HF_{pEF} and HF_{rEF}: Distinct Phenotypes or a Dynamic Continuum?

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Introduction
3.2 Terminology related to left ventricular ejection fraction

Other, more recent, trials enrolled patients with HF and an EF > 40–45% and no other causal cardiac abnormality (such as valvular or pericardial disease). Some of these patients did not have an entirely normal EF (generally considered to be >50%) but also did not have a major reduction in systolic function either. Because of this, the term HF with ‘preserved’ EF (HF-PEF) was created to describe these patients. Patients with an EF in the range 35–50% therefore represent a ‘grey area’ and most probably have primarily mild systolic dysfunction.

It is important to note that EF values and normal ranges are dependent on the imaging technique employed, method of analysis, and operator. Other, more sensitive measures of systolic function may show abnormalities in patients with a preserved or even normal EF, hence the preference for stating preserved or reduced EF over preserved or reduced ‘systolic function’.

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The diagnosis of HF-REF requires three conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF
3. Reduced LVEF

The diagnosis of HF-PEF requires four conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF
3. Normal or only mildly reduced LVEF and LV not dilated
4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfun

HF = heart failure; HF-PEF = heart failure with ‘preserved’ ejection fraction; HF-REF = heart failure and a reduced ejection fraction; LA = left atrial; LV = left ventricle

* Signs may not be present in the early sages of HF (especially in HF-PEF) and in patients treated with diuretics.

The middle child in heart failure: heart failure with mid-range ejection fraction (40–50%)

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¹National University Health System, Singapore; and ²Brigham and Women's Hospital, Boston, MA, USA

The specific LVEF cut-off for HFpEF that has been advocated by guidelines, and modified slightly by clinical trials (which have mostly chosen 45% rather than 50%), has not been based on any real pathophysiological or outcomes data advocating for one LVEF cut-off versus the other. However, by defining a cut-off for HFpEF that is higher than that used to define the HFrEF population, we have necessarily left a gap in the 40–50% middle range, leaving the ‘middle child’ of HF neglected. In the American College of Cardiology/American Heart Association guidelines, this range is referred to as an ‘intermediate group’, and dismissed with treatment for underlying risk factors/co-morbidities and with medical therapies similar to those used for HFrEF. Similarly, the European Society of Cardiology guidelines1 refer to HF with EF 35–50% as a ‘grey area’ to be regarded as mild systolic dysfunction (i.e. a lesser big brother)………………………………………………………………………………

The existence of an ‘evidence gap’ for the patients with mid-range LVEF occurred due to historical development of HF trials rather than due to a strong pathophysiological basis for a third entity in HF. Nonetheless, we refer to this neglected middle child of HF as HF with mid-range EF (HFmEF) herein.

Eur J Heart Fail 2014; 16:1049–1055
## 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

### Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
</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>1. Elevated levels of natriuretic peptides&lt;sup&gt;b&lt;/sup&gt;; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction</td>
<td>1. Elevated levels of natriuretic peptides&lt;sup&gt;b&lt;/sup&gt;; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

**Table notes:**
- BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.
- <sup>a</sup>SIGNs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.
- <sup>b</sup>BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.
Transitions of LVEF in Heart Failure
Hypertrophy Patterns in Heart Failure

Diastole | Systole
---|---
Normal

Addition of new sarcomeres

Concentric Hypertrophy (HFrEF or diastolic, LVEF ≥ 50%)

Eccentric Hypertrophy (HFpEF or systolic, LVEF < 50%)

Katz AM, Rolett EL. Eur Heart J 2016; 37:449-54
Progression of HFpEF to HFrEF: Does it Occur?

LV volume

LVEF

Major Cardiovascular Events
**Longitudinal Changes in LVEF**

Community cohort of incident HF patients diagnosed from 1984 to 2009 in Olmsted County, Minnesota (HFpEF=559, HFrEF=674, 48.3% male, mean age 75.0 years, mean follow-up 5.1 years). LVEFs assessed by echocardiography from initial HF diagnosis until death or last follow-up through March 2010.

**HFpEF:** LVEF decreased by 5.8% over 5 years (P<0.001) with greater declines in older individuals and those with CAD.

**HFrEF:** LVEF increased (average increase 6.9% over 5 years, P<0.001). Greater increases were noted in women, younger patients, individuals without coronary disease, and those treated with evidence-based medications.

Overall, 39% of HFpEF patients had an EF<50% and 39% of HFrEF patients had an EF≥50% at some point after diagnosis.

