.]

Borlaug, Circ Heart Fail 2010
Huis in t Veld/Handoko, Neth Heart J 2016
Poor prognosis of “early” HFpEF
Role of X-TTE

- $E/e'_{ex}$ correlated best with $PCWP_{ex}$
- $E/e'_{ex}$ not measurable in 20%, $TRV_{ex}$ not measurable in 51%

Obokata/Borlaug, Circulation 2017
Role of X-TTE

- ESC-guideline + E/e’@ex >14:
  sens 60->80%, spec 83->88%
  NPV: 88%, PPV: 74%

n.b.: 18% of HFpEF (X-RHC) normal BNP!
HFpEF: PWCP@rest ≥ 15mmHg
PCWP@ex ≥ 25mmHg

E/e’@ex < 14

Holter, spirometry, sleep studies, ...

VUmc “Zorgpad dyspneu/HFpEF”

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Obokata/Borlaug, Circulation 2017
Huis in ‘t Veld/Handoko, Neth Heart J 2016
HFpEF is more than preserved LVEF

• Almost all trials in “HFpEF” thus far relied on (NT-pro)BNP levels and LVEF as inclusion criteria
• Evaluation of LV diastolic dysfunction with (resting) echocardiography is inaccurate: role of X-TTE, X-RHC
• Heterogenous study population may partially explain neutral results of HFpEF-trials
Neurohormonal activation in HFpEF

renin-angiotensin-aldosteron system (RAAS) & sympathetic nervous system (SNS):
triggered by hypotension/hypovolemia

natriuretic peptide system (NPS):
triggered by wall stress

Wall stress $\approx$ pressure $\times \frac{\text{diameter}}{\text{wall thickness}}$

$\Rightarrow$ NP-levels in HFpEF < HFrEF
Neurohormonal activation in HFP EF

• Comparable hemodynamic dearrangement in HFP EF as HFrEF -> similar activation of RAAS/SNS?
Neurohormonal activation in HFpEF

Hogg, Progr Cardiovasc Dis 2005
Benedict, JACC 1994
Neurohormonal activation in HFpEF

• Comparable hemodynamic dearrangement between HFpEF and HFrEF
• RAAS/SNS/NPS are activated in HFpEF, but less than HFrEF
• The limited increase in RAAS/SNS-activation in HFpEF may partially explain the neutral results of RAAS/SNS-inhibition
Effect of RAAS/SNS-inhibition

LV ESPVR \sim \text{contractility}

LV EDPVR \sim \text{relaxation}

Ea(=PVR*HR) \sim \text{afterload}

Westerhof, Snapshots of Hemodynamics
RAAS/SNS-inhibition in HFrEF

Westerhof, Snapshots of Hemodynamics
RAAS/SNS-inhibition in HFpEF

Westerhof, Snapshots of Hemodynamics
Effects of RAAS/SNS-inhibition in HFpEF

- No effect of LV stiffness (LV EDV does not change)
- PV-analysis: the effect of afterload reduction in HFpEF on stroke volume is small compared to HFrEF
- This may partially explain the neutral effect of RAAS/SNS-inhibition
Upcoming HFpEF-trials

Medications:
- PARAGON-HF (sacubitril/valsartan)
- EMPEROR-preserved (empagliflozin=SLGT2 inhibitor)
- INDIE, INABLE (inhaled nitrite), KNO3CKOUT-HFpEF (oral nitrite), lozenge (concentrated beetroot juice), epicatechin (extract of dark chocolate), grape seed extract
- Sildenafil (PASSION), treprostinil, bosentan in PH-HFpEF, vericiguat (SOCRATES-PRESERVED) (vericiguat), riociguat, IW-1973
- BEAT-HF (alburetol), mirabegron (beta3-receptor agonist)
- Istaroxime (SERCA2A activator), perhexiline (FFA oxidation inhibitor), elamipretide (mitochondrial antioxidant), ferric carboxymaltose, erythropoietin
- Pirfenidon (antifibrotic drug), anakinra (IL-1 blocker)
- Stem cell therapy

Devices:
- REDUCE LAP-HF (intra-atrial shunt device)
- CORolla® TAA (cardiac elastic device)
- Vagus nerve stimulation
- Optimizer SMART (cardiac contractility modulation)
Take home message

• HFpEF ≠ HFrEF: difficult to diagnose

  Vumc Zorgpad dyspnea/HFpEF incorporated X-TTE & X-RHC for challenging cases

• HFpEF ≠ HFrEF: even harder to treat!
  Judicious use of diuretics
  No other proven therapies
  New therapies are urgently needed

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