A decline in LVEF of 5% associated with a 7% increase in mortality

An increase in LVEF of 5% associated with a 12% decrease in mortality

**Dunlay SM, et al. Circ Heart Fail 2012;5:720-726**
A total of 8183 transitions were observed. 22% of the cohort of 2413 pts experienced a transition from HFpEF to HFrEF, and 23% of pts experienced a transition from HFrEF to HFpEF.

Women were more likely than men to transition from HFrEF to HFpEF (hazard ratio, 1.85; 95% confidence interval, 1.38–2.47).

Patients adherent to BBs were more likely to transition from HFrEF to HFpEF (hazard ratio, 1.53; 95% confidence interval, 1.10–2.13) compared with patients who were nonadherent to BBs, whereas ACEi or ARB adherence was not associated with LVEF transitions.

Patients who had a previous myocardial infarction were more likely to transition from HFpEF to HFrEF (hazard ratio, 1.75; 95% confidence interval, 1.26–2.42).

Transitions of Heart Failure LVEF: the CHART-2 Study

ESC Heart Failure Long-Term Registry (n=9,134)

Staging of Hypertensive Heart Disease

Degree I
- LV diastolic dysfunction
- No LV hypertrophy

Degree II
- LV diastolic dysfunction and
- LV hypertrophy

Degree III
- Clinical heart failure with
- Preserved LV ejection fraction

Degree IV
- Eccentric LV hypertrophy
- Reduced LV ejection fraction

Messerli FH, et al. JACC Heart Fail 2017; 5:543-551
Physiological Significance of LVEF
Ejection Fraction

Misunderstood and Overrated (Changing the Paradigm in Categorizing Heart Failure)

Appropriate LV Geometry Is Necessary for the Production of a Normal LVEF

Myocardial fibre shortening - 15%
Myocardial fibre thickening - 8%

LV ejection fraction ~ 60%
LV end-diastolic volume
LV end-systolic volume

LV geometry

Intrasarcomeric cytoskeleton
Extracellular matrix
Extrasarcomeric cytoskeleton
Non-contractile myocardial components

Myocardial fibre at end-diastole
Myocardial fibre at end-systole

Longitudinal fibers

Circumferential fibers

Spiral fibers

15% fiber shortening

EF = 15%

15% fiber shortening

EF = 30%

15% fiber shortening

EF ≥ 60%

Sallin EA. Biophys J 1969; 9: 954-64
Normal Heart: Superficial, Circular, and Deep Fibers

Anderson RH, et al.
Conclusions
• LVEF is dependent on the architecture of the left ventricle and has exhausted its usefulness as a presumed marker of contractility and a means of categorizing heart failure.

• Underlying disease states may cross arbitrary LVEF boundaries, and multiple diseases may cause HF within any particular EF range.

• It is time to start thinking of a new, pathophysiologically driven classification, which will take into consideration several parameters of LV morphology and function.

• A new classification is a necessary first step towards a better understanding of the underlying mechanisms, accurately characterizing patients, tailoring treatment, and eventually improving outcome in HF.
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

HFpEF

Symptoms and signs of heart failure

LVEF > 50%
LV end-diastolic volume < 97 ml/m²

Diastolic Dysfunction

Impaired Relaxation
- Prolonged relaxation constant (τ)
- Reduced E’ velocity

Reduced Compliance
- Increase P/V slope coefficient (b)
- Increased E velocity

Additional criteria (○):
- Structural Changes
  - Suggestive/not diagnostic
  - LA enlargement (>40 ml/m²)
  - LV hypertrophy (>122-149 g/m²)
  - Atrial Fibrillation

Increased LV filling pressures
- LVEDP (>16 mmHg) or PAOP (>12 mmHg)

Increased E/E’ ratio
- E/E’ > 15 is diagnostic
  - if between 8-15 requires additional criteria (○)

Myocardial stretch
- BNP > 200 pg/ml
- NT-proBNP > 220 pg/ml
  - requires E/E’ > 8 or one of the additional criteria (○)
HFpEF: Definition and Epidemiology
Athens, May 26, 20015

Heart Failure with Preserved Left Ventricular Ejection Fraction (HFpEF)

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HFpEF: Transitory Stage to HFrEF or Distinct Phenotype?
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 M, Lam CSP. European Heart Journal 2014; 35: 1022–1032
Single Pathophysiological Time Trajectory with Variable Symptom Onset

LV dysfunction with reduced EF

De Keulenaer and Brutsaert.
Prog Cardiovasc Dis 2007; 49:275-283
Morphological and Functional Changes in HF
LVEF <45-50%

LV dysfunction with preserved LVEF
- Impaired relaxation
- Impaired longitudinal shortening

LV dysfunction with reduced LVEF

Asymptomatic
Symptomatic HF, LVEF

Hypertrophy
I

Remodeling
II

III

De Keulenaer and Brutsaert.
Prog Cardiovasc Dis 2007; 49:275-283
Transition Rates of LV Geometric Pattern During a Mean Follow-Up of 4 Years

<table>
<thead>
<tr>
<th>Baseline LV Geometric Pattern</th>
<th>LV Geometric Pattern on Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Geometry</td>
</tr>
<tr>
<td>Normal geometry (n = 2,874)</td>
<td>68 (1,960)</td>
</tr>
<tr>
<td>Concentric remodeling (n = 820)</td>
<td>53 (437)</td>
</tr>
<tr>
<td>Eccentric hypertrophy (n = 590)</td>
<td>47 (274)</td>
</tr>
<tr>
<td>Concentric hypertrophy (n = 208)</td>
<td>29 (60)</td>
</tr>
</tbody>
</table>

Values are % (n).
LV = left ventricular; n = number of observations.

Progression of HF

DHF and SHF are Different Phenotypes of the Same Disease

Brutsaert and De Keulenaer.
Current Opinion in Cardiology 2006; 21:240–8
The Natural History of Left Ventricular Geometry in the Community

Evaluation of 4,492 observations (2,604 unique Framingham Heart Study participants attending consecutive examinations) to categorize LV geometry at baseline and after 4 years. Four groups were defined on the basis of the sex-specific distributions of LVM and RWT (normal: LVM and RWT <80th percentile; concentric remodeling: LVM <80th percentile but RWT ≥ 80th percentile; eccentric hypertrophy: LVM ≥ 80th percentile but RWT < 80th percentile; and concentric hypertrophy: LVM and RWT ≥ 80th percentile).

Conceptual-Physiological Approaches to Cardiac Function

A. Hydrodynamic input-output system
   - Cardiac output
   - Stroke volume
   - Peripheral resistance
   - Arterial pressure
   - Swan-Ganz catheter
   - PICO catheter
   - EJECTION FRACTION
     - Elastance (Emax)
     - Pressure-volume curve
     - Dp/dtmax

B. Hydrodynamic compression system
   - Contractility
   - Load dependent relaxation
   - Force-frequency
   - LV twisting/torsion, LV untwisting and suction
   - Myocardial strain/strain rate
   - LV catheter
   - 2D Echo

C. Muscular pump
   - Tissue Doppler
   - Cardiac MRI
   - Brain natriuretic peptide
   - Endothelin-1, nitric oxide, Neuregulin-1
   - Cytokines

D. Pluricellular tissue pump
   - Biomarkers
   - Molecular imaging

De Keulenaer and Brutsaert. Circulation 2009; 119:3044-6
In the Cardiovascular Health Study (n=5,888), demographic and clinical characteristics and ventricular structure and function were compared in healthy normal subjects (healthy; n=499), subjects with HTN but not heart failure (HTN; n=2,184), and subjects with HTN and HFNEF (HFNEF; n=167).

Maurer, et al. JACC 2007; 49:972-81
Features of the Arterial Pulse Wave

Avolio, et al. Physiol Meas 2010; 31: R1–R47
Early Return of Wave Reflection Due to Arterial Stiffening

The Heart Failure Spectrum

De Keulenaer and Brutsaert. Circulation 2009; 119:3044-6
Heart failure (HF) is a growing public health problem affecting an estimated 170,000 Greeks, with 14,000 new diagnoses annually.

The incidence of HF is strongly dependent on age, with an estimated incidence of 1% at age 65 years that approximately doubles with each decade of age thereafter.

The lifetime risk of HF developing for both men and women at age 80 years is 20%, which is the same risk as for those 40 years of age despite a much shorter life expectancy.

HF is a leading cause of mortality, morbidity, and hospitalization in elderly persons.

# 2013 ACCF/AHA Guideline for the Management of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>EF (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Heart failure with reduced ejection fraction (HFrEF)</td>
<td>≤40</td>
<td>Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>II. Heart failure with preserved ejection fraction (HFpEF)</td>
<td>≥50</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFpEF, borderline</td>
<td>41 to 49</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.</td>
</tr>
<tr>
<td>b. HFpEF, improved</td>
<td>&gt;40</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>

Prevalence of Chronic Heart Failure in Southwestern Europe: the EPICA Study

Trends in Incident HFpEF and HFrEF in Olmsted County, Minnesota, USA

Conceptual Approaches to Cardiac Performance

De Keulenaer GW, Brutsaert DL. Circulation 2011;123:1996-2005
All-Cause Mortality in HFpEF

- In-hospital: 2.5-6.9% (Registries)
- RCTs: 13-23%/26-50 months
- Registries: 6-29%/ 1 year
- 50-60%/ 5 years (hosp.)

Hospitalizations in HFpEF


Early risk: 10-30% (CV)
One year: 20-30% (All)
Three years: 45-70% (All)
CV vs. Non-CV Deaths in RCTs of HFpEF

The Ventricle as a Dissipating Structure with Emerging Properties

De Keulenaer GW, Brutsaert DL. Circulation 2011; 123:1996-2005
HFpEF: Patients’ Characteristics and Comorbidities
### Characteristics of Hospitalized Patients with HF

<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/m² (%)</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>

*Steinberg B, et al. Circulation 2012;126:65-75*
Non Cardiac Comorbidities in the European Heart Failure Pilot Survey

A total of 3226 European outpatients with chronic HF (1249 and 1580 with HFrEF and HFrEF respectively) were included in this analysis of the ESC Heart Failure Pilot Survey. Co-morbidities considered were: diabetes, hyper- and hypothyroidism, stroke, COPD, sleep apnoea, chronic kidney disease (CKD), and anaemia. Prognostic implications of co-morbidities were evaluated using population attributable risks (PARs), and patients were divided into geographic regions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>HFrEF (LVEF &lt;40%)</th>
<th>HFrEF (LVEF ≥40%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<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>

Co-Morbidities in Patients with Heart Failure: the European Heart Failure Pilot Survey

Predicting Heart Failure With Preserved and Reduced Ejection Fraction

Development and validation of risk prediction models for HFpEF and HFrEF. Of 28,820 participants from 4 community-based cohorts, 982 developed incident HFpEF and 909 HFrEF during a median follow-up of 12 years. Three cohorts were combined, and a 2:1 random split was used for derivation and internal validation, with the fourth cohort as external validation.

HFpEF Pathophysiology
Review

Heart Failure in Patients with Preserved Ejection Fraction: Questions Concerning Clinical Progression

George E. Louridas * and Katerina G. Lourida

Department of Cardiology, University General Hospital AHEPA, Aristotle University, Thessaloniki 54124, Greece; katerina.lourida@gmail.com
* Correspondence: louridasg@gmail.com; Tel.: +30-693-2292978

Abstract: Over the last two decades, important advances have been made in explaining some pathophysiological aspects of heart failure with preserved ejection fraction (HFrEF) with repercussions for the successful clinical management of the syndrome. Despite these gains, our knowledge for the natural history of clinical progression from the pre-clinical diastolic dysfunction (PDD) until the final clinical stages is significantly limited. The subclinical progression of PDD to the clinical phenotype of HFrEF and the further clinical progression to some more complex clinical models with multi-organ involvement, similar to heart failure with reduced ejection fraction (HFrEF), continue to be poorly understood. Prospective studies are needed to elucidate the natural history of clinical progression in patients with HFrEF and to identify the exact left ventricular remodeling mechanism that underlies this progression.
Pathophysiological Models of HFpEF

A. Traditional

- Systemic hypertension
  - Vascular dysfunction

- Left ventricle
  - Concentric hypertrophy
  - Fibrosis
  - Diastolic dysfunction

- Left atrium
  - Remodeling
  - Diastolic dysfunction
  - Systolic dysfunction

- Pulmonary hypertension
  - Atrial fibrillation

- Right ventricle
  - Remodeling
  - Diastolic dysfunction
  - Systolic dysfunction

- 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

- Microvascular dysfunction and rarefaction

- Myofiber stiffness
  - Cardiomyocyte hypertrophy

- Fibrosis

- Global cardiac remodeling and dysfunction
  - Impaired coronary flow reserve
  - Impaired oxygen delivery, uptake, and utilization in skeletal muscle

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 heart failure.

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

Vlachopoulos C, et al.
Hypertension Research 2010; 33: 291–292
Microscopic Lesions in Hypertensive Myocardium

Prevention of HFpEF
Evolving Paradigms of Heart Failure Progression
A Randomized Trial of Intensive vs. Standard Blood-Pressure Control (SPRINT)

9361 persons (age ≥ 75 years ≈28%, women ≈ 35%) with a SBP ≥130 mmHg and increased cardiovascular risk, but without diabetes, assigned to a SBP target <120 mm Hg (intensive treatment) or a target < 140 mm Hg (standard treatment). The primary composite outcome was MI, other ACS, stroke, HF, or death from CV causes.

The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive Treatment (N = 4678)</th>
<th>Standard Treatment (N = 4683)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion for increased cardiovascular risk — no. (%) †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥75 yr</td>
<td>1317 (28.2)</td>
<td>1319 (28.2)</td>
</tr>
<tr>
<td>Chronic kidney disease‡</td>
<td>1330 (28.4)</td>
<td>1316 (28.1)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>779 (16.7)</td>
<td>783 (16.7)</td>
</tr>
<tr>
<td>Subclinical</td>
<td>247 (5.3)</td>
<td>246 (5.3)</td>
</tr>
<tr>
<td>Framingham 10-yr cardiovascular disease risk score ≥15%</td>
<td>2870 (61.4)</td>
<td>2867 (61.2)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>1684 (36.0)</td>
<td>1648 (35.2)</td>
</tr>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>67.9±9.4</td>
<td>67.9±9.5</td>
</tr>
<tr>
<td>Among those ≥75 yr of age</td>
<td>79.8±3.9</td>
<td>79.9±4.1</td>
</tr>
<tr>
<td>Body-mass index‖</td>
<td>29.9±5.8</td>
<td>29.8±5.7</td>
</tr>
</tbody>
</table>

**SPRINT: Primary Outcome and Death from Any Cause**

A. **Primary Outcome**

- Hazard ratio with intensive treatment: 0.75 (95% CI, 0.64–0.89)
- Standard treatment
- Intensive treatment

B. **Death from Any Cause**

- Hazard ratio with intensive treatment: 0.73 (95% CI, 0.60–0.90)
- Standard treatment
- Intensive treatment

**Table:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Treatment</th>
<th>Standard Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>(N=4678)</td>
<td>(N=4683)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome†</td>
<td>243 (5.2%)</td>
<td>519 (6.8%)</td>
<td>0.75 (0.64–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>97 (2.1%)</td>
<td>116 (2.5%)</td>
<td>0.83 (0.64–1.09)</td>
<td>0.19</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>40 (0.9%)</td>
<td>40 (0.9%)</td>
<td>1.00 (0.64–1.55)</td>
<td>0.99</td>
</tr>
<tr>
<td>Stroke</td>
<td>62 (1.3%)</td>
<td>70 (1.5%)</td>
<td>0.89 (0.63–1.25)</td>
<td>0.50</td>
</tr>
<tr>
<td>Heart failure</td>
<td>62 (1.3%)</td>
<td>100 (2.1%)</td>
<td>0.62 (0.45–0.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>37 (0.8%)</td>
<td>65 (1.4%)</td>
<td>0.57 (0.38–0.85)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>155 (3.3%)</td>
<td>210 (4.5%)</td>
<td>1.40 (0.60–0.90)</td>
<td>0.003</td>
</tr>
<tr>
<td>Primary outcome or death</td>
<td>332 (7.1%)</td>
<td>423 (9.0%)</td>
<td>2.90 (0.67–0.90)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

# EMPA-REG OUTCOME trial: CV Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N=2333)</th>
<th>Empagliflozin (N=4687)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%) state/1000 patient-yr</td>
<td>no. (%) state/1000 patient-yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>194 (8.3)</td>
<td>269 (5.7)</td>
<td>0.68 (0.57-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>From cardiovascular causes</td>
<td>137 (5.9)</td>
<td>172 (3.7)</td>
<td>0.62 (0.49-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction excluding silent myocardial infarction</td>
<td>126 (5.4)</td>
<td>223 (4.8)</td>
<td>0.87 (0.70-1.09)</td>
<td>0.23</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction excluding silent myocardial infarction</td>
<td>121 (5.2)</td>
<td>213 (4.5)</td>
<td>0.87 (0.70-1.09)</td>
<td>0.22</td>
</tr>
<tr>
<td>Silent myocardial infarction‡</td>
<td>15 (1.2)</td>
<td>38 (1.6)</td>
<td>1.28 (0.70-2.33)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>66 (2.8)</td>
<td>133 (2.8)</td>
<td>0.99 (0.74-1.34)</td>
<td>0.97</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>186 (8.0)</td>
<td>329 (7.0)</td>
<td>0.86 (0.72-1.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>69 (3.0)</td>
<td>164 (3.5)</td>
<td>1.18 (0.89-1.56)</td>
<td>0.26</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>60 (2.6)</td>
<td>150 (3.2)</td>
<td>1.24 (0.92-1.67)</td>
<td>0.16</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>23 (1.0)</td>
<td>39 (0.8)</td>
<td>0.85 (0.51-1.42)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>95 (4.1)</td>
<td>126 (2.7)</td>
<td>0.65 (0.50-0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke</td>
<td>198 (8.5)</td>
<td>265 (5.7)</td>
<td>0.66 (0.55-0.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

EMPA-REG OUTCOME Trial: Reduced Arterial Stiffness?

Management of HFpEF
Differential Diagnosis of Heart Failure in the Setting of Preserved LVEF

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

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

Restrictive CMP

Hypertrophic CMP

Storage disease
- Fabry
- LAMP2
- PRKAG2

Right ventricular failure
- Pulmonary arterial hypertension
- ARVC
- Sarcoidosis
- Tricuspid regurgitation

HF signs and symptoms normal LVEF

Desai AS, Jhund PS. Eur Heart J 2016;37:3135-40
Clinical Approach to Management of HFpEF

Signs and Symptoms of Heart Failure
‘Preserved’ Left Ventricular Ejection Fraction

Is this really HF-PEF?
- Take a thorough history (including a detailed family history)
- Look for diagnostic clues on basic evaluation (physical examination, electrocardiogram, echocardiogram, initial laboratory testing)
- Consider ‘mimics’, including pericardial disease as well as infiltrative, restrictive, and hypertrophic heart disorders
- Low threshold for advanced imaging, such as cardiac MRI

Are the Filling Pressures Optimized?
- Aggressively decongest patients with diuretics +/- nitrates
- Consider pulmonary artery catheterization to exclude pulmonary arterial hypertension and establish hemodynamic targets
- Implantable haemodynamic monitors may facilitate disease management for selected patients (such as those for whom bedside assessment of filling pressures is challenging or those with multifactorial dyspnoea)

Are There Reversible Causes?
- Treat hypertension to guideline-recommended targets
- Evaluate for coronary heart disease and consider revascularization in symptomatic patients
- Aggressive management of atrial fibrillation, with an emphasis on restoration and maintenance of sinus rhythm where possible

Are There Relevant Comorbidities?
- Identify and manage obesity, diabetes, chronic kidney disease, sleep apnoea, iron deficiency, anaemia
- Encourage sodium restriction and lifestyle modification

Is there a role for spironolactone?
- Avoid in patients with eGFR<30 mL/min/1.73 m² or potassium > 5.0 mmol/L

Desai AS, Jhund PS. Eur Heart J 2016;37:3135-40
Impact of CAD on Survival in HFpEF

Clinical, hemodynamic, echocardiographic, treatment, and outcome characteristics were examined in 376 consecutive patients with previous HFpEF hospitalizations who underwent coronary angiography. 255 (68%) had angiographically-proven CAD.

Outcomes of Patients with CAD and Angina: Analysis of the I-Preserve Trial

The mean follow-up for the 4128 pts was 49.5 months. Pts were divided into 4 groups according to history of CAD and angina: pts with no history of CAD or angina (n=2008), pts with no history of CAD but a history of angina (n=649), pts with a history of CAD but no angina (n=468), and pts with a history of CAD and angina (n=1003); pts with no known CAD or angina were the reference group.

Operating Characteristics of Stress Testing in HFP EF

### Estimated Hazard Ratios for Predictors of State Changes

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HFPEF to HFREF (95% CI)</th>
<th>HFPEF to Death (95% CI)</th>
<th>HFREF to HFPEF (95% CI)</th>
<th>HFREF to Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (male, referent)</td>
<td>0.93 (0.69–1.26)</td>
<td>0.97 (0.79–1.18)</td>
<td>1.85 (1.38–2.47)</td>
<td>1.01 (0.8–1.26)</td>
</tr>
<tr>
<td>Age (per 10-yr increase)</td>
<td>0.91 (0.80–1.03)</td>
<td>1.58 (1.42–1.76)</td>
<td>0.89 (0.79–1.00)</td>
<td>1.64 (1.46–1.84)</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.02 (0.93–1.12)</td>
<td>1.05 (1.00–1.1)</td>
<td>1.05 (0.95–1.16)</td>
<td>1.09 (1.03–1.15)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.75 (1.26–2.42)</td>
<td>0.87 (0.70–1.10)</td>
<td>0.8 (0.58–1.10)</td>
<td>0.96 (0.77–1.20)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.32 (1.03–1.87)</td>
<td>1.11 (0.91–1.37)</td>
<td>1.37 (0.97–1.93)</td>
<td>1.32 (1.06–1.65)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.11 (0.75–1.65)</td>
<td>0.82 (0.59–1.15)</td>
<td>1.68 (1.18–2.39)</td>
<td>0.99 (0.74–1.33)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0.65 (0.48–0.87)</td>
<td>0.98 (0.81–1.18)</td>
<td>0.67 (0.51–0.90)</td>
<td>1.04 (0.85–1.28)</td>
</tr>
<tr>
<td>Past HF history (no HFREF referent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has had HFREF in past</td>
<td>0.36 (0.25–0.53)</td>
<td>1.63 (1.03–2.57)</td>
<td>3.08 (2.07–4.56)</td>
<td>0.65 (0.44–0.96)</td>
</tr>
<tr>
<td>Has not had an prior assessment</td>
<td>0.84 (0.58–1.20)</td>
<td>...</td>
<td>3.19 (2.25–4.53)</td>
<td>...</td>
</tr>
<tr>
<td>SES* (above poverty referent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below poverty</td>
<td>1.17 (0.80–1.72)</td>
<td>0.82 (0.63–1.07)</td>
<td>1.01 (0.70–1.47)</td>
<td>0.93 (0.72–1.20)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.53 (0.29–0.99)</td>
<td>0.73 (0.48–1.12)</td>
<td>0.60 (0.34–1.07)</td>
<td>0.81 (0.48–1.36)</td>
</tr>
<tr>
<td>β-Blocker adherence (not adherent, PDC†&lt;0.80 referent)</td>
<td>0.97 (0.69–1.35)</td>
<td>0.62 (0.50–0.78)</td>
<td>1.53 (1.10–2.13)</td>
<td>0.68 (0.54–0.85)</td>
</tr>
<tr>
<td>Adherent (PDC ≥0.80)</td>
<td>1.55 (1.24–1.94)</td>
<td>0.94 (0.63–1.40)</td>
<td>1.34 (1.01–1.77)</td>
<td></td>
</tr>
<tr>
<td>Not prescribed β-blocker</td>
<td>0.94 (0.63–1.40)</td>
<td>1.55 (1.24–1.94)</td>
<td>0.94 (0.63–1.40)</td>
<td>1.34 (1.01–1.77)</td>
</tr>
<tr>
<td>ACE/ARB adherence ‡(not adherent, PDC &lt;0.80 referent)</td>
<td>0.72 (0.51–1.00)</td>
<td>0.45 (0.36–0.55)</td>
<td>1.07 (0.76–1.51)</td>
<td>0.49 (0.40–0.61)</td>
</tr>
<tr>
<td>Adherent (PDC ≥0.80)</td>
<td>0.47 (0.30–0.73)</td>
<td>1.05 (0.81–1.37)</td>
<td>0.95 (0.62–1.46)</td>
<td>1.81 (1.14–2.88)</td>
</tr>
</tbody>
</table>

All covariates are time constant except β-blocker and ACE/ARB adherence, which were time varying. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; HF, heart failure; HFPEF, heart failure preserved ejection fraction; HFREF, heart failure reduced ejection fraction; and PDC, percent of days covered.

*Socioeconomic status: below poverty if patient resided in area with >20% of housing in poverty or if <25% of residents had a high school education.
†Percent days covered: adherent if PDC was ≥80% and nonadherent if PDC <80%.
‡ACE/ARB adherence was examined in a separate model.

Impact of Revascularization on Survival in Patients With HFP EF With CAD

Survival After CABG in Patients With Preoperative HFpEF vs. HFrEF

Swedish nationwide population-based cohort study that included all patients who underwent CABG between January 1, 2001, and December 31, 2013, from the SWEDHEART register. The primary outcome was all-cause mortality. A secondary outcome measure was a combination of all-cause mortality and readmission for HF. The study included 41,906 patients, 37,234 without known HF (27,165 with pEF and 10,069 with rEF) and 4,672 with HF (1,216 with pEF and 3,456 with rEF). Their mean (SD) age was 67.4 (9.3) years, and 21.0% were female. Follow-up was 6.0 (3.3) years.

Dalén M, et al. JAMA Cardiol 2016; 1:530-8
Treatment of Pulmonary Hypertension/RV Dysfunction in HFP EF

### Associations of Cardiac and Non-cardiac Comorbidities with Heart Failure

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Risk factor for HF</th>
<th>Negative effect on LV structure/function</th>
<th>Worsening of HF outcomes</th>
<th>Improvement of HF symptoms/outcomes with specific treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>+++</td>
<td>+++</td>
<td>HFpEF (+++), HFrEF (-/+), +++</td>
<td>+++</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+/−</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
</tr>
<tr>
<td>Anaemia/iron deficiency</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
</tr>
<tr>
<td>Diabetes</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
</tr>
<tr>
<td>Sleep-disordered breathing</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
</tr>
<tr>
<td>Obesity</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
</tr>
<tr>
<td>Depression</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
</tr>
</tbody>
</table>

+++: definite; ++: probable; +: possible; +/−: doubtful.

HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

---

Future Management of HFpEF: The Nitrate/Nitrite/NO Pathway
Tao Hongjing who in the fifth century described the use of saltpeter (KNO₃) for the treatment of cardiovascular disease.
Nitric Oxide Generation

**Classic Pathway**
- Oxygen dependent

**Nitrate-Nitrite-NO**
- Hypoxia and acidosis

**Nitric Oxide Synthases**
- NO
- NO$_3^-$ / NO$_2^-$

Mechanisms by which Inorganic Nitrate Enhance Aerobic Capacity in HFpEF

**Effect of Inorganic Nitrate on Hemodynamics in HFpEF**

Randomized, double-blind, crossover study (n=17), comparing single dose of NO₃ rich beetroot juice (NO₃−, 12.9 mmol) with placebo. Supine-cycle maximal-effort CPx, with measurements of CO and skeletal muscle oxygenation. Study end points included exercise efficiency (total work/total O2 consumed), peak VO₂, total work, vasodilatory reserve, forearm mitochondrial oxidative function, and AI.

<table>
<thead>
<tr>
<th></th>
<th>Inorganic Nitrate</th>
<th>Placebo</th>
<th>Difference Between Inorganic Nitrate and Placebo Studies</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline MAP, mm Hg</td>
<td>88.4 (12.1)</td>
<td>88.2 (12.8)</td>
<td>0.18 (13.7)</td>
<td></td>
</tr>
<tr>
<td>Peak MAP, mm Hg</td>
<td>104.0 (17.3)</td>
<td>104.3 (16.0)</td>
<td>-0.3 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Change in MAP, %</td>
<td>18.0 (21.9)</td>
<td>18.2 (16.7)</td>
<td>0.2 (23.5)</td>
<td>0.98</td>
</tr>
<tr>
<td>Baseline HR, bpm</td>
<td>62.7 (8.8)</td>
<td>63.4 (9.1)</td>
<td>-0.7 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>115.2 (19.1)</td>
<td>113.8 (22.8)</td>
<td>1.5 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Change in HR, %</td>
<td>78.0 (24.1)</td>
<td>65.6 (21.0)</td>
<td>12.4 (13.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline CO, L/min</td>
<td>5.6 (1.5)</td>
<td>5.9 (1.8)</td>
<td>-0.3 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Peak CO, L/min</td>
<td>12.1 (3.9)</td>
<td>10.8 (3.6)</td>
<td>1.2 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Change in CO, %</td>
<td>121.2 (59.9)</td>
<td>88.7 (53.3)</td>
<td>32.5 (41.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Baseline SV, mL</td>
<td>81.9 (18.2)</td>
<td>83.4 (21.1)</td>
<td>-1.5 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Peak SV, mL</td>
<td>99.7 (24.0)</td>
<td>92.5 (26.0)</td>
<td>7.2 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Change in SV, %</td>
<td>22.6 (22.4)</td>
<td>12.7 (25.4)</td>
<td>9.8 (24.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Baseline SVR, Wood units</td>
<td>17.0 (5.2)</td>
<td>16.5 (5.3)</td>
<td>0.5 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Peak SVR, Wood units</td>
<td>9.7 (3.9)</td>
<td>11.2 (5.2)</td>
<td>-1.6 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Change in SVR, %</td>
<td>-42.4 (16.6)</td>
<td>-31.8 (20.3)</td>
<td>-10.6 (16.9)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are mean (SD). CO indicates cardiac output; HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; and SVR, systemic vascular resistance.

Effect of Inorganic Nitrate on Exercise Capacity in HFpEF

Inhaled Sodium Nitrite Improves Rest and Exercise Hemodynamics in HFpEF

In a double-blind, randomized, placebo-controlled, parallel-group trial, subjects with HFpEF (n=26) underwent cardiac catheterization with simultaneous expired gas analysis at rest and during exercise, prior to and following treatment with inhaled sodium nitrite (90 mg) or placebo.

Conclusions
• Up to 50% of patients with HF have a preserved LVEF (HFpEF), and this proportion has increased over time. Morbidity and mortality in HFpEF are high.

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

• Aggressive management of systolic hypertension in the elderly may decrease the incidence of HF and mortality.

• CAD is frequent in HFpEF and difficult to diagnose both clinically and non-invasively. Revascularization when appropriate should be implemented.

• Noncardiac comorbidities adversely affect prognosis and should be addressed, despite lack of compelling evidence that their treatment improves symptoms/outcomes in HFpEF.

• Modulation of the inorganic nitrate/nitrite pathway may represent a novel avenue by which to improve exercise capacity in HFpEF.